Computation Study of HIV-1 gp120 Antibody Recognition and Binding

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Elicitation of a protective antibody response against HIV-1 has not been successful to date. The desired vaccine needs to elicit an antibody response that is both neutralizing and effective over a broad range of HIV strains due to the high mutational rate of the virus. The monoclonal antibody b12 that targets the HIV-1 glycoprotein gp120 is one of a few anti-HIV-1 antibodies known to fulfil both criteria. A promising strategy is to elicit a b12 like antibody response prior to HIV infection by a vaccine that mimics the b12 binding site of the gp120 surface and incorporates all features necessary for optimal epitope presentation.

Starting from the crystal structure of the gp120-b12 complex (2NY7) [1] the interface is energetically analyzed to identify those residues crucial for the interaction. However, due to the conformational flexibility of the binding region in gp120, an analysis of the static complex alone will conceal important information about the initial steps of gp120 recognition. Therefore, molecular dynamics (MD) simulation (Amber10, parm99SB) of free gp120 and of the gp120-b12 complex are intended to reveal additional aspects of antibody binding. Also, the crystal structure of gp120 was determined using a mutated and disulfide stabilized gp120 protein. Hence, the dynamical investigation of gp120 after removal of mutations and artificial disulfide bonds will provide information whether and how these alterations influence the gp120 structure and thereby b12 binding.

First results show an enhanced conformational sampling of gp120 after the removal of mutations and artificial disulfide bridges particularly at the site of b12 interaction. While the energetic analysis of the gp120-b12 contact area reveals gp120 residues E370, I371, V372, N386, and D477 to play a key role for the binding of the neutralizing antibody b12.

[1] T. Tongqing, L. Xu, B. Dey, A.J. Hessell, D. Van Ryk, S.-H. Xiang, X. Yang, M.-Y. Zhang, M.B. Zwick, J. Arthos, D.R. Burton, D.S. Dimitrov, J.Sodroski, R. Wyatt, G.J. Nabel, P.D. Kwong, *Nature*, **2007**, 445, 732-737.
[2] R. Franke, T. Hirsch, H. Overwin, J. Eichler, *Chem Int Ed Engl*, **2007**, 46, 1253-1255.