Scientific Abstract:

We hypothesize that incorporation of HIV specific T cell receptors (TCR), which are effective against HIV escape mutants, into autologous CD8 T cells of HIV infected individuals may promote long lasting HIV specific immunity that will delay disease progression by eliminating HIV infected cells in vivo and reducing viral load. To evaluate this hypothesis, we first isolated a TCR specific for the HLA-A*02 restricted HIV gag epitope SLYNTVATL (SL9) from a patient with chronic HIV-1 infection (WT-gag-TCR). Frequency of SL9-epitopes have been inversely correlated with viral load (Ogg et al., 1998), and the SL9 epitope is highly conserved across clades and its anchor residues are rarely mutated (Kan-Mitchell et al., 2006). We subsequently performed directed evolution on this TCR using PCR mediated mutagenesis followed by selection by phage display to create mutated α and β TCR chains with higher affinity for HLA-A*02-SL9 complexes (Li et al., 2005). Polyclonal CD8 T cells were "converted" to monoclonal gag SL9 specific T cells, as lentiviral expressed TCRs outcompeted surface expression of endogenous TCRs. All TCRs induced equivalent stimulation of CD8 T cells in an SL9-specific manner, and no proliferation or cytokine response was observed against unloaded or CMV peptide (NLVPMVATV) loaded HLA-A*02 targets. The α/6 and 11/6 TCRs respectively demonstrated an approximate 2-fold and 4-fold increase in cytokine production in response to SL9 antigen, and both the α/6 and 11/6 showed similar superior control of HIV spread in culture (22% and 16% of the untreated control respectively), in comparison to the 11/β and WT TCR (68% and 83% of the control, respectively). All four TCRs were able to control SL9 escape mutants (SLYNTVATL, SLFNTVATL, SLFNTVAVL, SLFNTIAVL, SLYNTIATL, SLYNTVAVL, and SLYNTIAVL) to a similar level as each TCR could respectively control the SL9 epitope. To best balance improved efficacy with safety, we propose evaluating the α/6 SL9 TCR as an "affinity enhanced" TCR after initial safety is established for the WT-SL9-TCR. To do this, we have designed a Phase I, open label, dual cohort, dose escalation study to evaluate the safety of the WT and α/6 SL9 TCRs on autologous CD8 T cells in HIV patients. Cohort 1 patients are later stage patients who have failed two or more HAART regimens, have active viremia (>2000 copies/ml) and CD4 counts of 200/mm^3 or greater; cohort 2 patients are well controlled on HAART with undetectable viral load and CD4 counts of 450/mm^3 or greater. Prior to enrolling into Cohort 2, safety will be established in Cohort 1. CD8 T cells will be isolated from autologous apheresis product, and enriched by negative selection. CD8 enriched cells will be modified *ex vivo* by a lentiviral vector expressing either the WT or α/6 TCR, and then the cells will be further expanded using an artificial APC based T cell stimulation protocol that employs anti-CD3 and anti-CD28 monoclonal antibodies. The lentiviral vector will be produced in an isolated viral vector production suite at the Center for Biomedicine and Genetics (CBG) located at City of Hope. The cells will be manufactured at the GMP compliant Clinical Cell and Vaccine Production Facility (CVPF) at the University of Pennsylvania, which has safely produced 395 products and treated 223 patients to date. Patients will be treated at the Hospital at the University of Pennsylvania. A standard 3+3 dose-escalation design will be followed for each cohort, with an extension phase at the MTD. The cell dose in this extension phase will be administered as a single dose, competitive repopulation between the two SL9-TCRs (50% of each study drug), in order to better evaluate the relative pharmacodynamics of the T cells expressing the WT and α/6 TCRs in vivo in the different patient cohorts.

Rationale: Although antiretroviral therapy (ART) has revolutionized the treatment of HIV-1 infection, the need for life-long therapy, difficulties with medication adherence and long-term medication toxicities have led to a search for new treatment strategies. CD8 T cells play a crucial role in the initial control of HIV-1 infection, but except for a rare subset of non-progressors, the CD8 T cell effector response becomes ineffectual in part due to the evolution of viral escape mutants (Goulder and Watkins, 2004). TCR gene transfer into primary T cells is an attractive approach for adoptive T cell therapy because large numbers of effective HIV-specific T cells can be rapidly generated. Studies in both the SIV macaque model and of natural HIV infection have ascertained that immunodeficiency viruses incur a fitness cost when they escape from some CTL responses (Crawford et al., 2007; Friedrich et al., 2004; Leslie et al., 2004; Martinez-Picado et al., 2006; Friedrich et al., 2004; Leslie et al., 2004; Martinez-Picado et al., 2006). Patients that target the virus through these epitopes, which includes conserved gag epitopes, exhibit better viral control and an increased life expectancy (Leslie et al., 2004).