Phase I/II Study of a Prime-Boost Schedule of Human GM-SCF Gene Transduced Irradiated Allogeneic Cancer Vaccines (Allogeneic Prostate GVAX ™) in Hormone-Naïve Prostate Cancer Patients.

Scientific Abstract:

Prostate cancer is the most common form of adult male cancer in the U.S., eclipsing lung cancer in incidence. The American Cancer Society estimates that 184,500 new cases of prostate cancer will be diagnosed and approximately 39,200 men will die of the disease in the United States during 1998. To date, radical prostatectomy and radiation therapy are currently recognized curative treatments of clinically localized prostate cancer. However, no curative systemic therapy exists for metastatic disease. A significant unmet medical need for more effective therapy still exists for advanced prostate cancer.

The objective of the proposed study is to evaluate the safety and efficacy of vaccination with irradiated allogeneic prostate cancer cells transduced with the human Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) gene. This study in patients with advanced prostate cancer is undertaken with a view toward developing an effective means of treating disseminated cancers. The rationale for this trial is based on extensive preclinical studies performed at Johns Hopkins in rodent tumor models supplemented by *in vitro* studies of human prostate cancer cells and vaccine preparation. Three clinical trials recently completed evaluated the safety and efficacy of the identical gene delivery system in autologous tumor cells.

Rodent cancer cell lines genetically modified by the MFG-S retroviral vector containing cytokine genes have been screened for therapeutic anti-tumor activity. Screening included models of melanoma, sarcoma, renal cancer, lung cancer, colon cancer and prostate cancer. Out of ten immunostimulatory molecules tested, GM-CSF consistently showed superior antitumor immunity in every cancer line tested. In murine melanoma (B16) and murine RCC (RENCA) and hormone and chemotherapy resistant rat prostate cancer (Mat-Ly-Lu), GM-CSF gene transduction led to eradication of small previously implanted tumors. Lethally irradiated, GM-CSF gene transduced tumor vaccine cells lost none of their potency. The genetically manipulated cells did not grow or cause significant toxicities at the site of administration in preclinical studies on file with the Food and Drug Administration. Retroviral transduction has proven to be an efficient way to introduce the therapeutic gene into allogeneic prostate cell lines.

While autologous prostate cancer cells may be the best source of prostate cancer antigens for eliciting therapeutically useful immune responses, evidence has accumulated to suggest that allogeneic prostatic carcinoma cells might also serve as useful sources of prostate cancer antigens for prostate cancer vaccine construction. We believe it to be

likely that some prostate tissue specific antigens expressed by the cell lines chosen for use will result in the priming of a T-cell mediated immune response. The immune response should be directed to proteins expressed on the tumors of a large number of prostate cancer patients. In addition, with the proposed therapy, there is no limitation on the number of cells that can be obtained for transduction, which has been a problem with autologous target cell therapies.

Allogeneic Prostate GVAX™ Cancer Vaccine consists of cultured, irradiated allogeneic tumor cells that have been genetically modified with a retroviral vector (MFG-S) encoding human granulocyte/macrophage colony stimulating factor (huGM-CSF). The tumor cells are derived from two distinct human prostate tumor cell lines, LNCaP and PC-3. The vaccine is formulated in single-use vials as a frozen cellular preparation in glycerol and human serum albumin.

The study is a phase I/II open-label, outpatient, single arm clinical trial. We propose to enroll twenty patients with progressive, micrometastatic prostate cancer after surgery as defined by two successive abnormal elevations in PSA levels, without evidence of overt metastatic disease. Patients will receive a priming vaccination of 5×10^8 Allogeneic Prostate GVAX™ cells every two weeks for six months (total dose of 1.7×10^9), with six additional months of follow up. Patients will be observed for toxicity, changes in serum PSA including decreases from baseline and a change in the slope of PSA rise (PSA "velocity"), duration of PSA response, and time to clinical disease progression.