

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 would integrate and express the vector genes.

We investigated the possibility of *in vivo* transduction of growing brain tumors with the herpes simplex thymidine kinase (HS-tk) gene. Rats with a malignant brain tumor were given an intratumoral stereotaxic injection of murine fibroblasts that were producing a retroviral vector containing the herpes simplex thymidine kinase (HS-tk) gene or a control vector producer cell 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 glioma. The animals were then treated with the anti-herpes drug ganciclovir (GCV). Gliomas injected with the HS-tk producer cells regressed completely with GCV therapy while the tumors injected with β -galactosidase producers had large tumors. Staining for β -galactosidase positive cells in control animal brain revealed transduction of 40-80% 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 injection of the G1TkSvNa producer cell line into growing human brain tumors will regress with GCV therapy. The patient population consists of individuals with recurrent malignant tumors who have failed standard therapy for their primary or metastatic brain tumors. The expected survival of these patients is limited to weeks to a few months.