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## GENE THERAPY ELIMINATES BRAIN TUMORS THROUGH SELECTIVE RECRUITMENT OF IMMUNE CELLS

*In laboratory and animal studies, a two-pronged gene therapeutic approach resulted in tumor regression and long-term survival; next step is a human clinical trial*

LOS ANGELES (January 13, 2009) – Scientists seeking to harness the power of the immune system to eradicate brain tumors face two major hurdles: recruiting key immune cells called dendritic cells into areas of the brain where they are not naturally found and helping them recognize tumor cells as targets for attack.

Researchers at Cedars-Sinai Medical Center, however, have identified a sequence of molecular events that accomplish both objectives. Their findings, based on laboratory and animal studies, appear in the Jan. 13 issue of *PLoS Medicine*, an open-access online journal of the Public Library of Science.

The Cedars-Sinai team discovered that a protein – HMGB1 – released from dying tumor cells activates dendritic cells and stimulates a strong and effective anti-tumor immune response. HMGB1 does so by binding to an inflammatory receptor called toll-like receptor 2, or TLR2, found on the surface of dendritic cells.

“Toll receptors play a major role in the immune system’s recognition of bacterial and viral components, but now we have shown that they also trigger an immune response against tumors,” said Maria G. Castro, Ph.D., co-director of Cedars-Sinai’s Board of Governors Gene Therapeutics Research Institute and one of the article’s senior authors. “Activation of Toll receptors was essential for two key stages in initiating immune responses against the tumor – the migration of peripheral dendritic cells into the brain tumor and the subsequent activation of dendritic cells and stimulation of a specific anti-tumor cytotoxic T-cell mediated response.”

Building on more than 10 years of research in this area, the researchers used a combined gene therapeutic approach, using one protein (Flt3L) to draw dendritic cells from bone marrow into the brain tumors, and a second protein (Herpes Symplex type I Thymidine Kinase, or TK), combined with the antiviral gancyclovir to kill tumor cells and elicit long-term survival. In this paper, they uncovered a novel mechanism by which tumor cell death in response to the treatment leads to the release of an endogenous tumor protein, HMGB1, which is essential to trigger the anti-tumor immunological cascade. The study showed for the first time that HMGB1 released from dying brain cancer cells activates TLR2 signaling on tumor infiltrating dendritic cells, resulting in the activation and expansion of tumor-antigen specific T cells. This caused the regression of the brain tumors and increased survival time by six months in experimental brain tumor models.

Glioblastoma multiforme is the most aggressive type of brain tumor, with only five percent of patients surviving five years following diagnosis. While new drugs have had some impact on survival rates, the traditional

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approaches to cancer treatment – surgery, radiation and chemotherapy – have failed to provide major improvements in long-term survival.

Immunotherapy – eradicating brain cancer cells by harnessing the patient’s immune system – has been an attractive treatment approach, in theory. An effective anti-tumor immune response initially depends on dendritic cells that constantly “sample” the environment and can recognize unusual proteins, such as those belonging to cancers or infectious pathogens. However, since there are few dendritic cells in the brain, the immune responses in this organ are dampened when compared to those elicited in other parts of the body.

According to Pedro Lowenstein, M.D., Ph.D., director of the Board of Governors Gene Therapeutics Research Institute and co-senior author, “The discovery of a central role for HMGB1 and TLR2 in overcoming immune ignorance to brain tumor antigens provides a new therapeutic approach in the fight against brain tumors. Our conclusions relating to anti-glioma immune responses have also been extended to enhancing immune responses against a number of other metastatic brain cancers, such as melanoma.”

He stated that plans are underway to test this novel therapeutic approach in a human clinical trial for recurrent brain tumors in 2009.

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