

**NONTECHNICAL SUMMARY (Introductory statement and research plan)**

**Concept Summary:** This study will be the first in a series of clinical trials employing molecular biologic techniques to specifically kill tumor cells by introducing a gene into tumor cells using a virus as a carrier. A gene is a piece of deoxyribonucleic acid (DNA) the chemical which encodes the instructions which cells use to produce a specific chemical for use within the cells. This study will determine the maximal dose of a virus designed to carry a specific gene, the herpes simplex thymidine kinase gene, which can be safely administered to patients with recurrent malignant glioblastoma, a lethal form of malignant brain tumor. The virus, an adenovirus carrying the gene for herpes simplex thymidine kinase, will direct any cell which it infects to produce thymidine kinase. This enzyme (a chemical that speeds up chemical reactions) makes the cells capable of converting an otherwise harmless drug called ganciclovir into a form capable of killing cells which are dividing, such as tumor cells. This should produce tumor cell death with sparing of normal brain cells. To minimize the distance that the virus must travel through tissue to reach the tumor cells which are invading the brain, we will inject the ADV-tk into the tissue surrounding the cavity left after surgical removal of the tumor tissue. After 24 hours, the patients receive ganciclovir through a vein in two daily infusions for 7 days. We monitor for toxicity of the ADV-tk or the ganciclovir by repeated neurologic and general examination of the patients, laboratory tests, and magnetic resonance imaging of the brain. Animal studies have shown that MRI, a technique which produces pictures of brain tissue using computerized analysis of radiowaves generated by a powerful magnet, is sensitive to the changes in brain tissue that occur with inflammation in the area of viral infection by the ADV-tk. We will also test for the presence of ADV-tk in nasal secretions, urine and blood of patients after ADV-tk administration, to ensure that patients who might be carrying infectious ADV-tk remain in isolation.

As the first step, this study is not designed to determine the effectiveness of the treatment but to find the highest dose of ADV-tk which can be safely administered after surgery. However, we will monitor the patients to determine the interval of time between the ADV-tk administration and ganciclovir therapy and the reappearance of tumor tissue in the treated site.