ON THE ROAD TO A CLINICAL TRIAL FOR USING GENE THERAPY FOR AGGRESSIVE GLIOBLASTOMAS

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The Brain Science Foundation supported the pioneering research conducted by the Neurosurgical Oncology Laboratory at Brigham and Women's Hospital (BWH), under the direction of Peter Black, M.D. Ph.D. and Rona Carroll, Ph.D. with the assistance of Lata Menon, Ph.D.

The support of the Brain Science Foundation came at a crucial time as we aim to use targeted cell based gene therapy to increase the survival time of patients with grade IV Glioblastoma Multiforme (GBM), a deadly brain tumor.

THE CURRENT STATE OF TREATMENT

GBM tumors are the most common type of malignant brain tumor. Although the tumors can be surgically removed, diffuse tumor cells invade away from the main tumor mass into other parts of the normal brain and cause a recurrence of the tumor. Current treatment options for patients include surgery to remove the main tumor mass, followed by radiation and chemotherapy. Even with this aggressive treatment, the median survival period after diagnosis is only 12 to 18 months.

USING THERAPEUTIC AGENTS TO INHIBIT GMB RECURRENCE

Since GBMs are highly invasive, current treatments are limited in their ability to reach all the invading tumor cells. With the previous support of the BSF (to Dr Lata Menon), we have developed a cell-based system to target invading tumor cells and to deliver a therapeutic agent to the small islets of tumor cells leading to an inhibition of tumor recurrence. We are using mesenchymal stromal cells (hMSCs) as a cell based delivery system. hMSC are multipotent stem cells that possess the innate ability to home to sites of tumor or areas of injury. The mechanisms underlying hMSC migration are being investigated by Dr. Lata Menon with the support of her own BSF grant.

Mouse models of gliomas have show that hMSCs, when injected into the wall of the brain tumor cavity, will migrate to the invading tumor cells, allowing targeted drug treatment to stop the tumor cells from growing—reducing the risk of tumor recurrence without damaging healthy tissue. During the past year the outline of the clinical trial was designed.

For the proposed clinical trial we have assembled a large medical team including neurosurgeons, neurooncologists and hematologists. hMSC cells will be isolated from the patient's own bone marrow cells, which will greatly reduce the immune response. The MSCs will then be genetically modified to express the prodrug enzyme cytosine deaminase which will convert a nontoxic drug (5-fluorocytosine) given to the patient

orally into a potent chemotherapy agent (5-fluorouracil) at the site of the tumor cells. Therefore MSC will serve as a cellular delivery vehicle.

PROGRESS TOWARD A CLINICAL TRIAL

During the past year, we have also been busy assembling the necessary paperwork required to initiate a gene therapy clinical trial. Receiving approval from the Food and Drug Administration (FDA) for a clinical trial can take several years. We first submitted the paperwork to the FDA Recombinant DNA Advisory Committee (RAC), which is a requirement for any clinical trial in which genetic engineering is used. As expected the RAC has a number of comments, which we are currently addressing. For example, they requested more data on the immune response to the hMSCs in brain.

Along with the RAC, the lab has prepared materials for the Institutional Review Board to obtain approval for conducting human clinical trials at the Dana Farber / Brigham and Women's Cancer Center. In addition, the lab has also begun the paperwork for the Investigation of a New Drug Application as required by federal law.

Thanks to the support of the Brain Science Foundation, the project is moving forward towards a clinical trial - a critical step in the process to make cell based gene therapy a viable treatment option for patients with a GBM.