

## SCIENTIFIC ABSTRACT

A variety of gene therapy strategies have been designed to achieve antitumor effects. In this regard, the approach of molecular chemotherapy has been designed to achieve selective eradication of carcinoma cells via an expressed toxin gene. It has been observed that tumor cells transduced with selected toxin genes can exert a noxious effect, a so-called "bystander effect." This phenomenon, therefore, makes possible the transduction of only a minority of tumor cells with the subsequent potential to effect a much larger tumor cell kill. The most common molecular chemotherapy system utilized has been the Herpes Simplex Virus Thymidine Kinase (HSV-TK) gene given in combination with intravenous Ganciclovir (GCV). Clinical trials to date have used recombinant retrovirus mediated gene transfer and relied heavily upon bystander effect to achieve anti-tumor activity. Retroviral transfer methodology is hampered by the inability to produce high titer viral stock, by the ability to transfect only actively dividing cells and by the risk of insertional mutagenesis. In contrast, adenovirus vectors can be produced in high titer, can directly transfect target tissue regardless of whether cells are dividing, and has an established record of safety. The concept of molecular chemotherapy with direct in situ transduction of target cancer cells represents a novel strategy that we intend to exploit in this protocol. Preliminary studies that relate to this trial have demonstrated that

1. Human ovarian carcinoma cell lines can be transduced in vitro at high efficiency with recombinant adenoviral vectors,
2. A human ovarian carcinoma cell line stably transduced to express HSV-TK demonstrates in vitro bystander effect,
3. Human ovarian carcinoma cell lines are directly susceptible in vitro to the toxic effects of GCV when HSV-TK is delivered by an adenoviral vector,
4. Primary ovarian carcinoma cells are highly transduced with recombinant adenoviral vectors and can be selectively induced to the toxic effects of GCV by HSV-TK expressing adenovirus,
5. Adenovirus vector transfects ovarian cancer cells more efficiently in vivo than other vectors, and
6. Intraperitoneal delivery of a recombinant adenovirus encoding the HSV-TK gene is safe and efficacious in in vivo murine animal models when given in combination with intravenous GCV.

This protocol intends to determine 1) the maximally tolerated dose of, 2) the spectrum of toxicities encountered with, 3) the safety of administration of, and 4) the molecular efficacy of an intraperitoneal delivered adenovirus encoding the HSV-TK gene given in combination with intravenous GCV in previously treated ovarian and extraovarian cancer patients. A Phase I study will be performed to determine the maximally tolerated dose of this novel therapeutic and its associated clinical toxicity. Safety studies will be performed in the context of this trial to determine if the viral vector employed illicit a host immune response, propagates or replicates, or mutates into wild type virus. Lastly, molecular efficacy studies will be performed to determine if, in the context of human disease, the HSV-TK gene antibody transfects targeted ovarian cancer cells and is expressed.