SCIENTIFIC ABSTRACT

Dissemination of cancer cells to distant organs is responsible for most cancer deaths, which is currently the second leading cause of mortailty in the United States. Current treatment modalities are ineffective in producing durable remissions or significantly prolonging life for patients with metastatic cancers, except for a few less common cancers such as testis cancer, choriocarcinoma, some leukemias and lymphomas.

Genetic engineering technology has permitted the development of new treatment modalities for metastatic cancer. Tumor cells can be genetically altered to become susceptible to drugs to which they are normally resistant, or to become more immunogenic, enhancing induction of specific immune response and leading to immune-mediated tumor destruction.

Ganciclovir, a nucleoside analog, does not kill mammalian cells unless these cells have been infected with the Herpes simplex virus, which produces an enzyme thymidine kinase essential for converting ganciclovir to the toxic metabolite ganciclovir triphosphate. By introducing the Herpes simplex virus thymidine kinase gene (HSV-tk) into tumor cells, these cells are rendered susceptible to ganciclovir. Moreover, only a fraction of cells in a tumor needs to be transduced with HSV-tk for the tumor to necrose following exposure to ganciclovir ("bystander" effect). Tumor necrosis following ganciclovir treatment is associated with an intense infiltration of inflammatory cells indicating the elicitation of immune response. In vivo studies have shown that adenoviral vectors expressing HSV-tk (ADV-tk), when injected directly into tumor implants in syngeneic mice, are effective in killing these tumors following exposure to ganciclovir with minimal toxicity to normal tissues. Similar results were obtained with a variety of metastatic tumors, including colon, breast, lung, and pancreas.

This phase I study is designed to test the safety and efficacy of gene therapy for patients with cancers metastatic to the liver. Eligible patients will have one of their metastatic tumors in the liver percutaneously injected under ultrasound guidance with replication defective ADV-tk, followed by intravenous ganciclovir 5 mg/kg twice daily for seven days. The dose of ADV-tk will be escalated in three cohort levels of three patients each: 1×10^8 pfu, 5×10^8 pfu, and 2.5×10^9 pfu. The starting ADV-tk dose have been found to be safely tolerated in mice with minimal toxicity.

Patients will receive one injection of ADV-tk and will be hospitalized for the entire duration of the treatment. They will be assessed for toxicity by clinical monitoring and blood tests. Tumor responses will be assessed by radiographic studies of treated and untreated metastatic tumors in the same patient and by serum tumor markers. Immune responses will be assessed by pathological examination of treated and untreated tumors whenever possible, and for the development of antibodies to adenovirus, and T cells specifically sensitized to HSV-tk gene products.

The adenoviral vector (ADV-tk) used in this study has been previously approved by the RAC and FDA in trials of direct intratumoral injection in brain, head and neck, and prostate cancers. Moreover, ADV-tk used in this study will be obtained from the same batch approved by the FDA for these cancer therapy trials (BB-IND #6371).