Conformational Analysis of HIV gp41 Cross-Linking Scaffolds

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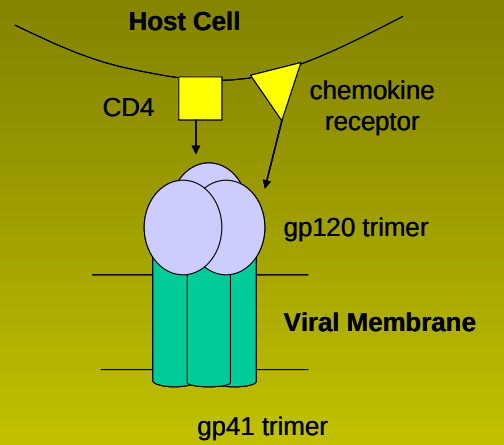
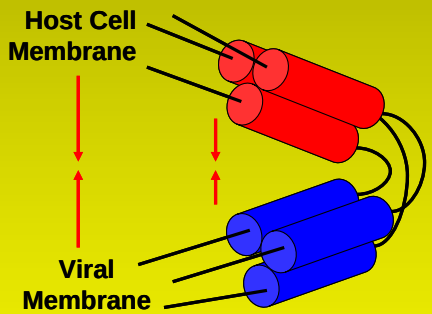
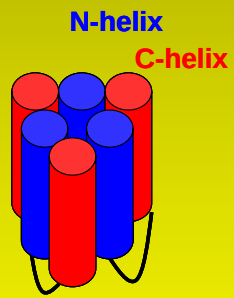
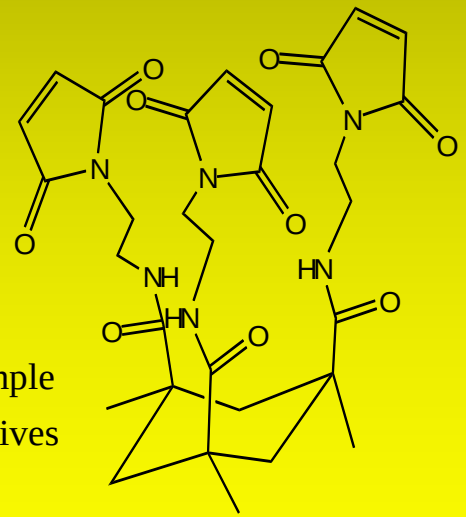
The HIV-1 envelope glycoproteins gp120 and gp41 remain non-covalently associated and oligomerize most likely as trimers on the surface of the virion. The crystal structure of a complex between gp120, CD4 and a neutralizing antibody has been solved showing that this complex has a ternary structure. Modeling studies reveal that gp120 is constrained to be three-fold symmetric. A series of trivalent CD4-mimetic miniproteins designed to match the distance between any two of the CD4 binding cavities by having three CD4M9 moieties tethered through a spacer to a three-fold symmetric template have been reported. In this work we examine twelve new C3 symmetric templates that could serve as scaffolds to which CD-4 mimetic peptides or miniproteins can be attached.









Mixed Low Mode and Monte Carlo searching techniques were performed to exhaustively sample the OPLS2005/GBSA(water) potential energy surfaces of C3 symmetric trisubstituted derivatives of cyclohexane, benzene, and triazacyclododecane. Conformational analysis was used to characterize the different rigidities, flexibilities and spatial orientations of each system to better understand their molecular behaviour. Geometric structure, molecular length, and hydrogen bonding patterns were analyzed and compared to temperature dependent NMR and biological inhibition studies.