

## APPENDIX C.

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### GENE THERAPY FOR RECURRENT PEDIATRIC BRAIN TUMORS

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Brain tumors are the second most common cancer in children. Supratentorial malignant gliomas account for 10-12% of childhood brain tumors. Although short-term survival appears to be superior to adults with malignant gliomas, no more than 20% of children with these tumors survive beyond 3 years. Associated supratentorial embryonal tumors (pineoblastomas, cerebral neuroblastomas, supratentorial PNET's) comprise an additional 5% of brain neoplasms in children, demonstrating survival rates similar to the malignant gliomas. The current proposal will study the feasibility of utilizing a novel approach of gene transfer therapy in children with recurrent or progressive malignant supratentorial tumors.

Building upon the preclinical and phase I adult studies at NIH (Dr. Edward Oldfield, NINDS), a phase I trial will utilize NIH 3T3 producer cells to deliver a retroviral vector (GITKSVNa) to transfect proliferating brain tumor cells with the ganciclovir-susceptibility gene associated with the herpes simplex enzyme thymidine kinase (HS-tk). The brain is felt to be the ideal anatomic location for gene transfer based upon the selective proliferating capacity of the neoplastic cells (in contradistinction to the post-mitotic parenchymal brain cells) and relative "immunologic privilege" allowing exposure of the producer cells for vector integration. Subsequent delivery of ganciclovir has been shown to produce selective cell kill of the transfected neoplastic cells.

A phase 1 trial in children (3-21 years old) will allow assessment of feasibility and potential unique toxicities following the phase 1 adult study at NINDS. The producer cells will be instilled via multiple stereotactically placed cannulas, preplanned to homogeneously deliver a total of between  $1 \times 10^8$  and  $2 \times 10^9$  cells within the tumor volume. Seven days following the operative procedure, the patient will start a 14 day course of ganciclovir administration. Patients will be monitored for CNS, hematologic, renal, or other toxicities. Measurement of tumor response will include serial MRI studies, including an investigational analytical assessment of dynamic enhancement that appears to correlate with metabolic potential, and MR spectroscopy, an evolving technique correlating measured biochemical changes with tumor viability.

A total of 6 patients will be accessioned to the phase 1 study to allow adequate evaluation of potential toxicities. Guidelines include both parental consent and the child's assent. The investigators propose to follow the current trial with phase II studies including (1) traditional tumor type-specific evaluation of response in children with recurrent malignant supratentorial tumors, and (2) an "upfront" phase II study in children with supratentorial malignant gliomas.