

3. Non-Technical Abstract

Primary brain tumors are the third leading contributor to cancer-related mortality in young adults, are the second leading contributor in children, and appear to be increasing in incidence both in the pediatric and geriatric populations. Gliomas are the most common type of primary brain tumors; 20,000 cases are diagnosed and 14,000 glioma-related deaths occur annually in the United States. Gliomas are heterogeneous with respect to their malignant behavior and, in their most common and aggressive forms, anaplastic astrocytoma (AA-grade III) and glioblastoma multiforme (GBM-grade IV), are rapidly progressive and nearly uniformly lethal. Currently available therapeutic modalities have minimal curative potential for these high-grade tumors and often exacerbate the already severe morbidities imposed by their location in the central nervous system. This pilot study seeks to establish the feasibility of generating engineered T lymphocytes with re-directed anti-glioma reactivity in this patient population and evaluate the safety of targeting relapsed or refractory malignant glioma with engineered anti-glioma CTL clones administered directly into resection cavities. The genetic modification of T cells to recognize and kill glioma tumor cells was accomplished by expressing in T cells an artificial antigen receptor that engages a glioma-specific cytokine receptor (IL-13R α 2). As a safety precaution, T cells will also express a suicide gene should toxicities warrant the ablation of instilled T cells. In the proposed study, five research participants with relapsed/refractory malignant glioma will have T cells harvested, genetically modified, and expanded to large cell numbers outside the body. Cytolytic T cell clones expressing the IL13-zetakine and the selection/suicide fusion protein designated HyTK will be administered into tumor resection cavities in a series of three escalating cell doses followed by three additional courses at the target cell dose of 10^8 cells. The safety of this procedure will be closely monitored. Additionally, patients will be evaluated for anti-tumor responses by serial brain MRIs, the immunogenicity of engineered T-cells when administered in this fashion, and the ability of ganciclovir to ablate clones should toxicities warrant this maneuver. This study will provide the necessary safety data to justify larger Phase I/II protocols.