

GENERAL AUDIENCE SUMMARY

Prostate cancer is the most commonly diagnosed human visceral cancer in men and the second leading cause of death among males over the age of 50 in the United States and Europe¹. Current treatment for localized prostate cancer is limited to surgery or radiation therapy, whereas androgen ablation therapy is the accepted treatment for metastatic prostate cancer. Prostate cancer cells require androgen for growth at early stages, and androgen withdrawal induces cell death or apoptosis in androgen-dependent prostate cancer cells. Unfortunately, 20-40% of patients with advanced prostate cancer fail to demonstrate an initial objective response to androgen ablation, and many develop androgen-independent prostate cancer, with the majority succumbing to the disease within 3 years. Thus, the need to develop alternative therapies for advanced prostate cancer is imperative.

Dramatic advances in apoptosis research have led to the identification and characterization of many components of the cell death machinery. One recently identified member of the tumor necrosis factor (TNF) family, TRAIL (TNF-related apoptosis inducing ligand), has generated a great deal of interest because it can kill a variety of cancer cells while being nontoxic to normal tissues^{2,3}. Although a variety of agents (e.g. proteins, chemicals, radiation) can induce apoptosis, they commonly are associated with unpleasant side-effects to the patient. TRAIL is unique because of its ability to kill a wide range of cancer cells but not normal, noncancerous cells and tissues. Previous data from our laboratory described the development of a recombinant, replication-deficient adenovirus containing the DNA of human TRAIL gene (Ad5-TRAIL). Transfer of the TRAIL gene by Ad5-TRAIL into human tumor cells in culture led to the rapid production and expression of TRAIL protein, resulting in the death of the tumor cells themselves. Furthermore, use of Ad5-TRAIL in animal models significantly suppressed tumor outgrowth when administered locally at the site of tumor implantation. While such gene therapy approaches have been successful in the laboratory the response in human has not been equally significant. This is due to inadequate activation of patients own immunity which is required for this approach to work. The blame for this mostly lies with inefficient gene transfer. In preliminary studies, we have found that the mixing of Ad5-TRAIL- with Gelfoam[®] (biodegradable collagen) results in enhanced gene transfer in solid tumors and benign dog prostate. Moreover, administration of Ad5-TRAIL with Gelfoam[®] resulted in augmented T cell immunity, significantly enhancing antitumor activity against established prostate cancers. Thus, the studies outlined in this proposal are designed to demonstrate the feasibility of using the novel recombinant adenovirus, Ad5-TRAIL, in combination with Gelfoam[®], a novel biodegradable delivery system, as a therapy for prostate cancer, and examine the ability of Ad5-TRAIL/ Gelfoam[®]-induced tumor cell death to activate systemic antitumor immune responses. The focus of this proposal is a phase I clinical trial to establish the safety of using the Ad5-TRAIL either in Gelfoam[®] in humans with prostate cancer.