A recombinant HIV envelope trimer selects for quaternary dependent antibodies targeting the trimer apex

Marit J. van Gils1, Devin Sok2, Matthias Pauthner2, Jean-Philippe Julien2, Bryan Briney2, John P. Moore3, Andrew B. Ward2, Ian A. Wilson2, Rogier W. Sanders1,3 and Dennis R. Burton2

1Dept. Medical Microbiology, AMC, University of Amsterdam, Amsterdam, The Netherlands; 2The Scripps Research Institute, La Jolla, CA, USA; 3Cornell University, New York, NY, USA

INTRODUCTION

Despite the high antigenic diversity of HIV envelope (Env), broadly neutralizing antibodies (bnAbs) have identified conserved regions that serve as targets for vaccine design. One of these regions is located at the apex of the trimer and is only fully expressed in the context of the correctly folded trimer. BnAbs targeting the Env trimer apex are favored candidates for vaccine design and immunotherapy because of their great neutralization breadth and potency. Methods to isolate bnAbs against this site, however, have been limited due to the quaternary nature of the epitope region. Here we report the use of a recombinant HIV envelope trimer, BG505 SOSIP.664 gp140, as an affinity reagent to isolate quaternary-dependent bnAbs from the PBMCs of a chronically infected donor.

RESULTS

- New bnAbs, named PGDM1400-1412, which target the quaternary-dependent apex region were isolated using BG505 SOSIP.664 gp140 trimer (figure 1).
- BnAbs PGDM1400-1412 show a wide range of neutralization breadth and potency, with PGDM1400 being exceptionally broad and potent with cross-clade neutralization coverage of 83% at a median IC50 of 0.003 μg/mL (figure 2).
- BnAbs PGDM1400-1412 have a very long CDR3 of 33-34 amino acids and target the glycan at amino acid position 160 in the Env apex (figure 3).

CONCLUSIONS

- Characterization of the PGDM1400-1412 antibodies reveals a highly diverse antibody response against the trimer apex.
- These results will provide molecular information that will be useful in the design of immunogens to elicit bnAbs to the apex region of Env.
- Our results highlight the utility of BG505 SOSIP.664 gp140 as a tool for the isolation of quaternary-dependent antibodies.
- In addition to isolating new bnAbs to the trimer apex, BG505 SOSIP.664 gp140 can potentially be used to isolate bnAbs targeting other quaternary epitopes.

Figure 1. BG505 SOSIP trimer selects memory B cells expressing HIV-specific bnAbs.

A. PBMCs from the PGT141-145 donor were sorted using BG505 SOSIP.664 and JR-CSF gp120 to select for bnAb memory B cells targeting quaternary epitopes.
B. 62 productive heavy chain and 158 productive light chain sequences were obtained, with a large enrichment for the PGT145 antibody gene family.
C. The heavy and light chain sequences are heavily mutated from the inferred germline.

Figure 2. Newly selected PGDM somatic variants display a range of neutralization breadth and potencies.

A. Heavy chain and Kappa chain phylogenetic tree of newly isolated somatic variants, which cluster separately from the PGT141-145 antibodies, show four distinct clusters with high sequence diversity between the different variants.
B. Percent neutralization breadth and median IC50 values of somatic variants PGDM1400-1406 against a 77 virus panel with PGDM1400 being exceptionally broad and potent.

Figure 3. BnAbs PGDM1400-1412 target the N160 apex glycan.

A. Cumulative frequency distribution of the percentage of viruses neutralized in a 106-virus panel at different IC50 cutoffs shows that PGDM1400 is the most potent and broad bnAb. A combination of PGDM1400 + PGT121 shows the coverage obtained by targeting two different sites of vulnerability on Env.
B. PGDM1400-1412 do not neutralize virus that contain the N160/K substitution as well as viruses produced in the presence of kifansine, indicating that the antibodies target the glycan at position 160.
C. Crystal structure of the PGDM1400 Fab illustrating the very long CDR3 loop of 33-34 amino acids.
D. Cryo-EM pictures of theBG505 SOSIP.664 trimer in complex with PGDM1400 Fab indicate that PGDM1400 binds to the Env apex at a different angle than PG9.