

A PHASE I STUDY OF IN-SITU, NEOADJUVANT, PRE-RADICAL  
PROSTATECTOMY RTVP-1 GENE THERAPY IN PATIENTS WITH LOCALLY  
ADVANCED ADENOCARCINOMA OF THE PROSTATE (SPORE #: 11-01-30-15)

SCIENTIFIC ABSTRACT

Prostate cancer is the leading internal malignancy in men and the second most common cause of cancer deaths. Androgen ablation therapy provides only temporary palliative treatment and eventually prostate cancer become androgen insensitive. Current curative therapies for prostate cancer include surgery and external radiation therapy; however, both have potential significant morbidity and their impact on disease control has been less than complete, especially with radiotherapy. A novel approach to the control of cancer growth is gene therapy, a field that has progressed rapidly. Direct introduction of therapeutic genes into malignant cells *in vivo* may provide an effective treatment of solid tumors including tumors of the prostate.

We previously identified a novel p53 target gene, RTVP-1 and demonstrated that over-expression of RTVP-1 induce apoptosis in human prostate cancer cell lines. We also showed that the expression of the human RTVP-1 gene is down-regulated in human prostate cancer specimens compared with normal human prostate tissue at the mRNA and protein levels. We further demonstrated in mouse model of prostate cancer that RTVP-1 possesses unique cytotoxic, antiangiogenic and immunostimulatory activities that make it potentially useful for human cancer gene therapy.

This study is designed to determine the safety of *in situ* RTVP-1 gene therapy in men with prostate cancer prior to radical prostatectomy. Objectives of proposed Phase I clinical trial are:

1. To assess the safety and toxicity of in-situ gene therapy with the RTVP-1 gene in patients with prostate cancer prior to radical prostatectomy.
2. To study *in vivo* the biologic effects of RTVP-1 gene therapy before radical prostatectomy in patients with locally advanced prostate cancer as measured by:
  - a. Morphologic and cytotoxic changes in the radical prostatectomy specimen (necrosis, apoptosis, inflammatory infiltrate, etc.)
  - b. Assessment of local and systemic immunostimulatory activity (local and systemic production of cytokines: IL-2, IL-6, IL-12, IFN $\gamma$ , and TGF $\beta$ ; local and systemic expansion of CD4+ and CD8+ T cells, NK cell activity and CTL activities)
  - c. Assessment of tumor neovascularity/antiangiogenic effects (tumor image analysis of CD34+, modulation of angiogenesis factors).

Patients will receive single prostatic injections of a solution containing replication-defective adenovirus vector delivering the hRTVP-1 gene. Each patient will be carefully monitored for toxic effects. Four to six weeks after the injection, patients will undergo a radical prostatectomy. Three to six patients will be tested with a low dose of virus and if there are no serious adverse side effects, the dose will be slowly escalated in subsequent groups of 3-6 patients or until unacceptable toxicity is reached. Biological effect of RTVP-1 gene therapy will be assessed by morphological and histological evaluation of radical prostatectomy specimens and by assessment of changes in local and systemic immunostimulatory activities.