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FACT SHEET AND RESEARCH TIMELINE:

**CEDARS-SINAI MEDICAL CENTER DEPARTMENT OF NEUROSURGERY
THE MAXINE DUNITZ NEUROSURGICAL INSTITUTE
THE JOHNNIE L. COCHRAN, JR. BRAIN TUMOR CENTER**



1996 – Cedars-Sinai neurosurgeons perform 26 brain surgeries for malignant brain tumors. In fewer than 10 years, they will be performing about 120 major brain surgeries *a month*.

July 1, 1997 – Neurosurgeon Keith L. Black, M.D., joins Cedars-Sinai Medical and establishes the Maxine Dunitz Neurosurgical Institute after 10 years at the University of California, Los Angeles (UCLA). Black comes with an established reputation as a prolific researcher, having

published his first scientific paper at age 17 and being recognized for his achievements in breaking through the blood-brain barrier to dramatically increase the amount of therapeutic drug reaching a brain tumor.



May 1998 – An experimental vaccine that uses the immune system to attack a tumor is first used in patient treatment. The vaccine remains a major focus of study today, often in combination with other therapies designed to increase its effectiveness.

1998-2007 – Research papers are regularly published in respected journals. One study builds on another as the scientists search for vulnerabilities in brain tumors' defenses. In the past few years, researchers:

- 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

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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.)
- 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.)

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- 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.)
- 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.)

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- 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.)

2005 – A residency training program in neurosurgery opens with a focus on preparing neurosurgeons who are as skilled in the research lab as they are in the operating room.

2006 – The Division of Neurosurgery becomes a free-standing Department of Neurosurgery. In December, Black is named department chair.

May 3, 2007 – The Johnnie L. Cochran, Jr. Brain Tumor Center is established to coordinate and streamline the evolution of basic research findings to clinical trials to approved medications and therapies.

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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.

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