

## ABSTRACT

### **Stereotactic Injection of Herpes Simplex Thymidine Kinase Vector Producer Cells (PA317/G1Tk1SvNa.7) and Intravenous Ganciclovir for the Treatment of Recurrent Malignant Glioma" (GTI 0107)**

This study will evaluate the safety and efficacy of *in vivo* gene transfer of the herpes simplex thymidine kinase (HSV-Tk1) gene using PA317/G1Tk1SvNa.7 vector producer cells (VPCs) in patients with recurrent malignant glioma. VPCs will be manufactured by Genetic Therapy, Inc., Gaithersburg, Maryland. Insertion of the HSV-Tk1 gene confers sensitivity to the anti-herpes drug ganciclovir. It has been demonstrated that the direct injection of the HSV-Tk vector producer cells into growing tumors in animals can result in their complete destruction with ganciclovir therapy. In addition, complete tumor ablation has been demonstrated in animal tumor models with HSV-Tk1 and ganciclovir. This selective destruction of growing tumors *in situ* is thought to result from the transfer of the HSV-Tk1 gene into the tumor cells and the production of toxic ganciclovir metabolites which result from the interaction of HSV-Tk1 and ganciclovir. This procedure can result in the cure of some experimental animals with limited systemic toxicity due to selective gene transfer into tumors.

The NCI pilot study, GTI 0100, has completed enrollment into the trial. A total of fifteen patients with malignant brain tumors were enrolled. All patients enrolled had failed previous therapy, which included surgery, and radiation therapy, and in some patients chemotherapy, and all patients had evidence of tumor progression after their most recent therapy. After distribution of the vector producer cells using computerized image-based stereotactic techniques, the patients received ganciclovir intravenously for 14 days. Twenty tumors were treated in the fifteen patients. Four patients received repeated therapy. The initial results indicate the presence of anti-tumor activity in several patients manifested as a decrease in tumor volume or loss of enhancement at the treated site. Patient follow-up is continuing at this time.

GTI 0100 used VPCs from the original PA317/G1TkSvNa.53 vector. In the new vector, PA317/G1Tk1SvNa.7, the HSVTk 3' untranslated region of the original vector was eliminated, which resulted in removal of an unnecessary open reading frame, removal of a splice donor, and a higher titer. Comparisons of the two constructs in *in vitro* and *in vivo* studies showed that the new vector expresses a higher Tk enzyme level and was more efficacious in transduction efficiencies and anti-tumor effects than the original vector.

This clinical trial will focus on maximizing the relative number of vector producer cells to the tumor mass by stereotactically injecting VPCs in to the tumor mass. Adults with recurrent malignant glioma which is accessible to stereotactic injection will be evaluated for the extent and location(s) of their disease before being entered into the study. Fifteen days after stereotactic injection of the tumor mass, ganciclovir will be administered at 5 mg/kg IV b.i.d. for 14 days. Upon completion of the treatment with HSV-Tk1 vector producer cells and ganciclovir, patients will be followed monthly for the first three months, then every three months for the next twenty-one months, and annually for life thereafter.