CEDARS-SINAI MEDICAL CENTER NEWS

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SCIENTISTS SEEK TO DEFEAT BRAIN CANCER BY CHIPPING AWAY ITS FOUNDATION FROM VARIOUS ANGLES

Nanomedicine, immunotherapy, stem cells and gene discovery are some of the specialty areas converging on deadly, aggressive brain tumors.

LOS ANGELES (April 21, 2008) – Scientists at Cedars-Sinai Medical Center's Maxine Dunitz Neurosurgical Institute, working from a variety of disciplines and perspectives, are dissecting the complex biological events from which malignant brain tumors emerge, grow and acquire defense mechanisms that make them highly resistant to treatment.

Under the direction of neurosurgeon Keith L. Black, M.D., chairman of the Department of Neurosurgery at Cedars-Sinai and director of the institute, the research teams have compiled a series of "firsts" over the past decade. They recently:

- Identified underlying processes by which immune activity controls key cancer-causing genes in gliomas. As a result of these and related discoveries, the researchers will attempt to design personalized treatment plans using combinations of vaccination, chemotherapy and stem cell-blocking agents. A dendritic cell vaccine developed by Black and his colleagues and currently in a Phase II patient trial has already been found to increase length of survival when combined with chemotherapy.

- Conferred a molecular property from certain immune system cells to others, combining the best of both cells. Certain T cells are more effective than others in stimulating an immune response, but they become scarcer with age. The researchers "transferred" a beneficial molecular property to cells that do not diminish with age, improving response against tumors and entry into the brain in preclinical trials. The goal is to induce anti-tumor immunity in patients who do not respond to vaccination and increase immune strength in those who do.

- Developed molecular signatures of brain tumor stem cells to identify mechanisms by which malignant tumors renew themselves and propagate. A tumor's unique molecular profile may eventually be used to develop an individualized treatment to block its signaling mechanisms. Previously, the Cedars-Sinai researchers isolated cancer stem cells from malignant brain tumors and documented that these cells are resistant to conventional chemotherapy.

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- Generated neural stem cells from adult bone marrow and documented that they have properties similar to neural stem cells from the brain, demonstrated the ability of neural stem cells to target and track brain tumor cells even as they migrate, described a mechanism that turns on the tumor-tracking activity of stem cells, and engineered stem cells to deliver a cancer-fighting protein (TRAIL) or an immune activating protein (interleukin-12) in preclinical models.

- Found that laminin-411, a protein that is synthesized by tumor cells and deposited in newly formed tumor blood vessels, is over-expressed in human glioblastoma multiforme (GBM). Subsequently, the researchers found they could reduce a tumor's ability to invade neighboring tissue by blocking the expression of laminin-411, and they identified over-expression of laminin-411 as a predictor of tumor grade and potential for recurrence, as well as patient length of survival.

- Developed a new nanotechnology-based drug delivery system precisely targeting cancer cells. Using this nanobioconjugate delivery system (named Polycefin), anti-cancer drugs in high concentration may accumulate selectively in tumor without affecting normal cells. The nanobioconjugate allows several agents to be delivered at the same time for a synergistic anti-tumor effect. A version of Polycefin designed to block the expression of laminin-411 protein prevented the formation of new tumor blood vessels and, as a result, increased survival in pre-human models of brain cancer.

- Significantly increased drug delivery across the blood-brain-tumor barrier (BTB), and extended this effort to include not only primary brain tumors but cancers metastasizing to the brain.

- Collaborated with other scientists on several studies using radioactive iodine (131I) and TM-601, a synthetic version of the venom of the giant yellow Israeli scorpion. TM-601 attaches to glioma cells and is taken into the cells permanently, making it useful for the localized delivery of radioactive iodine. A Phase III international clinical trial is planned, as is a Phase I and II study using TM-601 alone because it not only targets tumor cells but appears to inhibit tumor growth.

- Worked with colleagues at Cedars-Sinai's Minimally Invasive Surgical Technologies Institute (MISTI) to develop an optical system (time-resolved laser-induced fluorescence spectroscopy) that may make it possible to diagnose tumors without biopsies.

The Maxine Dunitz Neurosurgical Institute opened at Cedars-Sinai on July 1, 1997, designed by Black to concentrate the intellect, inspiration and energy of a few top scientists on the goal of discovering and defeating the complex and intricate mechanisms that support malignant brain tumors.

The institute's centerpiece is a dendritic cell vaccine for patients who are battling these cancers, which evade and resist the immune system. First used in patient treatment in May 1998, the vaccine is intended to activate an immune response to the cancer cells. It is currently in a Phase II clinical trial.

"According to early results, we have been able to increase the two-year survival from about eight percent to 42 percent," Black said. 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.

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