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RESEARCHERS AT CEDARS-SINAI FIND THAT A SMALL PROTEIN DELIVERED VIA A GENETICALLY ENGINEERED VIRUS INCREASED IMMUNE CELLS AND SLOWED THE GROWTH OF THE DEADLY BRAIN CANCER GLIOBLASTOMA MULTIFORME IN LABORATORY RATS

LOS ANGELES, CA (December 6, 2004)– Despite aggressive treatment, glioblastoma multiforme (GBM) – the most common and deadly of brain cancers – usually claims the lives of its victims within six to 12 months of diagnosis. This statistic has changed little over the years, largely because the cancer grows so quickly that neither surgery, radiation, or chemotherapy can stop it.

Now, researchers at Cedars-Sinai Medical Center have found that a small protein called hsFlt3L delivered via a genetically engineered virus increased the number of immune cells in the brain and significantly slowed tumor growth, increasing the survival of laboratory rats in pre-clinical studies. The study, published in the December issue of the journal, *Molecular Therapy*, may lead to a new way to treat patients with GBM.

“Importantly, our study is the first to show that GBM tumors shrank or were completely eliminated in lab rats, which is likely due to the ability of the protein, hsFlt3L to stimulate the production of fully mature immune cells within the brain,” said Maria Castro, Ph.D., co-director of the Board of Governors Gene Therapeutics Research Institute at Cedars-Sinai Medical Center and the senior author of the study. “Since gene therapy has given us the tool to deliver this protein, our hope is to translate these laboratory studies into clinical trials in patients with GBM.”

GBM tumors develop in the supportive tissue of the brain and grow quickly, often becoming very large before a person experiences symptoms and is diagnosed. Surgery is typically performed to remove as much of the tumor as possible and followed with radiation and/or chemotherapy to slow progression of the disease. But despite aggressive treatment, the tumor recurs and patients usually die within a year’s time.

Because GBM is so aggressive, the disease has been the target of a number of laboratory studies and clinical trials investigating the effectiveness of gene therapy to deliver novel therapeutic agents to the brain. Most of these have investigated the use of the suicide gene from the herpes simplex virus to develop a gene therapy approach that kills cancer cells, in the presence of the antiviral drug, gancyclovir. In laboratory studies, this type of gene therapy has proved almost 100 percent effective. But in clinical trials, it has had limited effectiveness, suggesting that the virus is not able to deliver the suicide gene effectively into a large tumor mass.

“Importantly, results from these studies showed us that gene therapy was safe, but that we needed to design a viral vector that would harness the power of the immune system to help eliminate the tumor,” commented Dr. Castro.

Genetically engineered viruses are used to transport genes and/or proteins into cells and have been used in gene therapy research for the last ten years. Just like a viral infection, they work by tricking cells into accepting them as part of their own genetic coding. To make them safe, scientists remove the genetic viral genes that cause infection and engineer them so that they stop reproducing and also carry therapeutic genes.

In this study, researchers from the “Board of Governors Gene Therapeutics Research Institute” team, led by Drs. Castro and Pedro Lowenstein, investigated the effectiveness of an anti-brain tumor therapy using hsFlt3L, a protein that has a unique ability to increase the number of immune cells when delivered into the brain. Specifically, these immune cells are called dendritic cells and work by presenting antigens – or foreign invaders that enter the body – and inducing the generation of cell-killing T-lymphocytes.

Because the brain lacks dendritic cells and is protected by the blood brain barrier, the investigators tested an adenoviral vector that had been genetically manipulated to selectively express hsFlt3L to find out if it would increase the number of dendritic cells in the brain of laboratory rats with GBM.

To evaluate whether hsFlt3L could shrink brain tumors and prolong survival, rats with GBM were injected with increasing doses of the engineered virus expressing hsFlt3L or a saline placebo that was used as a control. The investigators found that 70 percent of the rats treated with hsFlt3L survived long-term, for over a year, when the higher dose was used, and that it did not cause adverse immune reactions in the normal brain. In contrast, the rats treated with placebo substances died from their tumors within one week after the start of the treatment.

“Taking into account both the effectiveness of the treatment in the preclinical GBM animal model and also the lack of overt adverse side effects to the surrounding normal brain, we hope to start clinical trials using this combined immune and suicide gene therapy approach within the next three years,” said Dr Castro.

Among rats treated with hsFlt3L, the investigators found that 33 percent were completely tumor free at three months, while all those who survived for six months or longer had no tumors at all. Moreover, no rats died between the three and six months’ time points.

“These results show that tumor growth was greatly inhibited in rats treated with hsFlt3L and reflect an ongoing battle between the tumor and the immune system,” said Dr. Castro. “In other words, hsFlt3L stimulated an immune response as evidenced by an increase in the number of dendritic cells in the brain and led to complete elimination of the tumor in most of the rats, while slowing down tumor growth in the others. The combined data presented has important implications for using immunotherapy to treat brain tumors in patients with GBM.”

Cedars-Sinai Medical Center is one of the largest non-profit academic medical centers in the Western United States. For the fifth straight two-year period, Cedars-Sinai has been named Southern California’s gold standard in health care in an independent survey. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthrough in biomedical research and superlative medical education. The Medical Center ranks among the top 10 non-university hospitals in the nation for its research activities.

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