

SCIENTIFIC ABSTRACT

PHASE I/II STUDY OF AUTOLOGOUS HUMAN GM-CSF GENE TRANSDUCED PROSTATE CANCER VACCINES IN PATIENTS WITH METASTATIC PROSTATE CARCINOMA

This phase I/II 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 pre-clinical studies in rodent tumor models supplemented by *in vitro* explorations of the genetic modification of human prostate cancer cells and vaccine preparation.

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 and colon cancer and prostate cancer. In over 10 immunostimulatory molecules tested, GM-CSF consistently showed superior antitumor efficacy 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 eradicated 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.

With the MFG retroviral vector used in optimized *in vitro* culture conditions, over 40% of human PCA cells are transducible with a single transduction in primary culture. In clinical trial simulations at Somatix Therapy Corporation over 90% of primary cultures of PCA cells from were transduced successfully with a single transduction in the range of GM-CSF secretion with preclinical efficacy. No drug selection was required. In these feasibility studies MFG retroviral transduction with the human GM-CSF gene increased baseline GM-CSF secretion by 100 fold over non-transduced PCA cells. Irradiation experiments defined a dose where patient derived PCA cells were rendered non-replicative. Fortunately, post-transduction GM-CSF secretion was not diminished by irradiation.

The overall objective of the Phase I portion of these studies is to evaluate this modality with respect to safety of clinical administration and induction of antitumor immune responses. Escalating doses of lethally-irradiated, autologous prostate cancer cells expanded in short-term culture and transduced with the human GM-CSF gene will be tested to determine highest safely tolerated cell dose in the dose range feasible from prostate cancer cell harvest following surgery. The dose range tested has preclinical antitumor efficacy in PCA. Following the Phase I testing, Phase II studies will test efficacy. Three primary objectives of the Phase I portion of this study are:

1. To evaluate the safety of skin injections of cultured, lethally-irradiated, autologous MFG-S-GM-CSF gene transduced PCA cells secreting huGM-CSF at 40-1000ng/10⁶ vaccine cells/24 hrs.
2. To describe and quantitate the acute toxicities, if any, of irradiated GM-CSF gene transduced PCA cell vaccine therapy.
3. To assay both *in vitro* and *in vivo* the contribution of PCA cell GM-CSF gene transduction to the induction of specific antitumor immune responses in men with advanced PCA.