

Immunogenicity of Virus Like Particles (VLP) with modified envelope (Env) protein

HIV uses a special strategy to evade the immune system during the course of infection in a human, based on features of envelope protein. The HIV Env glycoprotein that forms spikes on the surface of virus particles is a complex of two subunits: the surface gp120, which mediates the binding of the virus to specific cell-surface receptors, and gp41-surface-transmembrane-cytoplasmic subunit, which promotes membrane fusion (Fig 1 A). The native Env, which is the main target for immune system is thought to be present in a metastable state on the surface of viral particles. The immune system is not able to develop protective antibodies against those sorts of Env proteins, but indeed it may induce non-neutralizing antibodies against HIV. The specific regulation of membrane fusion is important in biological functions such as viral entry. A conformational change of the Env protein, which can make it sensitive to immune system, is triggered either by receptor binding or by inside-out signaling from the cytoplasmic domain (CT) of gp41. Unfortunately, conformational changes of the Env protein that is triggered by a receptor binding take place in endosomes inside of cells (Fig.1 A). Genetically modified CT domain can affect the conformation of the external domain of gp41 on the cell surface and it may also enhance exposure of receptor-binding segments in gp120 (Fig. 1B).

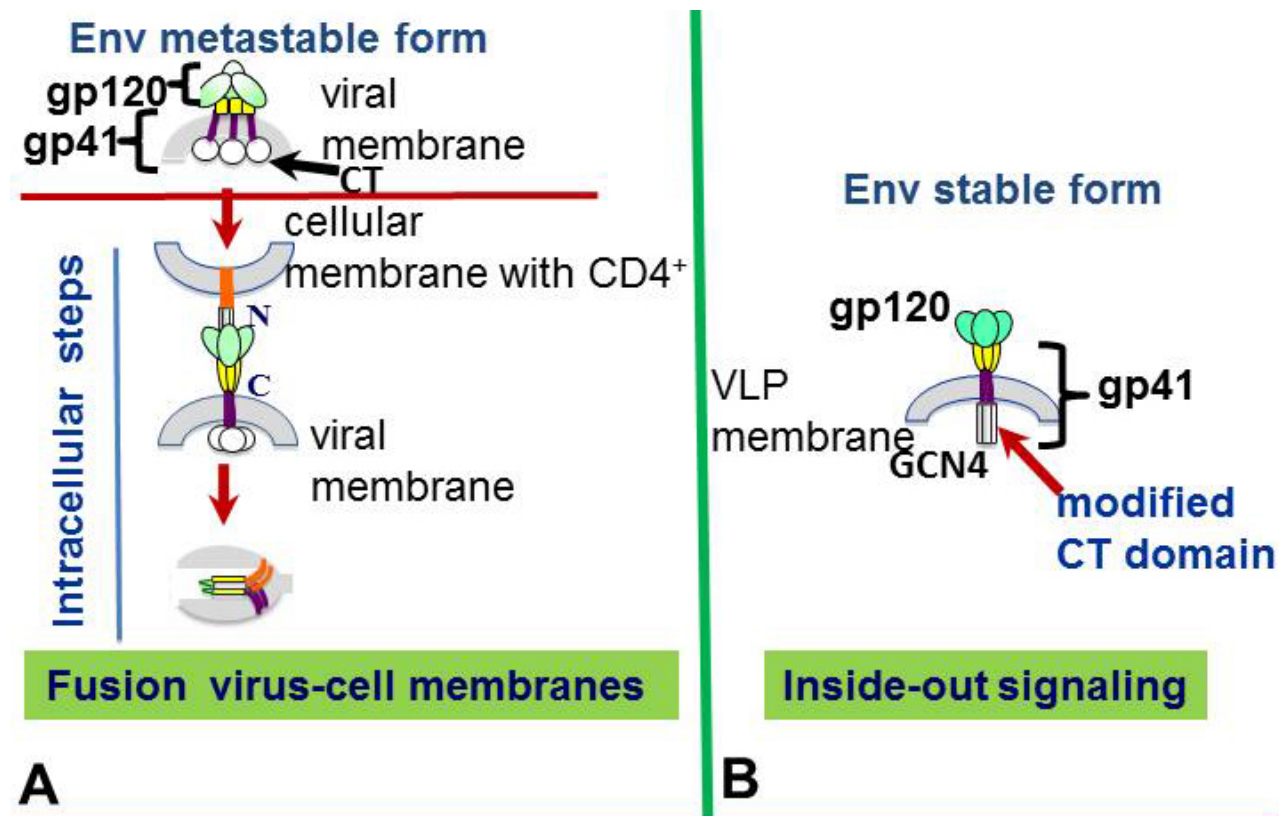


Fig. 1. Stabilizing the native trimers of HIV-1 envelope protein (Env). (A) Stabilization of Env proteins initiated by binding of HIV particles to CD4 receptor. (B) Stabilization of Env proteins by incorporation of trimerization sequence GCN4 into CT domain.

VLPs are assembled as noninfectious retrovirus-like particles that closely mimic the morphology of naturally occurring virions, their production requires only the Gag polyprotein. The immune system is effective in recognizing antigens in a particulate form, which mimics that of native virions. An important characteristic of VLP is that it contains a trimeric Env with a native conformation, and rendering a possibility for Env spikes to be stabilized, avoiding immune misdirection and the induction of non-neutralizing antibody responses. Using a leucine zipper trimerization sequence from the yeast GCN4 transcription factor, trimeric forms of target proteins can be stably expressed. Native envelope proteins are incorporated into VLP at low levels.

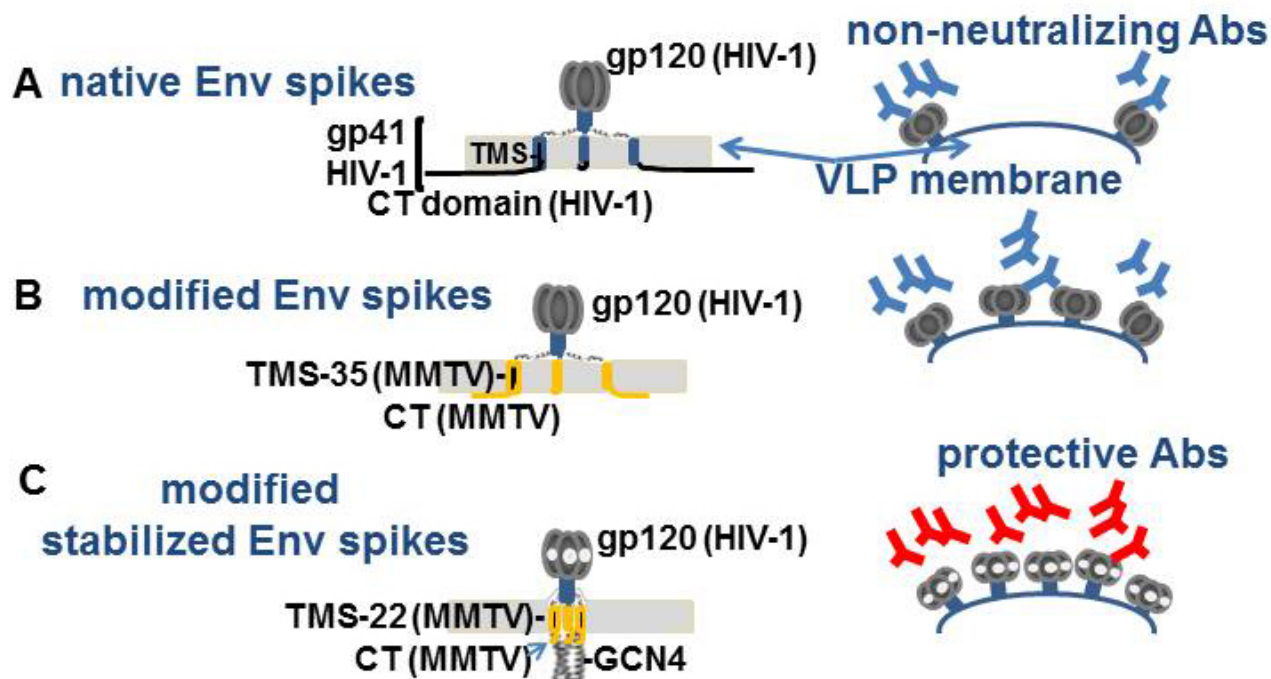


Fig. 2. Modification of HIV-1 Env trimers for production of more effective VLP vaccine. (A) HIV-1 Env trimers are composed of three gp120-surface subunits and three gp41-transmembrane subunits. Gp41 containing a 22 amino acids (aa) transmembrane spanning domain (TMS) and a full-length 150–200 aa cytoplasmic domain (CT) (B) Modified Env protein containing a 35aa TMS domain (TMS-35) and CT from the MMTV Env, which exhibited high levels of incorporation into VLP. (C) Modified Env protein containing a shorter 22 aa version of the TMS (TMS-22) derived from the MMTV Env and containing a GCN4 trimerization sequence in the ?? which is predicted to

result in enhanced trimer stability, to induce broadly reactive neutralizing antibody responses in immunized animals. Protective antibodies showed in red; non-neutralizing antibodies showed in blue.

Modified proteins containing the external parts of Env HIV-1 exposed on VLP and the transmembrane spanning region derived from another Env protein of mouse mammary tumor virus MMTV (Fig. 2 A,B,C) exhibited significantly increased levels of incorporation into VLPs and induced strong immune responses in guinea pigs, compared to VLP containing native Env HIV-1 glycoproteins (Fig. 2 B, C). Immunized animals with VLPs with high Env content and containing the CT trimerization sequence had increased neutralization activity and avidity of antibodies (Fig. 2 C). An immunization with different Env provides the opportunity to stimulate responses specific to conserved epitopes further enhanced these immune responses. In particular, VLPs containing the modified Env are found to be as effective as HIV-1 vaccine antigens.

Andrei Vzorov Ph.D

Department of Microbiology and Immunology,

Emory University, Atlanta, USA

Ivanovsky Institute of Virology, Gamaleya Federal Research Center of

Epidemiology and Microbiology, Moscow, Russia

Publication

[Effects of modification of the HIV-1 Env cytoplasmic tail on immunogenicity of VLP vaccines.](#)

Vzorov AN, Wang L, Chen J, Wang BZ, Compans RW

Virology. 2016 Feb