TECHNICAL ABSTRACT

Over recent years the Scott Department of Urology at Baylor College of Medicine has developed a comprehensive program of gene therapy for prostate cancer. This translational research program has resulted in the first in situ gene therapy clinical trials involving adenovirus vector delivery of "suicide gene therapy" with Herpes Simplex Virus-thymidine kinase (HSV-tk) plus the pro-drug ganciclovir in patients with local prostate cancer recurrence following radiation therapy. These studies have now been completed and have been extended into additional clinical trials. These efforts as well as pre-clinical experimental studies with mice have led us to conclude that a necessary component of any successful gene therapy approach directed against prostate cancer that may have spread to other parts of the body (metastases) must include a component that activates the host immune system. In our preclinical studies using ADV/RSV-tk (and ganciclovir), treated mice were found to have immune cells (lymphocytic infiltration) in the treated tumors. Further studies revealed suppression of pre-established lung metastases by ADV/RSV-tk + ganciclovir treatment of the primary prostate tumor, which suggested an immune response. Activation of other specific immune cells called cytotoxic T lymphocytes (CTL's) and natural killer (NK) cells are considered to play an important role in antitumoral activity and may provide a new approach for systemic treatment of human prostate cancers. One possible way to achieve the further immune stimulation against tumors is to administer specific cytokines, which are known to play a role in immune activation. Since the discovery of interleukin-12 (IL-12) less than 10 years ago, much knowledge has been gained on the importance of this cytokine in immunoregulation and its antitumoral properties. IL-12 has been demonstrated to activate and enhance NK and CTL activity, stimulate proliferation of T and NK cells and induce production of IFN-γ by NK and T cells. The antitumoral properties of IL-12 have been demonstrated in multiple preclinical studies. These studies revealed a dose dependent effect of IL-12 causing regression of a variety of tumor cell lines, inhibition of metastasis and in some studies a long lasting protective immune response. In our preclinical (mouse) trials, adenovirus-mediated expression of mouse IL-12 was used to treat a prostate cancer model we developed. We demonstrated a significant reduction in prostate tumor weight and suppression of pre-established lung metastasis as well as a survival advantage in IL-12 virus treated mice.

The purpose of this study is to conduct a Phase I clinical trial to extend preclinical studies involving in situ IL-12 gene therapy for prostate cancer. We will conduct necessary safety evaluations on a new adenovirus that contains the human genes for IL-12. This virus will then be evaluated for safety in men with prostate cancer that has recurred after radiation therapy. These men have no other treatment option. We will inject the IL-12 virus into the prostate starting with a low dose and carefully watch the men for any toxic side effects and hopefully a beneficial effect.