

***A Phase II Study of Autologous CD4-zeta Gene-Modified T Cells in HIV Infected Patients with Undetectable Plasma Viremia on Highly Active Anti-Retroviral Drug Therapy.***

**Scientific Abstract:**

Adoptive immunotherapy of viral infection using antigen-specific T cells has been studied by several investigators, and is discussed in the clinical protocol. Riddell *et al* have explored this strategy using isolated T cell clones with HLA-restricted antigenic specificity for CMV (31, 32 clinical protocol references). CMV-specific CD8+ T cells isolated from MHC-identical bone marrow donors were expanded *ex vivo* and administered to 14 allogeneic bone marrow transplant recipients. Recovery of CMV-specific CTL activity was seen in each case and adoptively transferred CTL persisted *in vivo* for up to 12 weeks. No patient developed CMV disease. However, cellular immunity to CMV declined in patients deficient in CMV-specific CD4+ T cells, suggesting that CD4+ helper T cell function was necessary for the persistence of the transferred CD8+ CTL.

Studies of cytomegalovirus (CMV) and influenza virus for which small animal models are available have revealed that CD8+ cytotoxic T lymphocytes (CTLs) represent the major component of this cellular immunity. Although optimal animal models for HIV infection await development, evidence that CD8+ CTLs represent the major and earliest immune response to HIV infection is supported by correlative data from HIV-infected patients. The clinical data available suggest that a breakdown of the host cell-mediated immune response may be responsible for progression to symptomatic AIDS. *In vitro* studies have not only confirmed that HIV-specific CD8+ T cells exhibit cytolytic activity toward HIV-infected targets, but have also revealed that CD8+ T cells have the ability to inhibit replication of HIV in lymphocyte cultures. Data supportive of the central role of CD8+ T cells in HIV infection suggest that adoptive transfer of HIV-specific CD8+ T cells may have potential as an immunotherapy for HIV-infected individuals.

Cell Genesys, Inc. has designed HLA-unrestricted chimeric T cell receptors that can redirect the antigenic specificity of peripheral blood mononuclear cell (PBMC)-derived T lymphocyte populations to recognize HIV antigen(s) of choice expressed on the surface of infected cells. Upon binding to viral antigen, these receptors initiate T cell activation resulting in induction of effector functions, including cytolysis of the viral-infected cell, proliferation, and secretion of interleukin-2 (IL-2). We have developed chimeric receptors composed of antigen recognition and signaling domains. The receptor chosen for clinical investigation is composed of the extracellular domain of the human CD4 receptor fused to the cytoplasmic domain of the zeta chain of the T cell receptor. CD4 recognizes the gp120 moiety of the HIV envelope, and zeta is responsible for signal transduction in T cells. Using retroviral-mediated transduction with replication-defective

retroviral vectors, we can routinely generate CD8+ and CD4+ T cells expressing high, stable levels of the CD4-zeta receptor. The CD4-zeta CD8+ T cell population exhibits highly efficient cytolytic activity against T cells infected with HIV-1 laboratory strains and patient isolates. Due to a possible deficiency of HIV-specific CD4 “helper” function in HIV infected patients, it may be advantageous to also administer CD4+ cells that express the CD4-zeta receptor. CD4+ T cells that express CD4-zeta proliferate and secrete cytokines upon engagement with cells expressing HIV antigen.

The proposed study is an investigator blinded, two-armed, randomized, Phase II trial; arm A will receive highly active anti-retroviral drug therapy (HAART) plus CD4-zeta gene-modified CD4+ and CD8+ T cells, and arm B will receive HAART plus unmodified T cells. The subjects participating in the study will be HIV infected patients with undetectable plasma viral load.