



Licensing Opportunity

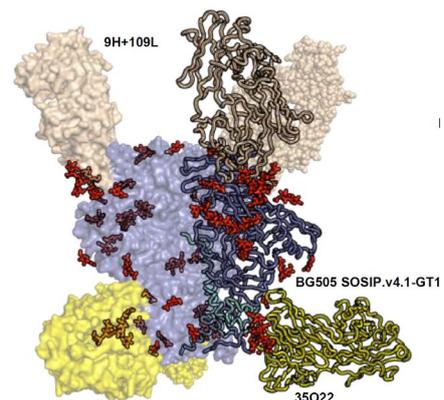
Improved HIV vaccine candidates activating naïve B-cells expressing germline bNAb precursors

Market sector: Immunology, vaccines, infectious disease, HIV, antibody production.

No experimental vaccine has proven to be efficient at inducing protective immunity against HIV-1 infection. One approach to this problem is the generation of an HIV-1 envelope glycoprotein (Env) based vaccine that induces broadly neutralizing antibodies (bNAbs), antibodies that can neutralize HIV strains from different subtypes ([van Gils and Sanders, 2013](#)). Induction of anti-HIV bNAbs by vaccination has proven difficult, but it is known that the human immune system can generate them since approximately ~30% of HIV infected individuals develop bNAbs over time. Although the bNAbs do not benefit these individuals because of viral reservoirs and rapid viral escape, the presence of this type of antibodies prior to infection is protective in animal models ([Medina-Ramírez M et al, 2017](#)). Consequently, understanding how bNAbs are induced and harnessing the process can help to design efficacious vaccines and immunization protocols.

In order to generate bNAbs through vaccination, it will be necessary to implement approaches that mimic the virus-escape guided affinity maturation pathway seen in ~30% of HIV infected individuals that have developed these. This can be achieved through immunization schemes composed of a precursor priming immunogen, followed by one or several boosts of different escape-based immunogens in a sequential fashion and aimed at guiding the affinity maturation pathway towards antibodies with the desired breadth and potency.

The critical first step in such a strategy is activation of naïve B cells expressing germline (gl) antibody precursors that have the potential to evolve into bNAbs. We reengineered a stabilized form of the HIV envelope glycoprotein, BG505 SOSIP.664 ([De Taeye et al., 2015](#)) to engage gl-precursors of bNAbs that target either the trimer apex or the CD4 binding site of Env (JEM ref). The resulting BG505 SOSIP.v4.1-GT1 trimer is highly stable, is a real-mimic of the HIV envelope protein and has the capacity to bind multiple naïve precursors. This protein is suitable for use in vaccination protocols aimed at inducing broadly neutralizing antibody responses needed to build effective protection against infection with HIV.



Overall architecture of BG505 SOS IP.v4.1-GT1-N137A at 3.2 Å in complex with Fab fragments of gl bNAb's. Taken from [Medina-Ramirez et al, 2017](#)

Technology:

At the AMC, we used the available BG505 SOSIP.664 structures to engineer a variant with enhanced binding to inferred germline bNAbs, including those targeting the CD4 binding site and

the V1V2-apex. Neutralization titers of gl-bNAbs of viruses obtained from clinical isolates 1-12 months after infection from patients that developed moderate to strong neutralization breadth were analyzed. From this, sequence changes relevant to epitopes in the trimer apex were determined and combined together in several Env variants. Additional modifications in the CD4bs resulted in the BG505 SOSIP.v4.1-GT1 (GT1) variant. GT1 was selected on the basis of expression, native-like trimer formation, and gl-bNAb binding. *In vitro* studies showed (in contrast to the SOSIP.664 parent molecule) activation of gl-VRC01 B-cells. *In vivo* studies in knock-in mice expressing the predicted germlines of VRC01 and PGT121 bNAbs reveal that immunization with the GT1 trimer results in elicitation of antibodies directed against the CD4 binding site and trimer apex, respectively.

The BG505 SOSIP.v4.1-GT1 trimer incorporates a number of Env stabilizing mutations also proprietary to the AMC. As a result the protein is stable and forms native like structures (confirmed by EM and X-ray crystallography studies) and hence suitable as antigen in vaccination protocols aimed at eliciting HIV neutralizing antibody responses.

Applications:

- HIV vaccine

Key benefits:

- Activation of naïve B-cells expressing bNAb precursors
- Stable and native-like antigen

Stage of Development:

Proof of concept has been established *in vitro* and *in vivo* in knock-in mice. Upon immunization the new HIV vaccine candidate leads to induction of gl-bNAbs to two different epitopes.

Patent / IP status:

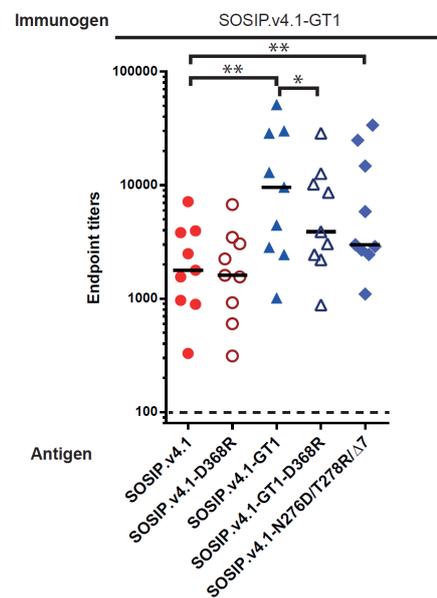
The initial EP patent application (provisional number EP17188050.3) was filed in August 2017.

Main inventors:

- Dr. Max Medina-Ramirez is working at AMC. He is an expert on engineering of trimeric viral spike protein vaccines. His work focuses on the generation of HIV protein vaccines with the capacity to initiate germline bNAbs responses.
- Prof. Rogier Sanders is working at AMC and Weill Medical College of Cornell University in New York City. He is an expert on trimeric viral spike protein vaccines. One focus of his research is on improving the immunogenicity of HIV protein vaccines by optimizing the antigenic structure of trimeric spike proteins by structure-based protein engineering.

Key publications:

- Medina-Ramírez M, Garces F, Escolano A, Skog P, de Taeye SW, Del Moral-Sanchez I, McGuire AT, Yasmeeen A, Behrens AJ, Ozorowski G, et al (2017) Design and crystal structure of a native-like HIV-1 envelope trimer that engages multiple broadly neutralizing antibody precursors in vivo *J Exp Med.* 214, 2573-2590.
- van Gils, M.J., and Sanders, R.W. (2013). Broadly neutralizing antibodies against HIV-1: templates for a vaccine. *Virology* 435, 46–56.
- de Taeye, S.W., Ozorowski, G., Torrents de la Peña, A., Guttman, M., Julien, J.-P., van den Kerkhof, T.L.G.M., Burger, J.A., Pritchard, L.K., Pugach, P., Yasmeeen, A., et al. (2015). Immunogenicity of stabilized HIV-1 envelope trimers with reduced exposure of non-neutralizing epitopes. *Cell* 163, 1702-1715.



BG505 SOS IP.v4.1-GT1 initiates antibody responses in knock-in mice expressing the predicted germlines of VRC01. Taken from Medina-Ramirez et al, 2017