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BACKGROUNDER FOR IMMEDIATE USE

**ON THE TRAIL OF A KILLER FOR A DECADE, AND CLOSING IN:  
JULY 1, 2007 MARKS THE 10<sup>TH</sup> ANNIVERSARY OF CEDARS-SINAI'S  
MAXINE DUNITZ NEUROSURGICAL INSTITUTE**

*With an adversary as deadly, complex and deceptive as brain tumors, researchers at the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai Medical Center measure progress in small but deliberate steps*



**LOS ANGELES (April 12, 2007)** – Every time a molecular mystery is uncovered, a piece of a puzzle comes into focus. When a research team discovers a gene or detects a biochemical mechanism that allows a deadly brain tumor to grow, another part of a problem is solved. One clue builds on another, and as one finding leads to the next, more effective treatments – and the possibility of eventual cures – edge closer.

Nearly 10 years ago, on July 1, 1997, neurosurgeon Keith L. Black, M.D., took a big step in search of killer – malignant, fast-moving brain tumors for which no effective treatments had ever been developed. Founding the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai Medical Center, he set out to concentrate the intelligence, inspiration and energy of a few top scientists on a single goal, much as the Manhattan

Project set out to develop an atomic bomb at an accelerated pace in the 1940s. In this case, the goal would be to discover and defuse the complex and intricate biological mechanisms that enable malignant brain tumors to mushroom.

After a decade of work, Black and his colleagues can look back on a series of “firsts,” a collection of evidence, and a trail that may lead to the gradual demise of a feared disease. An experimental therapy is in place and being fine-tuned as the potential vulnerabilities of brain tumors are being identified and exploited.

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“Projects like ours, which put together some of the best and brightest clinicians with some of the best and brightest scientists, are to a great degree driving the future of science,” says Black, Institute director and chair of Cedars-Sinai’s Department of Neurosurgery, noting that he and his research teams publish about 20 scientific articles in peer-reviewed journals each year.

“We have a relatively small budget and about 35 full-time researchers in the lab, but we have been able to develop a vaccine for brain cancer, ways to deliver drugs across the blood-brain barrier, and optical technology that may allow us to diagnose tumors without the need for biopsy,” notes Black. “We have found new molecular targets that are important in tumor invasion, and immune factors that we can exploit to make tumors more sensitive to chemotherapy. We also have shown that stem cells derived from adult bone marrow can track and attack malignant cells migrating away from a brain tumor.”

While clearly capable of making major scientific breakthroughs, a close-knit, integrated center such as the Maxine Dunitz Neurosurgical Institute has the agility to quickly translate new techniques and technologies into patient care. And even as newly designed technologies are making their way through biotech companies affiliated with the medical center for development, the Institute is attracting new funds for future exploration. The Brain Trust, a community organization that has supported the Institute’s research efforts since the beginning, as well as other supporters has raised over \$20 million, and Black and several of the Institute’s researchers receive several National Institutes of Health grants totaling over \$1.5 million a year.

### **Until now, little progress in slowing aggressive, incurable brain tumors**

“The whole area of brain tumor research had been stagnant for about 40 years. In the 1960s radiation therapy was found to be beneficial for brain tumors, but the median survival for the most common malignant brain tumor is still less than a year, even after 40 additional years of research,” Black says. “One of the areas that we felt had a lot of promise was the concept of using the immune system to attack the tumor. We knew that brain tumors, in order to survive, had to evade being recognized by the immune system. So we put together a team of neurosurgeons, immunologists and molecular biologists to see if we could develop a vaccine for the most aggressive form of brain cancer, glioblastoma multiforme.”

The vaccine, which is used in patients who have developed these malignant tumors, is intended to alert the immune system to the cancer cells and activate an immune response to kill remaining tumor cells. It was first used in patient treatment in May 1998.

When a tumor is removed, foreign proteins are collected, cultured and introduced in a Petri dish to dendritic cells taken from the patient’s blood. Dendritic cells are the immune system’s most powerful antigen-presenting cells – those responsible for helping the immune system recognize invaders. The “new” dendritic cells are then injected into the patient where they are intended to recognize and destroy lingering tumor cells. Several injections are scheduled over a six-week period.

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In their efforts to battle brain tumors, using immunotherapy and other innovative approaches, Institute researchers have made a number of discoveries. In the past few years, for example, they:

- Found that up-regulation of laminin-8, a protein product of several genes, may be a critical step in brain tumor progression and the ability of a tumor to develop blood vessels needed for growth. Laminin-8 was associated with poor patient prognosis. (*Cancer Research*, July 15, 2001.)
- Documented in an animal study that they could circumvent the blood-brain tumor barrier (BTB) to selectively deliver drugs directly to the area of brain tumors without increasing delivery to normal brain tissue. Without intervention, the BTB prevents most of a cancer-killing medication from reaching the tumor. (*Journal of Pharmacology and Experimental Therapeutics*, June 2002.)
- Engineered neural stem cells, which have a natural ability to target and track glioma cells, to secrete interleukin 12. In this mouse study, inoculation with IL-12-secreting neural stem cells resulted in significant prolongation of survival. Not only did treated mice survive longer, they demonstrated a high level of long-term immunity when additional glioma cells were implanted three months after the first ones. (*Cancer Research*, Oct. 15, 2002.)
- Generated for the first time neural progenitor cells from whole adult bone marrow. If these neural stem cells can be transplanted to treat stroke, brain tumors and neurodegenerative disorders, they could provide a renewable source of stem cells, available from a patient's bone marrow instead of the brain and without the ethical and tissue-rejection issues associated with the use of embryonic or fetal stem cells. While this study was conducted in rats, similar optimistic results have been seen in human tissue. (*Experimental Neurology*, Dec. 2002.)
- Engineered neural stem cells to deliver TRAIL, a protein known for its cancer-fighting properties. In laboratory studies, unmodified TRAIL cells attacked human glioblastoma cells, with nearly all tumor cells being killed within 24 hours. TRAIL-secreting neural stem cells also resulted in significant cancer cell death, and the genetically engineered stem cells maintained their viability for as long as 10 days. (*Cancer Research*, Dec. 15, 2002.)
- Discovered that an antigen, Tyrosinase-Related Protein-2 (TRP-2), previously found in melanomas, is also expressed in glioma cells and could be used as a target of immunotherapy. (*Journal of Immunotherapy*, July/Aug. 2003.)
- Reduced tumors' ability to invade neighboring tissue by blocking the expression of laminin-8. This study supported the hypothesis that laminin-8 is involved in the spread of these malignancies and it reinforced the possibility that a therapy may be developed to arrest the tumors by targeting the gene. (*Molecular Cancer Therapeutics*, Oct. 1, 2003.)

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- Documented that recently produced cancer-fighting cells are the major determinant of prognosis and survival of glioma patients. While age at diagnosis has been the best predictor of tumor recurrence and survival, this research contributed to the recognition that a robust immune system is the underlying key – a younger person’s immune system is better able to fight cancer. Patients with high numbers of recently generated CD8+ T lymphocytes respond more favorably to immune therapy vaccine. (*Journal of Immunology*, Nov. 1, 2003.)
- Described the type of neural stem cells that are able to track brain cancer cells as they migrate from a tumor to form new satellites, and described a mechanism that turns on the tumor-tracking activity. The stem cells are considered potential transporters to deliver cancer-killing agents. (*Neoplasia*, May/June 2004.)
- Identified three antigens that are expressed in glioblastoma cells and used them as targets for the dendritic cell vaccine. In laboratory studies and in a small patient trial, cancer-killing immune cells recognized glioma cells expressing the antigens, HER2, gp100, and MAGE-1, and the vaccine appeared to play a role in prolonging patient survival. The median length of survival of patients whose treatment included the vaccine was 133 weeks – about two and a half years. A similar group of patients receiving the same level of care but not the vaccine had a median survival of only 30 weeks – seven and a half months. (*Cancer Research*, July 15, 2004.)
- Reported that an optical device was able to quickly and accurately discriminate between brain tumor and normal tissue. If the technology continues to progress as anticipated, neurosurgeons will be able to shine a laser light during surgery to diagnose brain tumors instantaneously and discern the borders of tumors with greater precision than ever. Time-resolved laser-induced fluorescence spectroscopy is based on the fact that when molecules are stimulated by light, they respond by becoming excited and re-emitting light of varying colors that can be captured and measured. (*Photochemistry and Photobiology*, July/Aug. 2004.)
- Found that over-expression of laminin-8 is a predictor of a tumor’s grade, its potential for recurrence, and the patient’s length of survival. (*Cancer*, Aug. 2004.)
- Reported that the combination of immunotherapy and chemotherapy significantly slowed tumor progression and extended survival of patients with glioblastoma multiforme. The results suggest that chemotherapy synergizes with previous therapeutic vaccination to generate a uniquely effective treatment. Average length of survival was extended to about 26 months when patients received the combined therapies, compared to 18 months for those who received vaccine alone and 16 months for those undergoing chemotherapy alone. (*Clinical Cancer Research*, Aug. 15, 2004.)
- Isolated “cancer stem cells” from malignant brain tumors. These stem cells share the multi-potent and self-renewing properties of normal stem cells but instead of producing healthy cells, they propagate cancer cells in their own image. (*Oncogene*, Dec. 16, 2004.)

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- Described the molecular mechanism that appears to make malignant brain tumors more vulnerable to chemotherapy after they have been treated with the dendritic cell vaccine. TRP-2, the protein fragment reported in gliomas in 2003, was identified as a potentially “powerful molecule” linking chemotherapy and immunology. The immune system recognizes TRP-2 as a foreign invader, making it a significant target for immunotherapy and making the tumor more vulnerable to follow-up chemotherapy. (*Oncogene*, Aug. 2005.)
- Exploited a biochemical pathway to make gliomas much more sensitive to a drug and a natural process of cell death called apoptosis. (*Journal of Biological Chemistry*, published online Nov. 30, 2005.)
- Attached a newly discovered cytokine, interleukin 23, to neural stem cells derived from bone marrow, creating a tool to track and kill malignant brain tumors cells and provide long-term protection against their return. The animal study was expected to lead to a human trial in the near future. (*Cancer Research*, March 1, 2006.)
- Found in an animal study that the intratumoral injection of bone marrow-derived dendritic cells and interleukin 23 produced a strong systemic immune response with long-term protective effects. The approach may have therapeutic potential for treating human glioma and was expected to be the subject of an upcoming clinical trial. (*Cancer Research*, Sept. 1, 2006.)
- Documented that cancer stem cells are resistant to conventional chemotherapy and contribute to disease relapse. Theoretically, these cells are the ultimate source from which a tumor grows – and therefore, the ultimate target for therapies. (*Molecular Cancer*, Dec. 2, 2006.)
- Manipulated stem cells taken from adult human bone marrow to generate aggregates of cells called spheres that are similar to those derived from neural stem cells of the brain. The cells migrated and behaved like actual neural stem cells when transplanted into the brain tissue of chicken embryos. (*Journal of Neuroscience Research*, Feb. 2007.)

“Each of these steps is a natural extension of the work we’ve done in the past as we seek to develop an effective strategy to activate an immune response against brain tumors,” says Black.

### **Clinical observations stimulate scientific curiosity and guide research**

In a setting such as the Maxine Dunitz Neurosurgical Institute, scientific endeavors are much more than theoretical. Clinicians and research teams are confronted, focused and driven each day by the clinical realities of the patients in their care.

These clinical observations were integral to discoveries regarding the synergism between immunotherapy and chemotherapy, elevated laminin-8 levels and the invasive capabilities of tumors, innovative diagnostic and treatment technologies that are now in development, and the recognition that the most significant correlation with survival, patient age, is due to

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the more robust immune response in younger patients.

“One of the primary problems from a clinician’s point of view is the microscopic infiltration of tumor cells into normal tissue. This observation prompted our effort to engineer stem cells that can track down the tumor cells that migrate,” Black says. “The clinical reality that 98 percent of all drugs that could be of potential benefit in the brain are unable to get across the blood-brain barrier was the driving factor behind our discovery that tumor capillaries are different than normal brain capillaries. Our objective was to open the barrier to therapeutic drugs without damaging healthy tissue, but most major pharmaceutical companies simply try to make a drug more liquid soluble, which can’t always be done.”

The dendritic cell vaccine itself evolved from numerous observations of the immune system, the behavior of brain tumors, and the interactions of the two.

“By understanding how tumors are able to evade the immune system, we’ve been able to create a vaccine to allow the T cells to recognize tumor cells and launch an immune response. By knowing about various molecular pathways, we’re able to make the T cells more effective, and by identifying which protein antigens are expressed on the tumor cell, we can potentially now make a vaccine based on those particular proteins. Every finding ties in to allow us to develop our next generation of strategies, which we believe will be more potent than our first generation,” Black notes.

“We have now treated close to 80 patients with the vaccine, and our data show that we have been able to increase in early Phase II studies the two-year survival from about eight percent to 42 percent,” he adds. In one study, the median length of survival of patients with recurrent glioblastoma whose treatment included the vaccine was 133 weeks – about two and a half years. A similar group of patients receiving the same level of care but not the vaccine had a median survival of only 30 weeks.

### **Building infrastructure for the next ambitious steps**

“Now we are poised to capitalize on our initial vaccine and take it to the next level. Among other initiatives, we’re planning to seek National Institutes of Health funding to conduct much larger, more definitive Phase III studies on the vaccine, and we’re looking to extend our collaboration with other first-tier scientific institutes to make the vaccine more potent and to make stem cell technology for brain tumor therapy a reality,” says Black, adding that the current challenge is to develop the staff – clinical coordinators, research nurses, FDA regulatory specialists and others – to coordinate collaborative ventures and multi-center trials. Plans must be made, too, to produce the vaccine for distribution.

“We also need to expand our clinical team to deal with the increased volume that we’re seeing,” he says. “Patients are becoming more sophisticated and they recognize that, just like with heart surgery, outcomes are better in the centers that do a lot of very specialized surgeries. The year before the Maxine Dunitz Neurosurgical Institute was founded Cedars-Sinai neurosurgeons performed 26 craniotomies for malignant brain tumors. Now we’re doing in the neighborhood of 120 major brain surgeries a month.”

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“The first year the Institute opened, we performed 300 major neurosurgical cases. Now we’re doing close to 1,300 annually, so we’re building a team of highly talented neurosurgeons and related specialists to provide the same levels of patient care and research even as demand increases,” says Black. “We’re focusing our resources to move to the next phase of advancing neuroscience, positioning the Institute to assume a leadership role in such areas as stem cell work and minimally invasive strategies.”

In addition to providing top-tier research and patient care, the Institute is developing a multi-faceted educational component, which received a major boost with the 2005 opening of a residency training program in neurosurgery. Black’s goal is to prepare neurosurgeons who will be as skilled in the research lab as they are in the operating room. He also hopes to expand the medical center’s neuro-oncology program, noting that only about 200 such specialists are currently practicing in the nation.

Research experience and other educational opportunities are available to students at the undergraduate, graduate and post-graduate levels, but they also start early. Every year, about 120 7<sup>th</sup>- and 8<sup>th</sup>- grade students from Los Angeles area schools attend a free program, Brainworks, which encourages their interest in science and research. And each summer, more than a dozen students work in the Institute’s laboratories, some volunteering their time to gain experience, several funded by National Institutes of Health programs and two receiving support through the Pauletta and Denzel Washington Family Gifted Scholars Program in Neuroscience awarded by Cedars-Sinai’s Division of Neurosurgery.

Additional information on the history of Neurosurgery at Cedars-Sinai Medical Center may be found at: [http://www.cedars-sinai.edu/pf\\_6622.html](http://www.cedars-sinai.edu/pf_6622.html).

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The first in Southern California and one of only 10 hospitals in the state 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 19 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, 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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