

ABSTRACTS OF SUBMITTED PRESENTATIONS

S41 Enhanced immunogenicity of CMV CTL epitope analogues derived from peptide scanning combinatorial libraries.

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The pp65₄₉₅₋₅₀₃ CTL epitope from CMV is universally recognized among CMV-seropositive individuals who express HLA A*0201. A new approach to enhance the immunogenicity of T cell epitopes is the use of positional scanning synthetic combinatorial libraries (PS-SCL). Utilizing a nonamer PS-SCL, the pp65₄₉₅₋₅₀₃ epitope was modified after screening a T cell clone (TCC) from which the native peptide sequence was derived (3-3F4). Two peptides with amino acid substitutions at P1, 2, 7 and 8 are between 10³-10⁴ more immunogenic than the native epitope, but are only recognized by the screening TCC, 3-3F4. Although the native CTL epitope terminates as a free acid, both tetra-substituted peptides only function as CTL epitopes when the carboxyl terminus is amidated. Selective substitution of the native sequence based on PS-SCL predicted changes, identified three amidated mono and di-substituted peptides, that are better recognized than the native epitope by some TCC from a cohort expressing HLA A*0201. *In vitro* stimulation (IVS) of peripheral blood mononuclear cells (PBMC) with each of those peptide ligands, stimulated a memory CTL response among a high percentage of CMV-seropositive individuals. Despite the altered sequence of the pp65₄₉₅₋₅₀₃ CTL epitope, the peptide-stimulated effector T cells lyse CMV-infected targets. These data suggest that increasing the immunogenicity of CTL epitopes while maintaining universality of recognition is possible, as the result of the sequence diversity of the PS-SCL.

S42 Evaluation of Immunotherapy in the SIV Infected Rhesus Macaque Model

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A focus of antiretroviral therapy has involved combining two nucleoside analogue RT inhibitors with a protease inhibitor. This final effective combination triple therapy or highly active anti-retroviral therapy (HAART) has resulted in improved prognoses of infected individuals. However, this therapeutic regimen appears incapable of eliminating viral infection and there remains a need for additional therapeutics which complement the chemotherapy regimens. In this regard immunotherapy represents an attractive adjunctive approach. Primates are a relevant system for HIV immunogen evaluation. In our study Rhesus macaques were infected with 10 AID of SIV239. After reaching viral set-point viral replication was suppressed in the macaques using PMPA. One group of animals was inoculated with SIV DNA vaccines encoding the env/gag/pol. A second group of primates was immunized with the SIV DNA and co-immunized with IL-4, a typical Th2 type cytokine. A third set of primates was co-immunized with IL-12, a typical Th1 cytokine. A final group of animals remained unimmunized. The animals were assessed for cellular immune responses and the profiles observed were similar to the types of immune response observed in human subjects on HAART. Following immunization the animals were removed from therapy. The objective of this study was to determine the impact a Th1 versus a Th2 cytokine profile has on the viral loads. Preliminary viral load results demonstrated that the IL-4 co-immunized macaques had viral loads four logs higher than any of the other groups suggesting that Th1 versus Th2 profiles do impact on viral replication. Further studies are on-going.