

Project Title: Gene Therapy for the Treatment of Malignant Brain Tumors with In Vivo Tumor Transduction with the Herpes Thymidine Kinase Gene/Ganciclovir System.

Principal Investigators: Kenneth W. Culver, M.D. and John Van Gilder, M.D.

Scientific Abstract

Murine retroviral vectors can infect a wide variety of proliferating mammalian cell types (e.g. lymphocytes). Non-proliferating tissues (e.g. neurons) are not transduced by murine retroviral vectors. These findings suggest that this type of vector may be useful for the selective introduction of genes into growing tumors in the brain, since the tumor is essentially the only tissue that will integrate and express the vector genes.

We have investigated the possibility of direct in vivo gene transfer into growing brain tumors in animals. Rats with a malignant brain tumor were given an intratumoral stereotaxic injection of murine retroviral vector-producer cells (VPC) that were producing vectors containing the Herpes Simplex-thymidine kinase (HS-tk) gene or a control VPC line containing the β -galactosidase gene. The animals were rested 5 days to allow time for the HS-tk retroviral vectors that were produced *in situ* to transduce the neighboring proliferating gliosarcoma. The animals were then treated with the anti-herpes drug ganciclovir (GCV). Tumors injected with the HS-tk VPC regressed completely with GCV therapy while the tumors injected with β -galactosidase VPC developed large tumors. Staining for β -galactosidase (+) cells in control animal brain revealed transduction of 10-50% of the tumor cells without evidence of transduction of the surrounding normal brain tissue. No significant toxicity was observed in toxicity studies in mice, rats and non-human primates.

Based upon these findings, we have proposed a human clinical trial to determine if the direct implantation of the G1TkSvNa VPC line into growing human brain tumors will induce regression with GCV therapy. The patient population primarily consists of individuals with recurrent malignant tumors who are currently considered ineligible for the approved NIH trial due to the size of the tumor. The RAC has previously approved an initial trial at NIH involving the stereotaxic injection of brain tumors. In this protocol, patients will undergo surgical debulking of the tumor followed by repeated treatments of HS-tk VPC into the tumor bed in an attempt to induce complete regression of the tumor with GCV therapy. These are patients who have failed standard therapy for their tumor and are expected to survive for several weeks to a few months.