TECHNICAL ABSTRACT

Interleukin-12, a heterodimeric cytokine secreted by activated monocytes and macrophages, has been shown in murine tumor models to inhibit tumor growth and modulate immune responses by enhancing the cytolytic activity of natural killer (NK) and cytotoxic T-lymphocytes (CTL), inducing gamma interferon (IFN-γ) production by natural killer and activated T cells. Clinical trials of systemically administered human recombinant interleukin-12 have been completed, but showed minimal antitumor activity despite significant dose-dependent toxicities, including elevation in serum aminotransferases, stomatitis, lymphopenia, and thrombocytopenia.

We have constructed an E1/E3 deleted replication defective adenoviral vector (Adv.RSV-mIL12) expressing the murine interleukin-12 cDNA under the control of the Rous sarcoma virus promoter. We have shown that intratumoral injection of Adv.RSV-mIL12 was effective in inducing tumor regression, long term survival and induced antitumor immunity mediated by natural killer and CD8+ T cells in an orthotopic murine model of established hepatic or subcutaneous metastases using syngeneic murine tumor cell lines (MCA26 colon carcinoma, JC mammary adenocarcinoma and B16-F10 melanoma). We have conducted preclinical toxicity studies ion intratumoral Adv.RSV-mIL12 delivery in mice with established liver metastases, and found that therapeutic effective doses were well tolerated with no toxicities, while higher doses induced dose-dependent toxicities in the liver, lung, white blood cell and platelet counts.

We have constructed a replication defective E1 deleted adenoviral vector expressing the human interleukin-12 cDNA (Adv.RSV-hIL12 or ADV-hIL12) using the same methodology as Adv.RSV-mIL12. We have produced under GMP conditions large-scale preparation of ADV-hIL12 which passed FDA-mandated lot release criteria for use in Phase I clinical trials. In this trial, we propose to inject ADV-hIL12 into accessible tumors (skin, chest wall, nodes or primary tumor) in patients with metastatic breast cancer. We will collect data on tumor regression and immune responses by measurement of tumor sizes on physical examination and radiologic studies, blood tests and tumor biopsies. The dose of ADV-hIL12 will be escalated from 10^{10} to 3.0×10^{13} vector particles per patient in cohorts of three patients each. Dose limiting toxicity (DLT) is defined as any grade 3 or higher toxicity, and the maximal tolerated dose (MTD) as the highest cohort level at which less than two instances of DLT are observed among six patients treated. Approximately 30-36 patients will be enrolled at the Mount Sinai School of Medicine in New York. The trial is supported by the U.S. Department of the Army.