A Murine CD4 Derived Peptide Scaffold to Intervene gp120-CD4 Interaction

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The binding of the cellular receptor CD4 (hCD4) by the viral protein gp120 initiates HIV-1 infection in human. Mice are HIV-1 resistant as murine CD4 (mCD4) is not bound by HIV-1 gp120 [1] despite a high sequence homology between hCD4 and mCD4. In contrast, we found a mCD4 derived peptide (mCD4-M) to be gp120 binding competent and specific. Such a peptide presents a suitable scaffold for the design of a compound to intervene the gp120-CD4 interaction in preventing HIV-1 infection. This study provides a structural explanation for the binding specificity of CD4 proteins, identifies a likely binding mode of the murine peptide, and makes suggestions for the design of peptides to interfere gp120-CD4 interaction.

A homology model of the mCD4-gp120 complex reveals that clashes of inserted residues, which have no structural equivalent in hCD4, are the molecular basis for the lack of mCD4 binding. In contrast, the peptide exhibits a higher conformational flexibility as shown by a 100 ns molecular dynamics (MD) simulation (Amber10, parm99SB). Thereby, clashes are avoided and inserted residues may even contribute to interface stabilization. However, the greater flexibility of the peptide also leads to the detachment of the peptide's C-terminal stand D implying that fixation of the C-terminus should enhance binding. In fact, cyclization by a disulfide bond yields a peptide with a higher gp120-binding affinity than the linear scaffold.

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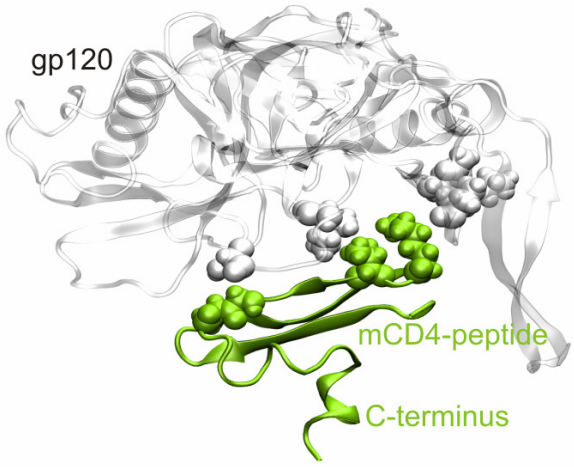
Peptide-gp120 interface. Conformational flexibility of the peptide avoids clashes found in murine CD4 but leads to the detachment of the C-terminus. Clashing residue pairs of the murine protein with gp120 are shown in spacefill.



[1] N. R. Landau, M. Warton, D.R. Littman, *Nature*, **1988**, 334, 159-162.