

**Public release date: 1-Sep-2006**

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Contact: Sandra Van  
[sandy@prpacific.com](mailto:sandy@prpacific.com)  
800-880-2397  
Cedars-Sinai Medical Center

## Combined therapies may boost immune response and long-term protection against brain tumors

LOS ANGELES (Sept. 1, 2006) – One therapy for treating brain tumors alerts the immune system to the presence of foreign material. A second therapy enhances the first and prolongs the immune system's response. Now, in an animal study conducted at Cedars-Sinai Medical Center's Maxine Dunitz Neurosurgical Institute, researchers have combined the two in a form that appears effective when injected directly into a malignant brain tumor.

The result, extended length of survival, even after "rechallenge," is detailed in the Sept. 1 issue of the journal *Cancer Research*.

Dendritic cell immunotherapy, pioneered at the Institute in the treatment of deadly, recurring brain tumors called gliomas, is one component of the experimental procedure. The treatment is usually performed after a patient's tumor has been surgically removed. Proteins from the tumor are collected, cultured and introduced in a Petri dish to dendritic cells taken from the patient's blood. The "new" dendritic cells are then injected into the patient's bloodstream. When they encounter lingering tumor cells, they initiate an immune response.

Dendritic cells are specialized "antigen-presenting cells" responsible for alerting the immune system to foreign matter and eliciting an attack. They normally exist in the body to clear debris, such as dead cells, detecting antigens in the process.

The new approach bypasses the tumor-cell extraction and culturing process of dendritic cell immunotherapy. Instead, dendritic cells derived from the patient's bone marrow are attached to a virus engineered to express interleukin-23 (IL-23), a recently discovered cytokine, a protein that regulates immune responses. The dendritic cells are then injected directly into an existing tumor.

IL-23 allows dendritic cells to recognize antigens, such as live glioma cells, that otherwise escape surveillance without immune therapy manipulation. It also has several other properties that significantly improve the immune system's effectiveness against gliomas, which are highly aggressive cancers.

"Interleukin-23 promotes the function of dendritic cells and memory T-cells, important components in providing an initial response and long-term immunity against tumor cells," said John S. Yu, M.D., neurosurgeon, co-director of the Comprehensive Brain Tumor Program at the Maxine Dunitz Neurosurgical Institute, and senior author of the *Cancer Research* article.

An article by Yu and his colleagues in the March 1, 2006 issue of the same journal documented IL-23's potential effectiveness against gliomas and its impact on memory cells, which enable the immune system to "remember" antigens and respond in subsequent encounters. In that

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animal study, the researchers injected bone marrow-derived neural stem cells that were genetically engineered to produce IL-23. The stem cells tracked tumor cells and the IL-23 produced an immune response and long-term protection.

In the newly published study, 80 percent of animals receiving intratumoral injection of dendritic cell-interleukin-23 (DC-IL-23) survived beyond the observation period of 120 days, a far higher percentage than animals in control groups. Furthermore, surviving animals continued to live even after rechallenge, the implantation of additional glioma cells, and remained tumor-free at the end of the study.

"Dendritic cells and interleukin-23 appear to work very well together against glioma cells. Intratumoral injections brought about robust infiltration of tumor-killing T-cells and established a strong systemic response specific to the tumor cells," Yu said.

"These findings build on our previous observations as we work to develop an effective strategy to activate an immune response against brain tumors, and we're looking forward to rapidly translating this approach into a clinical trial," said Keith L. Black, M.D., director of the Maxine Dunitz Neurosurgical Institute and interim chair of the medical center's Department of Neurosurgery.

This study was supported by grants from the National Institutes of Health. The Maxine Dunitz Neurosurgical Institute researchers worked with colleagues in Cedars-Sinai Medical Center's Department of Surgery and the University of Perugia, Italy.

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Citation: *Cancer Research*, Sept. 1, 2006, "Induction of potent antitumor immunity by intratumoral injection of IL-23 transduced dendritic cells."

The first of seven hospitals in California whose nurses have been honored with the prestigious Magnet designation, Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For 18 consecutive years, it has been named Los Angeles' most preferred hospital for all health needs in an independent survey of area residents. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. It ranks among the top 10 non-university hospitals in the nation for its research activities and is fully accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). Additional information is available at [www.cedars-sinai.edu](http://www.cedars-sinai.edu).

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