

SECTION 1 SCIENTIFIC ABSTRACT

Prostate cancer kills approximately 40,000 men annually. Although conventional therapies produce a high rate of cure for patients with early stage disease, a significant fraction of cancers recur and such therapies result in high morbidity. The prognosis for androgen-independent prostate cancer is much worse, for there is no effective treatment and a vast majority of these patients eventually succumb to the disease. There is a real need to develop new therapies that would reduce the morbidity associated with conventional therapies, decrease the incidence of tumor recurrence, and improve the outlook for recurrent and androgen-independent cancer.

Up to 80% of prostate cancer patients who receive radiation therapy as their primary treatment will fail biochemically (develop a rising PSA) within 5 years. Unfortunately, limited therapeutic options exist for such patients. Further external beam radiation is not an option because of radiation-induced complications. Cytotoxic chemotherapy is not curative and is typically reserved for palliation with symptomatic progression or asymptomatic patients with significant biochemical progression following hormonal therapy. Of the four remaining therapeutic options, including salvage radical prostatectomy, salvage RT with interstitial implants, salvage cryoablation of the prostate, and androgen deprivation, none has demonstrated a high degree of efficacy in eradicating tumor with a reasonable degree of safety. The ten year overall survival rate of patients with locally recurrent prostate cancer is only 35% as the disease invariably progresses to hormone-refractory metastases.

The scientific rationale for this Phase I trial derives from research conducted in Drs. Kim's and Freytag's laboratories during the past six years. Our research program has developed a novel, trimodal gene therapy approach for the treatment of prostate cancer. An E1B-attenuated, replication-competent adenovirus (Ad5-CD/TKrep) is used to selectively and efficiently deliver a cytosine deaminase (CD)/herpes simplex virus thymidine kinase (HSV-1 TK) fusion gene to tumors. Preclinical studies in animals have demonstrated that the Ad5-CD/TKrep virus itself generates a potent anti-tumor effect by replicating in, and preferentially destroying, human prostate cancer cells. The therapeutic effect of the Ad5-CD/TKrep virus can be significantly enhanced by invoking two suicide gene systems (CD/5-FC and HSV-1 TK/GCV), which render malignant cells sensitive to specific pharmacological agents and sensitizes them to radiation. The safety and efficacy of Ad5-CD/TKrep viral therapy in conjunction with 5-FC and GCV prodrug therapy is currently being evaluated in patients with local recurrence of prostate cancer (BB-IND 8436, RAC 9906-321).

Despite encouraging results in preclinical models and humans, all cancer gene therapies are limited by a low gene transduction efficiency *in vivo*. The primary purpose of this Phase I trial is to evaluate the toxicity of administering the replication-competent Ad5-CD/TKrep adenovirus to primary prostate adenocarcinoma using different vector formulations [saline, polyethylene glycol 400 (PEG 400), Gelfoam®]. A second objective is to evaluate the efficiency of gene transduction *in vivo*. Patients will undergo radical prostatectomy shortly after injection of the virus and the extent of gene transfer will be

determined. The goal is to define a non-toxic vector formulation that will result in high efficiency of gene transduction *in vivo*. When used in a neoadjuvant setting with radiation, our oncolytic viral/suicide gene therapy combination may demonstrate efficacy against locally advanced tumors in patients with high risk, but clinically localized, prostate cancer (stage T1c, T2a, T2b, T2c). Based on an accrual rate of one patient per month, this Phase I study should be completed in 12 months.