Inferring immunogenic properties of Env trimers by reactivity to bnAb inducer plasma

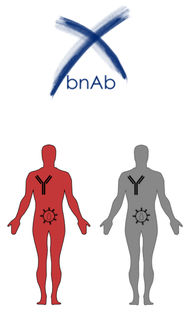
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Background

- HIV-1 vaccine development depends on the identification of HIV-1 Env trimer immunogens with the capacity to induce bnAb activity.
- Here, we validated 29 candidate stabilized Env trimer immunogens for their capacity to engage polyclonal bnAb and nnAb responses in the XbnAb cohort
- **XbnAb cohort: 304 bnAb inducers** & **304 nnAb controls** identified in the Swiss 4.5k study (Rusert, Nat Med 2016)



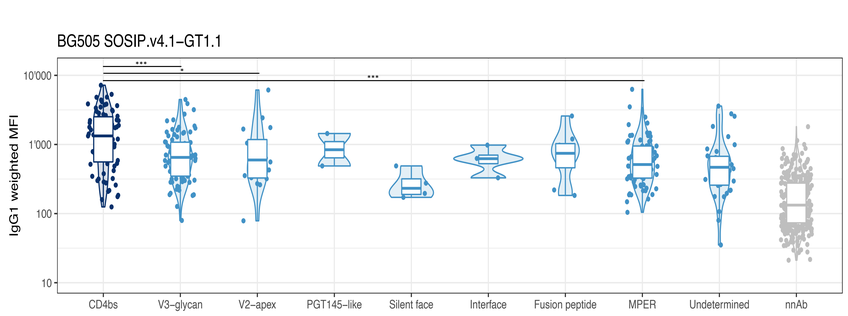
Methods

- **Binding antibody multiplex assay (BAMA)** IgG1,-2, and -3 responses to 29 stabilized soluble Env trimer immunogens
- **Ranking of best bnAb-engaging trimer** immunogens according to:
  - MFI magnitude in bnAb inducer plasma
  - Differentiation between bnAb and nnAb plasma
  - Reactivity with different subtype plasma
  - Reactivity with plasma of different bnAb specificities

Rank	Env-Trimer-Antigen	Subtype
1	BG505 SOSIP.v4.1-GT1.1-N160Q	A
2	**BG505 SOSIP.v4.1-GT1.1**	A
3	BG505 SOSIP.v4.1-GT1.1-D368R	A
4	**ConM SOSIP.v7**	consensus M
5	**ConCv5_KIKO**	consensus C
6	ConCv5_GTv1	C
7	ConCv5_KI	C
8	BG505 SOSIP.v4 T332N	A
9	gp120_426c_CH	C-gp120 (A)
10	AMC008 SOSIP.v4	B
11	BG505 SOSIP.v4 T332A	A
12	Du422 SOSIP.v4	C
13	gp120_16055_CH	C-gp120 (A)
14	**BG505 DS-SOSIP T332N**	A
15	V1V2_WITO_CH	B-V1V2 (A)
16	gp120_CH505_CH	C-gp120 (A)
17	sC23v4_KIKO	C
18	**BG505 SOSIP T332N**	A
19	sC22v4_KIKO	C
20	gp120_16055_CH_CD4bs(-)	C-gp120 (A)
21	V1V2_CAP256SU_CH	C-V1V2 (A)
22	AMC011 SOSIP.v4	B
23	BG505 SOSIP_TM	A
24	V1V2_c1080_CH	AE-V1V2 (A)
25	AncCv5	ancestor C
26	3355_77 DS-SOSIP	B
27	ZM197M SOSIP.v4	C
28	3355_77 SOSIP	B
29	gp120_426c_CH_CD4bs(-)	C-gp120 (A)

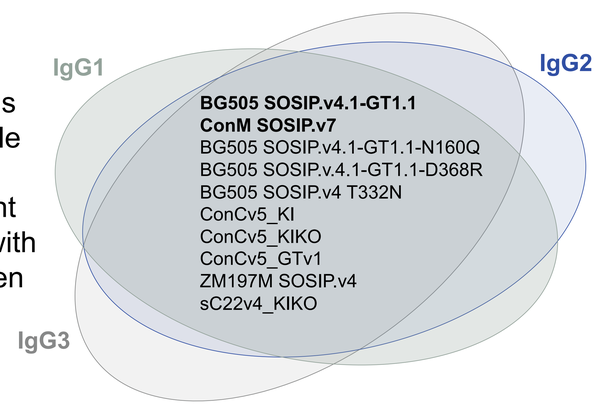
Differential capacity of soluble Env trimer immunogens in binding plasma antibodies from bnAb inducers and non-neutralizers provides unique clues to their immunogenic potential that can be exploited for immunogen development and selection.

BG505 SOSIP.v4.1-GT1.1 recapitulates its CD4bs bnAb germline targeting capacity by preferentially binding CD4bs bnAb plasma



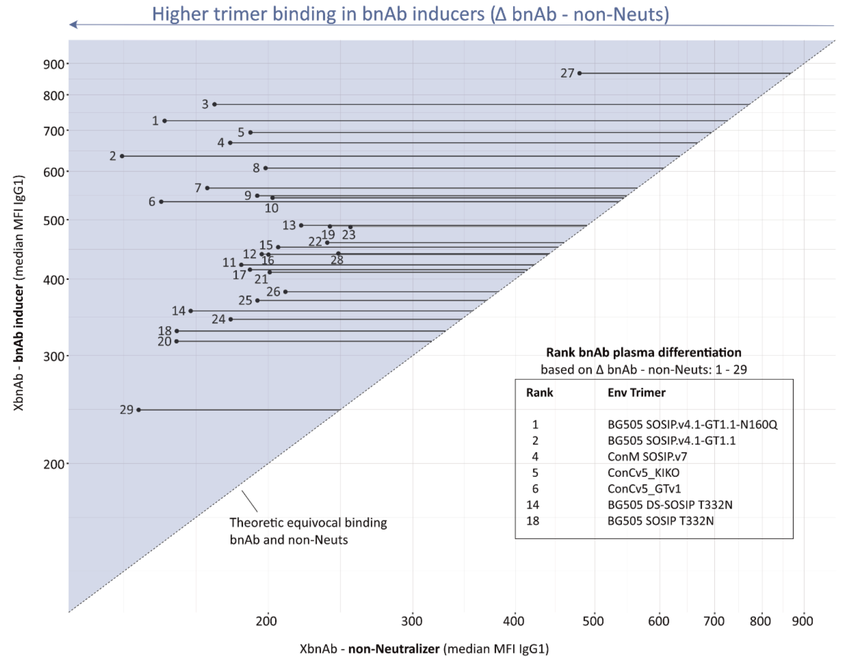
Subtype (B versus non-B) discrepancies.

Candidate immunogens show highly comparable reactivities between subtypes. No significant difference was found with most immunogens when adjusting for ethnicity.



Env trimers display differential capacity to differentiate between bnAb and nnAb inducers

High-ranked trimers based on IgG1 reactivity
- BG505 SOSIP.v4 1-GT1.1 (and derivatives)
- ConM SOSIP.v7
- ConCv5 (and derivatives)



Conclusions

- Profiling of trimers binding activities in individuals from the XbnAb cohort identifies **potential immunogens** for future immunization studies
- Both BG505 SOSIP.v4.1-GT1.1 and ConM SOSIP.v7 were identified as best bnAb-engaging immunogens

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