

SCIENTIFIC ABSTRACT

Phase I Study of Non-Replicating Autologous Tumor Cell Therapy Using Cell Preparations with and without GM-CSF Gene Transduction in Patients with Metastatic Renal Cell Carcinoma

This phase I study in patients with advanced kidney 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 murine tumor models supplemented by *in vitro* explorations of the genetic modification of human renal cell cancer (RCC) cells and vaccine preparation.

Murine cancer cell lines genetically modified by the MFG 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. Of 10 immunostimulatory molecules tested, only GM-CSF consistently showed superior antitumor efficacy in every cancer line tested. In both murine melanoma (B16) and murine RCC (RENCA), GM-CSF gene transduction enhanced the eradication of previously implanted tumors. Lethally irradiated, GM-CSF gene transduced murine cancer cells lost none of their potency. The genetically manipulated cells did not grow or cause significant toxicities at the site of administration.

With the MFG retroviral vector used in newly optimized *in vitro* culture conditions, over 30% of human RCC cells are transducible with a single transduction. In pilot studies, 20 of 22 consecutive primary cultures of RCC cells were transduced successfully. No drug selection was required. In these feasibility studies MFG retroviral transduction with the human GM-CSF gene increased baseline GM-CSF secretion by 10 to 20 fold over non-transduced RCC cells. Irradiation experiments defined a dose where patient derived RCC cells were rendered non-replicative. Fortunately, post-transduction GM-CSF secretion was not diminished by irradiation.

The overall objective of this phase I trial is to evaluate escalating doses of irradiated renal carcinoma cells with and without human GM-CSF gene transduction for safety of clinical administration and induction of antitumor immune responses. In order to distinguish toxicities related to cell dose from potential toxicities due to expression of GM-CSF, two clinical dose escalation studies are contained in one trial. In one set of patients, escalating doses of irradiated, autologous renal cell carcinoma cells (RCC) expanded in short-term culture and transduced with the human GM-CSF gene will be tested to determine the highest safely tolerated dose. Equivalent cell doses of similarly expanded, irradiated, non-transduced tumor cells will be tested in another set of RCC patients. Three specific primary study objectives are:

1. To evaluate the safety and tolerability of skin injections of cultured, irradiated, autologous RCC cells as well as similarly prepared RCC cells transduced with the human GM-CSF gene secreting the cytokine at 24-48 ng/10⁶ RCC cells/24 hr. The dose range of irradiated RCC cells under evaluation is 4X10⁶ to 1X10⁹.
2. To describe and quantitate acute clinical toxicities and long-term clinical toxicities of untransduced and GM-CSF gene transduced cell injections.
3. To assay both *in vitro* and *in vivo* the contribution of RCC cell GM-CSF gene transduction to the induction of specific antitumor immune responses relative to irradiated non-transduced RCC cells at equivalent cell doses.