

2. Nontechnical Abstract

Study title: The safety and antiviral efficacy of cellular adoptive immunotherapy with autologous CD8⁺ HIV-specific cytotoxic T cells combined with interleukin-2 for HIV seropositive individuals.

Studies of the natural history of HIV infection have demonstrated that HIV-infected individuals who develop and maintain strong CD8⁺ cytotoxic T cell (CTL) responses against HIV-infected cells have lower levels of virus and slower disease progression. Therefore, our lab has attempted to augment the cytotoxic T cell response to HIV by isolating from the blood of HIV infected individuals, clones of CD8⁺ T cells that kill HIV infected target cells, expanding these CD8⁺ T cell clones to several billion, and administering them back to the patient by intravenous infusion. In a previous study (RAC 9508-119), the CTL were modified using a retrovirus (termed the LN retrovirus) which introduced the neomycin phosphotransferase gene into the cell's DNA. This marker gene served as a tag to assist in evaluating the persistence of the infused cells in the patient and the migration of these cells to lymph nodes where HIV resides. This initial study demonstrated that the LN-marked T cells augmented the immune response to HIV, migrated to sites of HIV infection in lymph nodes and mediated antiviral activity. (See Attached Manuscript Section 6. Appendix) Although these results were very encouraging, the transferred CTL persisted at high levels for < 7 days and the antiviral effect was transient. The failure of the transferred CD8⁺ T cells to survive may reflect a requirement for a growth factor, termed interleukin -2, which is normally produced by CD4⁺ T helper cells and in animal models and in tissue culture is necessary for the growth and survival of CD8⁺ CTL.

In the proposed study, we plan to administer CD8⁺ HIV-specific CTL with a low dose of interleukin-2 to determine if the persistence of the transferred CTL can be improved and the antiviral activity of this therapy prolonged. As in the prior study, the LN retrovirus will be used to mark the cells to provide a sensitive measure of the frequency of these cells in the blood and to determine if IL-2 improves their survival. The study design will administer up to 3 infusions of CTL. The first infusion of LN marked CTL will be given without IL-2 to define the survival characteristics of the CTL alone. A second infusion of LN marked CTL will be given followed by daily subcutaneous injections of IL-2 to define the toxicity of coadministering IL-2 and CTL and to determine if the addition of IL-2 improves the survival of the transferred cells. If improved T cell persistence is demonstrated without side effects, a third infusion of CTL which are not modified with the LN retrovirus will be given with IL-2. We will enroll up to 24 patients and study up to 5 dose levels of IL-2. The LN retrovirus to be used in this study is identical to that used in our prior study (RAC 9508-119).