Scientific Abstract

Central to the realization of the potential of gene therapy for malignancy is the ability to accomplish efficient and specific gene delivery to cancer cells. In addition, the methods used to evaluate gene transfer are invasive, variable, and associated with sampling bias. To this end, the Gene Therapy Program at UAB has developed a major focus in the area of vector improvement. Specifically, we have shown that our "tropism-modified" adenoviral vectors accomplish dramatically enhanced gene transfer to human tumor cells when compared to adenoviral vectors traditionally employed. We have also genetically modified the vector to allow for non-invasive in vivo gene transfer imaging. It is our hypothesis that modifications of adenoviral vectors to increase their specificity and efficiency will allow enhanced tumor cell transduction, and by virtue of this achievement, an enhanced therapeutic effect in the context of a cancer gene therapy approach for carcinoma of the ovary. Accordingly, pursuant to validating the hypothesis, this research proposal includes a human gene therapy protocol for patients with persistent or recurrent ovarian and extraovarian cancer. This Phase I protocol will: 1) Determine the maximally tolerated dose of intraperitoneal delivery of RGD modified adenovirus encoding Herpes Simplex Virus thymidine kinase (HSV-TK) given in combination with intravenous ganciclovir (GCV) in previously treated ovarian and extraovarian patients. The spectrum of toxicities encountered with intraperitoneal delivery of this vector will be identified. 2) Determine the efficiency and specificity at which RGD modified adenovirus accomplishes gene transfer to intraperitoneal ovarian cancer cells when compared to mesothelial cells. 3) Determine antibody response generated against the RGD modified adenovirus encoding HSV-TK when administered intraperitoneally to patients with recurrent ovarian adenocarcinoma. 4) Determine the ability to scintigraphically image adenoviral encoded somatostatin receptor (hSSTr) following administration of radiolabeled octreotide (Tc-99m-P829) as a noninvasive method of evaluating gene transfer. This novel vector strategy has been highly promising in preclinical studies. It is anticipated that the study described herein will establish the safety and provide an indication of efficacy of this approach in human subjects with ovarian cancer and allow the rapid evaluation of the clinical utility of this novel therapeutic in future Phase II/III trials.