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HIGHLIGHTS:
Numerous studies are underway to develop effective methods for treating stroke and degenerative brain diseases using neural stem cells. Now the "cancer-tracking" ability of neural stem cells is being investigated as a potential weapon against malignant brain cancers. In an animal study, researchers at Cedars-Sinai Medical Center's Maxine Dunitz Neurosurgical Institute used neural stem cells that were modified to secrete interleukin 12 in the treatment of gliomas, extremely aggressive brain tumors that are highly resistant to therapy. The study is the subject of the cover article of the Oct. 15 issue of the journal *Cancer Research*.

RESEARCHERS TRACK ELUSIVE BRAIN TUMOR CELLS IN MICE WITH NEURAL STEM CELLS MODIFIED TO DELIVER INTERLEUKIN 12 AND BOOST IMMUNE RESPONSE

LOS ANGELES, CA (October 15, 2002) – Researchers at Cedars-Sinai Medical Center's Maxine Dunitz Neurosurgical Institute have successfully tested a new treatment for brain cancer by utilizing neural stem cells to track and destroy cancer cells within the brain. Scientists hope the encouraging results may eventually lead to an effective treatment for glioma, the most aggressive form of primary brain tumor in humans. The study, conducted in mice with experimental brain cancer, is featured on the cover of the Oct. 15 issue of the journal *Cancer Research.*

The prognosis has historically been extremely poor for patients diagnosed with malignant gliomas. These tumors have very poorly defined margins, and glioma cells often spread deep into healthy brain tissue making their effective surgical removal extremely difficult. Often, pockets of tumor cells break off from the main tumor and migrate deep into non-tumorous areas of the brain. Therefore, even if the original tumor is completely removed or destroyed, the risk of recurrence is high as cells in these distant "satellites" multiply and eventually re-form a new brain tumor. Due to these characteristics, treating brain cancer has been extremely difficult.

The new experimental treatment involves the use of neural stem cells for tracking and targeting brain tumor cells that spread out into normal brain. Scientists show that neural stem cells, when injected into brain tumors, can follow tumor cells as they migrate away from the main tumor mass. This capability led scientists to genetically engineer neural stem cells to produce interleukin 12, an immune stimulating chemical known to kill glioma cells. The interleukin 12 producing neural stem cells were then injected into brain tumors in mice and could kill tumor cells that had spread deep into normal brain tissue, at considerable distance from the primary tumor. Mice treated with this novel strategy survived significantly longer than control-treated mice. In fact, 30% of animals treated in this new manner developed long-term immunity to brain cancer, indicating the potency of this therapy.

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Scientists demonstrated that the neural stem cells were able to kill the spreading tumor cells by delivering interleukin 12 directly to these migrating glioma "satellites". Previous research at the Maxine Dunitz Neurosurgical Institute has demonstrated that interleukin 12 can activate cancer killing cells from the immune system to attack and destroy brain tumor cells. The ability of neural stem cells to deliver this immune stimulating protein directly to small pockets of brain tumor cells that can not be accessed using surgery, represents a promising new method that could be used to eliminate all remaining tumor left behind after routine surgery. This could hopefully lower the incidence of tumor recurrence and improve survival in patients with malignant gliomas.

"The current focus of experimental neural stem cell therapeutics is primarily based around their use in the treatment of neurodegenerative disorders and stroke. We have demonstrated that combining the tumoricidal potency of interleukin 12 with the extensive tumor tracing capability of neural stem cells, results in a synergistic therapeutic benefit," according to the authors. "This further extends the scope of neural stem cell therapy to include their use as vehicles for protein delivery to *in vivo* glioma, and therefore represents a promising new treatment modality for malignant brain tumors."

Moneeb Ehtesham, M.D., a postdoctoral fellow at the Institute, is the article's first author. John S. Yu, M.D., co-director of the Comprehensive Brain Tumor Program at the Institute, is senior author. The work was supported in part by National Institutes of Health grant NS02232 to Dr. Yu.

Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For the fifth straight two-year period, it has been named Southern California's gold standard in health care in an independent survey. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthrough biomedical research and superlative medical education. Named one of the 100 "Most Wired" hospitals in health care in 2001, the Medical Center ranks among the top 10 non-university hospitals in the nation for its research activities.

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