Scientific Abstract

The purpose of this Phase I study is to explore the safety and immunologic efficacy of subcutaneous injections containing increasing numbers of autologous lymphoma or B-CLL cells expressing CD40L and IL2. Although the malignant B cells of non-Hodgkin lymphoma and B-CLL express tumor-specific peptides (including those derived from immunoglobulin molecules) and major histocompatibility complex class I antigens, they lack the capacity for co-stimulatory signaling to T cells. This contributes to their protection from host antitumor immunity. The current protocol proposes to generate tumor-specific immune responses in patients with advanced lymphoma or CLL by transferring the human CD40 Ligand gene to their tumor cells ex vivo and thereby activating them through their CD40 molecules. This in turn upregulates co-stimulatory molecule expression on these cells and will also stimulate maturation of host antigen-presenting cells to further facilitate an antitumor immune response. We will transfer CD40L using an E_1E_3 gene deleted adenoviral vector. To enhance adenoviral vector mediated gene transfer we will first upregulate virus receptor expression on target cells by co-culturing the lymphoma cells with human embryonic lung fibroblasts (MRC-5). To further potentiate the immunostimulatory effects of CD40 activation with of tumor cells, we will also use adenovectors to transduce the Interleukin-2 gene. Animal and human in vitro studies have both shown that the combination of CD40L and IL2 gene transfer produces greater antitumor effector T cell function than either gene alone.