

## ABSTRACT (FOR GENERAL SCIENTIFIC AUDIENCES)

Background: There were an estimated 189,000 new diagnoses of prostate cancer made in the U.S. in 2002. Definitive treatment of prostate cancer is limited to radical surgery or radiation therapy for localized or regional disease. Metastatic prostate cancer is treated in a palliative manner by androgen ablation. The appearance of hormone-independent cancer denotes cancer progression for which no curative treatment is available. Gene transfer technology offers the potential for the development of new therapies for prostate cancer. The proposed project will employ the unique apoptotic agent, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and the discovery of a collagen-based matrix that enhances gene delivery and augments immune activation to develop novel approaches for the treatment of prostate cancer.

Objective/hypothesis: The long-term objective of the project is to develop an effective treatment for prostate cancer. Specifically, treatment involves the viral-mediated transfer of the gene for the cytotoxic protein TRAIL into the prostate, resulting in prostate tumor cell apoptotic death and activation of systemic antitumor immunity.

Specific Aims: **(1)** Determine the local and systemic toxicity associated with intraprostatic injection of Ad5-TRAIL delivered in Gelfoam<sup>®</sup>. **(2)** Examine the distribution of Ad5-TRAIL within the human prostate after transrectal injection. **(3)** Determine the effect of transrectal injection of Ad5-TRAIL on existent prostate cancer. **(4)** Determine the effect of Ad5-TRAIL-induced apoptosis on immune activation to prostate antigens.

Study Design: The preclinical studies performed to date demonstrate the potential efficacy for Ad5-TRAIL-based gene therapy for the treatment of prostate cancer. Ad5-TRAIL infection of human prostate tumor cells *in vitro* results in the production and expression of TRAIL protein on the surface of the tumor cells, inducing apoptotic cell death. Moreover, injection of Ad5-TRAIL at the site of tumor implantation *in vivo* results in the significant suppression of tumor outgrowth. The primary objective of the proposed Phase I clinical trial will examine the local and systemic toxicity associated with intraprostatic injection of Ad5-TRAIL. Secondary objectives for the trial will determine the degree of Ad5-TRAIL distribution within the prostate delivered in Gelfoam<sup>®</sup>, the effect of Ad5-TRAIL injection on existing prostate cancer, and the effect of Ad5-TRAIL-induced tumor cell apoptosis on immune activation to prostate antigens.

Relevance: Given the prevalence of prostate cancer, it is essential to identify and develop alternate forms of therapy for prostate cancer. Moreover, successful long-term treatment of prostate cancer must not only reduce the localized tumor burden, but must also target undetectable metastases that may exist at the time the primary tumor is identified and treated. TRAIL has proven to be a potent antitumor agent in several preclinical studies, but there are limitations in the current formulations of the molecule that restrict its potency. Production of a adenoviral vector that allows for localized delivery of the TRAIL gene into cancerous lesions has been shown to function as well as, or better than, systemic delivery of recombinant protein. The results from the proposed studies will identify methods to augment the activity of Ad5-TRAIL by addressing the important issue of increasing transgene distribution and expression, and the activation of systemic antitumor responses.