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HIV-1 Env structure and vaccine design

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Roughly one third of the HIV-1 genome is devoted to the HIV-1 envelope (Env) glycoprotein spike, which comprises three gp120 and three gp41 subunits. Structural characterization of the HIV-1 Env by electron microscopy, NMR, and X-ray crystallography reveals considerable conformational alterations, not only between trimeric ground state, CD4 receptor-bound conformation, and postfusion conformation of the spike, but also between monomeric and trimeric configurations of the subunits as well as between free- and antibody–bound states. One important structure, however, that of the prefusion HIV-1 spike, has resisted atomic level determination. This structure has been on the 10 list of most wanted structure for more than 20 years, because it is the target of the majority of broad HIV-1-neutralizing antibodies – and therefore of importance to vaccine design. In late 2013, the structure of a prefusion HIV-1 spike, based on a BG505 SOSIP.R6.664 construct, was reported by both X-ray crystallography (4.7 Å) and electron microscopy (5.8 Å). While these structures described the trimeric configuration of most of the HIV-1 gp120 subunit, the description of the gp41 subunit was limited to two helical regions comprising only about half the gp41 ectodomain, and the sequence register for the alpha helices was not reported. Recently, we were able to obtain x-ray diffraction data to 3.5 Å resolution on a prefusion crystal structure of the entire HIV-1 spike. The structure utilizes the same BG505 SOSIP.R6.664 construct as previously published, but crystallized in space group P6(3) with the antigen-binding fragments (Fab) of two antibodies, PGT122 and 35O22. The new structure provides atomic-level details for the complete prefusion structure of gp120 and the majority of the trimeric ectodomain of gp41 (up to residue 664). Also visualized are details of the gp120-gp41 interface and of antibodies such as 35O22. In addition to the complete HIV-1 Env ectodomain structure, implications for HIV-1 vaccine design will be described.

[1] *Kwong and Mascola (2012) Immunity 37, pp. 412-425,* ***[2]*** *Julien et al. (2013) Science 342, pp. 1477-1483,* ***[3]*** *Lyumkus et al. (2013) Science 342, pp. 1484-1490*

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