

Study identifies biomarker that safely monitors tumor response to new brain cancer treatment

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A specific biomarker, a protein released by dying tumor cells, has been identified as an effective tool in an animal model to gauge the response to a novel gene therapy treatment for glioblastoma mulitforme. The finding, reported in the July 1 issue of *Clinical Cancer Research*, paves the way for a Phase 1 clinical trial expected to begin in late 2009.

The gene therapy is a two-pronged strategy devised by scientists at the Cedars-Sinai Board of Governors Gene Therapeutics Research Institute. It uses a genetically engineered, harmless virus to deliver a combination of proteins and a drug to kill tumor cells, which triggers an ongoing immune response against <u>malignant brain tumors</u> cells.

The Cedars-Sinai team led by Pedro R. Lowenstein, M.D., Ph.D., director of the Board of Governors Gene Therapeutics Research Institute, and Maria G. Castro, Ph.D., co-director of the Institute, developed this gene therapy strategy during 10 years of laboratory research.

"Using this therapy, we have shrunk and completely eliminated very large brain tumors in animals and have trained their immune systems to develop memory so that recurrent tumors are also destroyed," said Castro, principal investigator of the study. "The biomarker identified in this study will help us determine the effectiveness of the therapy in patients with glioblastoma multiforme."



In this study, the researchers identified the most effective and least toxic combination of therapeutic agents that would offer the best results. They found that a protein released by dying tumor cells may be used as a "biomarker" to gauge the effectiveness of treatment. This protein, called "high mobility group box 1" (HMGB1), regulates gene expression in healthy cells by binding to the cells' DNA. When cancerous cells are killed, however, HMGB1 is released into the general blood circulation. This research shows that measuring the levels of HMGB1 in the blood could be a non-invasive but essential way to monitor the effectiveness of cancer therapeutics in patients. These findings will be used to fine-tune the therapy as it enters the Phase I clinical trial.

Traditional treatments have little impact on long-term survival of patients with glioblastoma multiforme, the most common malignancy in the brain, diagnosed in about 18,000 people in the United States every year.

The immune system is considered a potential ally, but the brain has few dendritic cells -- key sentries of the immune system that detect foreign proteins and provide the very initial signals for the T cells to mount an anti-tumor immune attack. Without the surveillance of dendritic cells, brain tumors go undetected and proliferate rapidly.

In the technique devised by Castro and Lowenstein, one of the proteins (the immune stimulatory cytokine Flt3L) attracts dendritic cells from bone marrow into the tumor while another protein (thymidine kinase) and the antiviral drug gancyclovir combine to kill tumor cells. The dying tumor cells are detected by the newly recruited dendritic cells, which initiate the anti-tumor response. The biomarker identified in this study is a result of the ongoing battle between the T cells and the <u>tumor cells</u>. As such, the <u>biomarker</u> will be a useful direct reporter of the ensuing fight to kill the tumor.



Source: Cedars-Sinai Medical Center

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