

## Reactivation of neutralized HIV-1 by dendritic cells

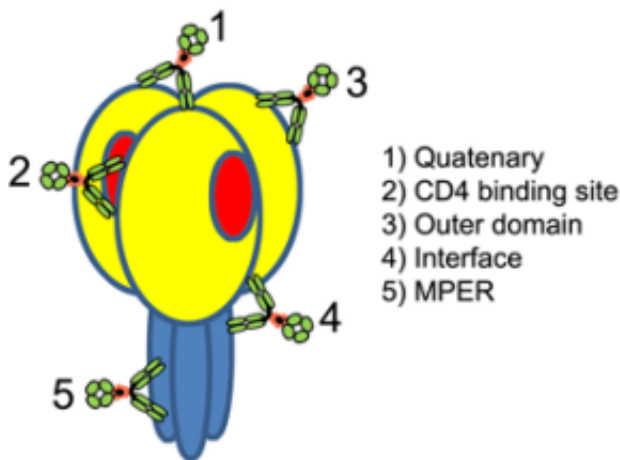


Fig.1. Yellow: gp120, Red: CD4, pocket, Blue: gp41

HIV-1 can be bound by neutralizing antibodies that target the envelope glycoprotein (Env) and thereby block viral entry into HIV-1 susceptible cells. HIV-1 specific antibodies are formed within the first two weeks in patients, but usually these antibodies do not block entry and are therefore referred to as non-neutralizing antibodies. Gradually during disease progression antibodies develop better specificities against the HIV-1 Env and after a few years antibodies are generated that can neutralize multiple HIV-1 strains in 50% of the patients. Antibodies bind the Env trimer, composed of three glycoprotein 120 and 41 subunits, at different regions. The top of the Env, composed of the variable region 1 and 2 (V1V2) of gp120, can be targeted by quaternary antibodies that bind at least two gp120 subunits. Antibodies that bind the pocket within and between the gp120 subunits, that is used to bind the host CD4 receptor, are termed CD4 binding site antibodies. The outer domain of gp120 is extensively shielded with N-linked glycans and is difficult to access by antibodies. These antibodies usually target an oligomannose glycan patch and antibody binding is thus glycan-dependent. Interface antibodies bridge binding of gp120/gp41 and antibodies binding the rod-shaped gp41 stem can bind to the membrane proximal external region (MPER) of gp41 (Fig. 1).

Dendritic cells survey tissues for pathogens that are captured by C-type lectin receptors that recognize specific carbohydrate glycan residues exposed on the exterior of viruses, bacteria and fungi. Once captured, pathogens are processed into peptides and presented to T and B cells to elicit a defensive immune response. Previously we showed that antibody neutralized HIV-1 can be efficiently captured by dendritic cells and infectious virus subsequently passed to HIV-1 susceptible T cells, thereby reversing the neutralized profile (van Montfort et al., J. Immunol. 2007). In the article "Reactivation of neutralized HIV-1 by dendritic cells is dependent on the epitope bound by

the antibody” we followed processing of antibody bound HIV-1 by dendritic cells to understand how the virus could subvert neutralization. Antibodies targeting the different Env regions, including the most recently discovered antibodies were studied and virus transfer from immature and mature dendritic cells was examined. The glycan-dependent antibodies demonstrated diverse effects on HIV-1 spread by dendritic cells. For example, some glycan-dependent antibodies shielded N-glycans and thereby blocked HIV-1 capture by C-type lectins on dendritic cells. Other antibodies did not hamper HIV-1 capture, but significantly increased efficiency of HIV-1 dissemination via dendritic cells. Importantly, we observed that a single amino acid change in the antibody epitope could negate neutralization, but not binding of the antibody to the virus. In particular, the binding, but non-neutralizing glycan-dependent antibody could strongly enhance virus dissemination by mature dendritic cells. This could describe a mechanism where HIV-1 can easily escape and misuse binding of a potent antibody. In more detail we studied CD4 binding site and MPER antibodies. All CD4 binding site antibodies efficiently blocked virus spread from dendritic cells, whereas all neutralizing MPER antibodies did not and allowed efficient virus dissemination via dendritic cells. We could show that an example CD4 binding site antibody remained firmly bound to HIV-1, whereas the MPER antibody quickly dissociated from the virus after capture by dendritic cells. Collectively, dendritic cells can undo virus neutralization, which could have consequences for HIV-1 vaccines aiming at the induction of neutralizing antibodies.

## Publication

[Reactivation of Neutralized HIV-1 by Dendritic Cells Is Dependent on the Epitope Bound by the Antibody.](#)

van Montfort T, Thomas AA, Krawczyk PM, Berkhout B, Sanders RW, Paxton WA  
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