Olfactory cells may act as 'Trojan horse,' carry anticancer therapy to deadly brain tumors

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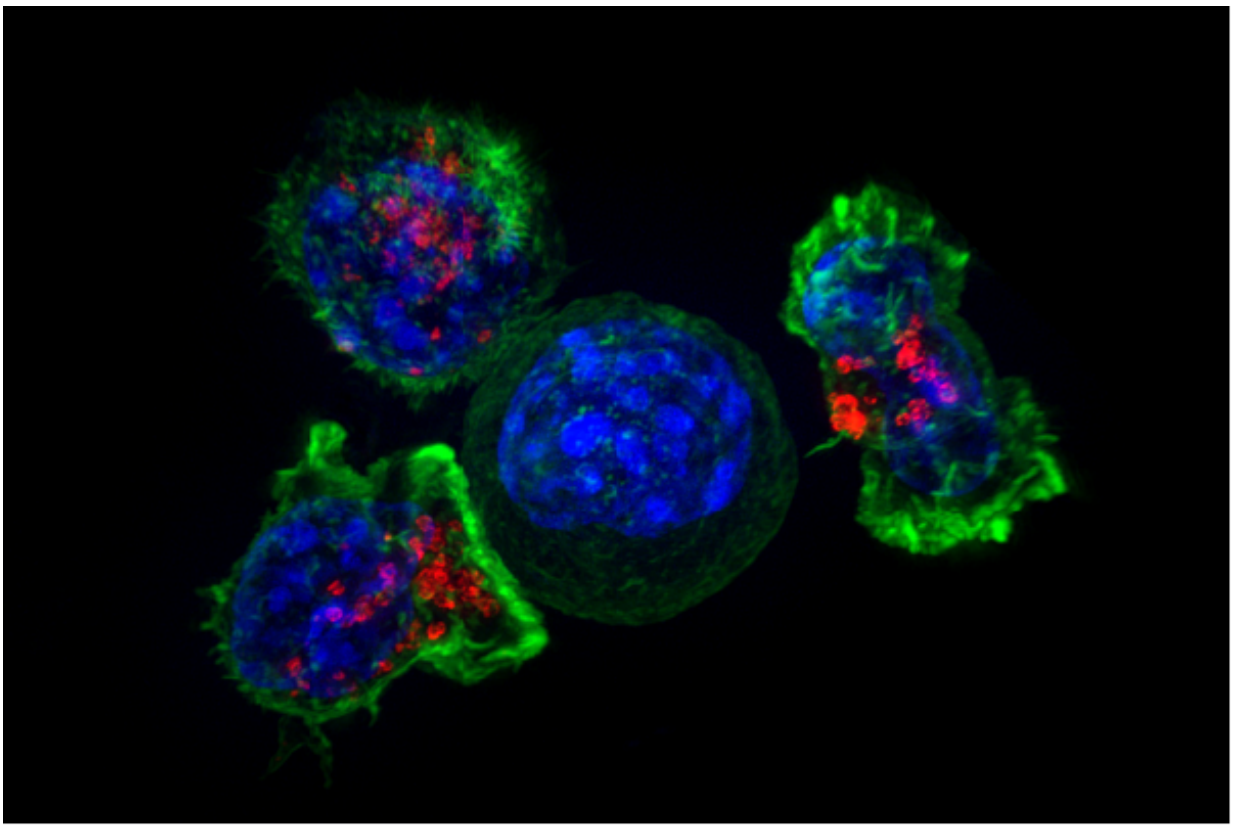

Killer T cells surround a cancer cell. Credit: NIH

A special type of cell essential to the ability of olfactory neurons to regenerate may be genetically engineered to deliver anticancer therapy to

the dangerous brain tumors called glioblastomas. In their report published in the *Journal of the National Cancer Institute*, Massachusetts General Hospital (MGH) researchers describe using olfactory ensheathing cells to deliver an anticancer agent only to tumor cells and how the treatment reduced tumor size and prolonged survival in a mouse model.

"Glioblastomas are the most aggressive and malignant type of brain tumors, and despite intensive treatment with surgery, chemotherapy and radiation therapy, they almost always recur, leading to a five-year survival rate of less than 10 percent," says Bakhos Tannous, Ph.D., of the Neuro-Oncology Division in the MGH Department of Neurology, senior author of the report. "Olfactory ensheathing cells—which are present in the nose throughout life in all mammals, including humans—can migrate from the nasal cavity to sites of inflammation and have the potential of acting as a 'Trojan horse,' delivering cell-killing therapies that bypass the barriers that keep other anticancer agents out of the brain."

Olfactory neurons—the cells in the nasal cavity that perceive odors and pass signals along to the brain—have the ability to regenerate, which is rare within the nervous system. New neurons in the nasal cavity must project fibers called axons to the olfactory bulb within the brain itself. Olfactory ensheathing cells (OECs) surround the growing axons, assisting in their regeneration and also engulfing debris from dead and damaged cells. The ability of OECs to promote neural regeneration has led to studies of their potential in the treatment of spinal cord injuries and the neurodegenerative disorder amyotrophic lateral sclerosis.

Because of the direct connection between the nasal cavity and the brain, intranasal drug delivery is being studied as a means of bypassing the blood brain barrier. The ability of OECs to travel into the brain and their attraction to inflammatory molecules—including those secreted by

tumor cells—led the MGH team to investigate their potential use against glioblastomas. They first showed that labeled OECs introduced into the nasal cavity of mice with experimentally induced human gliomas not only traveled to sites where tumor cells had been injected but also followed tumor-initiating cells as they infiltrated adjacent brain tissue.

The team then genetically engineered OECs to express a fusion protein called CU that converts a nontoxic prodrug called 5-FC into a cell-killing chemotherapy agent called 5-FU. After confirming in cellular experiments the ability of CU-expressing OECs to convert 5-FC to 5-FU, leading to the death of tumor cells, the team administered either CU-expressing OECs or a control agent into the nasal cavities of mice a week after tumor-initiating cells had been injected into the animals' brains. Seven days later, both groups of animals received daily injections of 5-FC for another seven days. Two weeks after that, mice that had received the transgenic OECs has significantly smaller tumors at the injection site, less tumor migration through the brain and greater death of tumor cells than the control group. The single OEC treatment also led to significantly longer average survival among the treated mice.

"Our findings indicate that, upon intranasal delivery, CU-expressing OECs migrate through their natural route towards the brain, target brain tumors in a very specific manner and convert 5-FC into an active 5-FU drug at the tumor site, leading to an efficient, tumor-cell-killing effect through what is called a 'bystander effect'," says Litia Carvalho, Ph.D., a postdoctoral fellow in Tannous's lab and the lead author of the study.

Tannous, an associate professor of Neurology at Harvard Medical School, adds, "Due to their strong attraction to inflammatory cues secreted by tumor cells, we believe OECs could be used as a therapeutic tool against different types of brain cancer and tumors located in other parts of the body, something we are actively investigating."

More information: Litia A Carvalho et al, Olfactory Ensheathing Cells: A Trojan Horse for Glioma Gene Therapy, *JNCI: Journal of the National Cancer Institute* (2018). DOI: 10.1093/jnci/djy138