

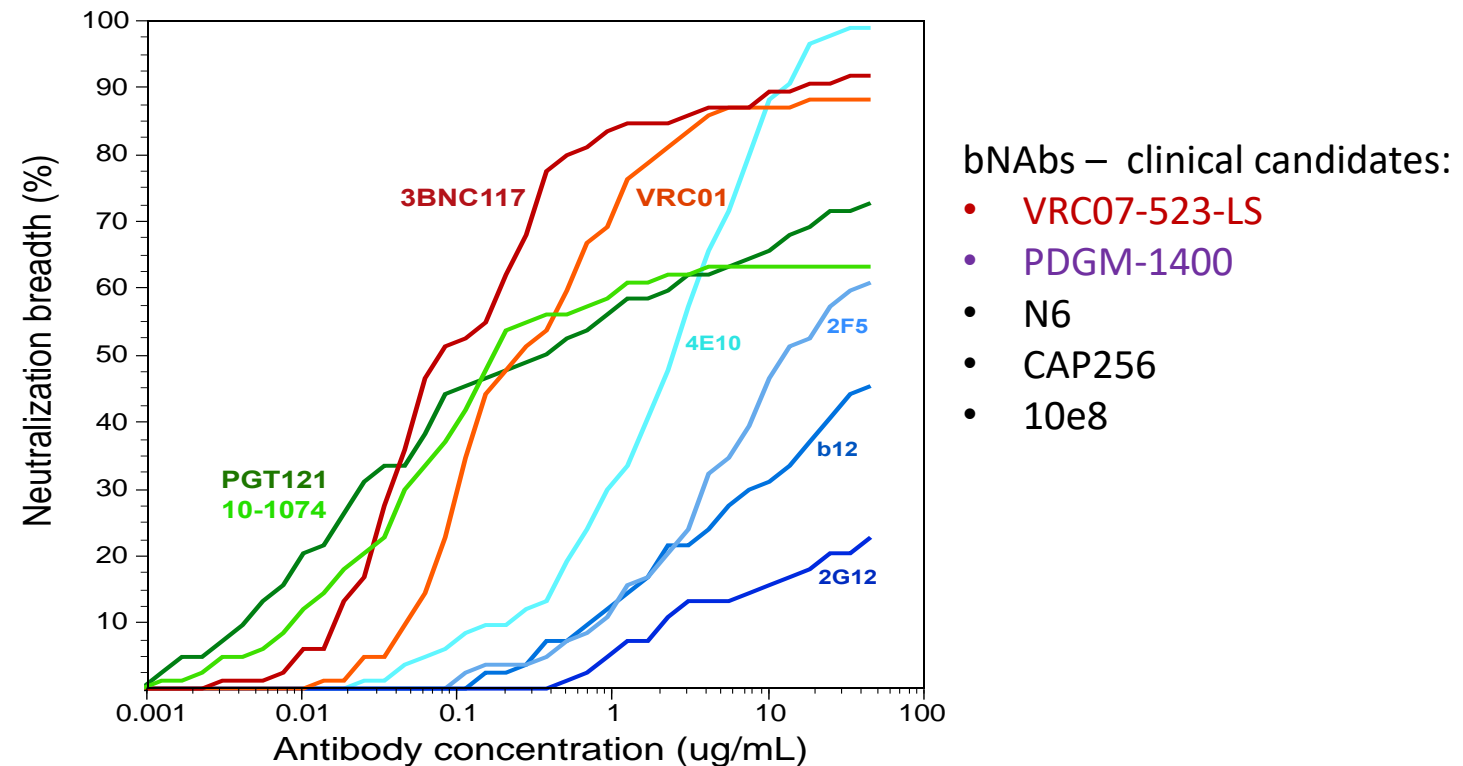
Effects of Broadly Neutralizing Antibody Combinations in HIV-1 Infection

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Broadly neutralizing antibodies with improved breadth and potency being evaluated clinically


In vitro neutralizing activity against multi-clade viral panels, measured by TZM.bl assay



VRC01, Wu *et al.*, Science 2010; 3BNC117, Scheid *et al.*, Science 2011; PGT121, Walker *et al.*, Nature 2011; 10-1074 Mouquet *et al.*, PNAS 2012

Potential roles of bNAbs in HIV-1 therapy

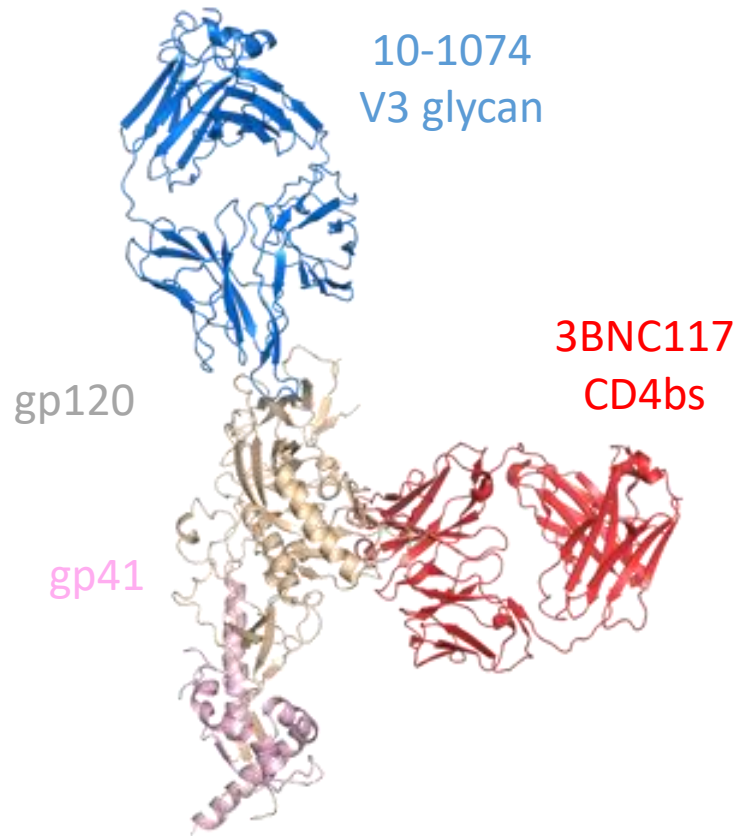
- Maintenance 

Safety: As a class, mAbs are **considered safe**
Adherence: mAbs **have long half-lives**, that can be prolonged to ~ 2 months
- Long-term control 

mAbs might “**boost**” or “improve” existing **immune responses**
mAbs have potential to **directly eliminate infected cells** and therefore interfere with the HIV latent reservoir

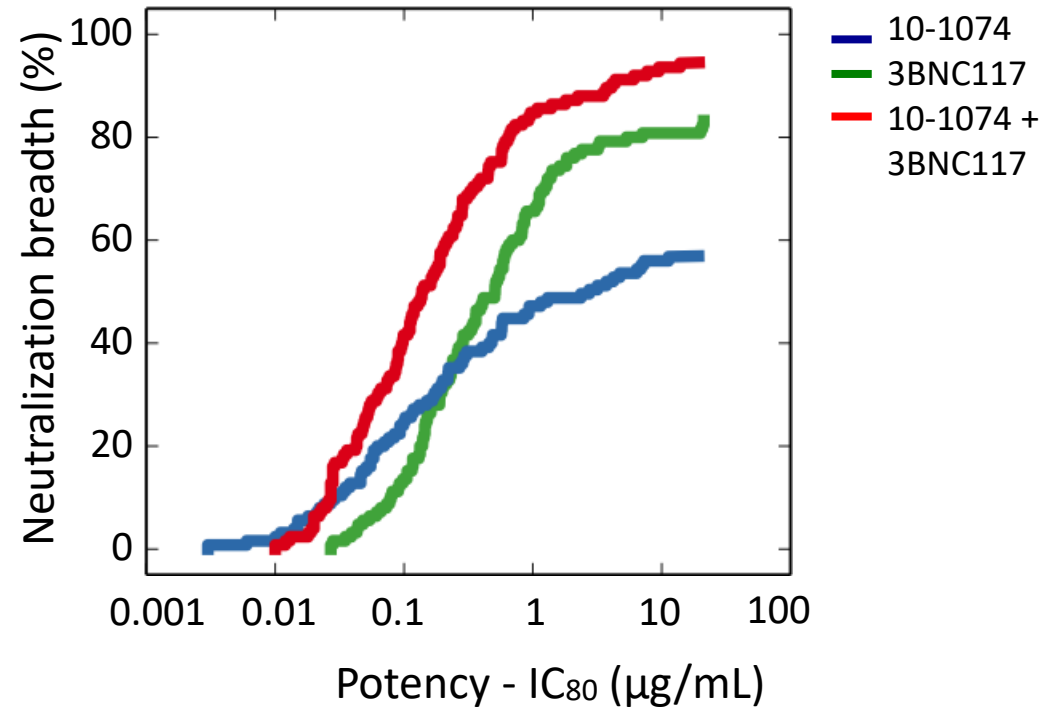
3BNC117 and 10-1074

Target Independent Epitopes



Non-overlapping epitopes

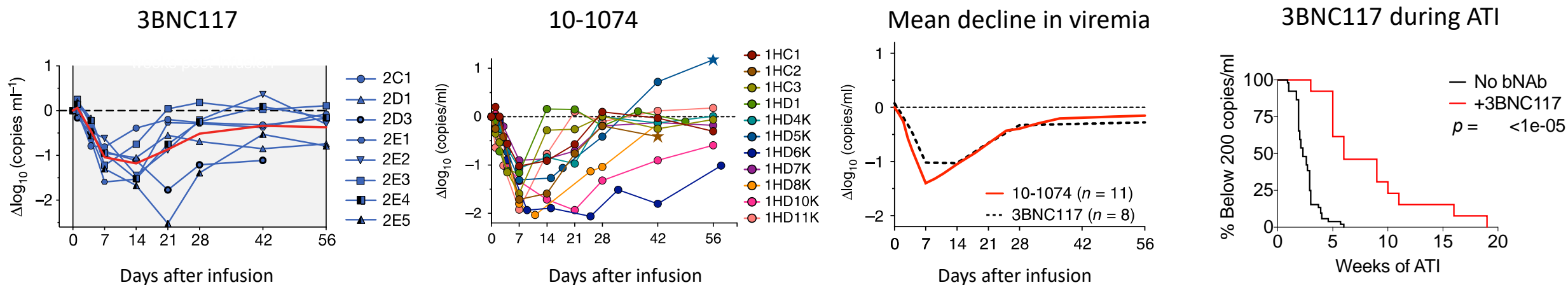
Gristick et al NSMB 2016



Coverage of **96%** of 125 strains (multi-clade)
Median IC_{50} of **0.04 $\mu\text{g/ml}$** and IC_{80} **0.15 $\mu\text{g/ml}$** .

Kong et al, J Virol 2015

First-in-Human Studies 3BNC117 and 10-1074



Mean decline in plasma viremia of $\sim 1.5 \log_{10}$ cp/ml.

3BNC117 monotherapy **delayed viral rebound by a median of 8 weeks**

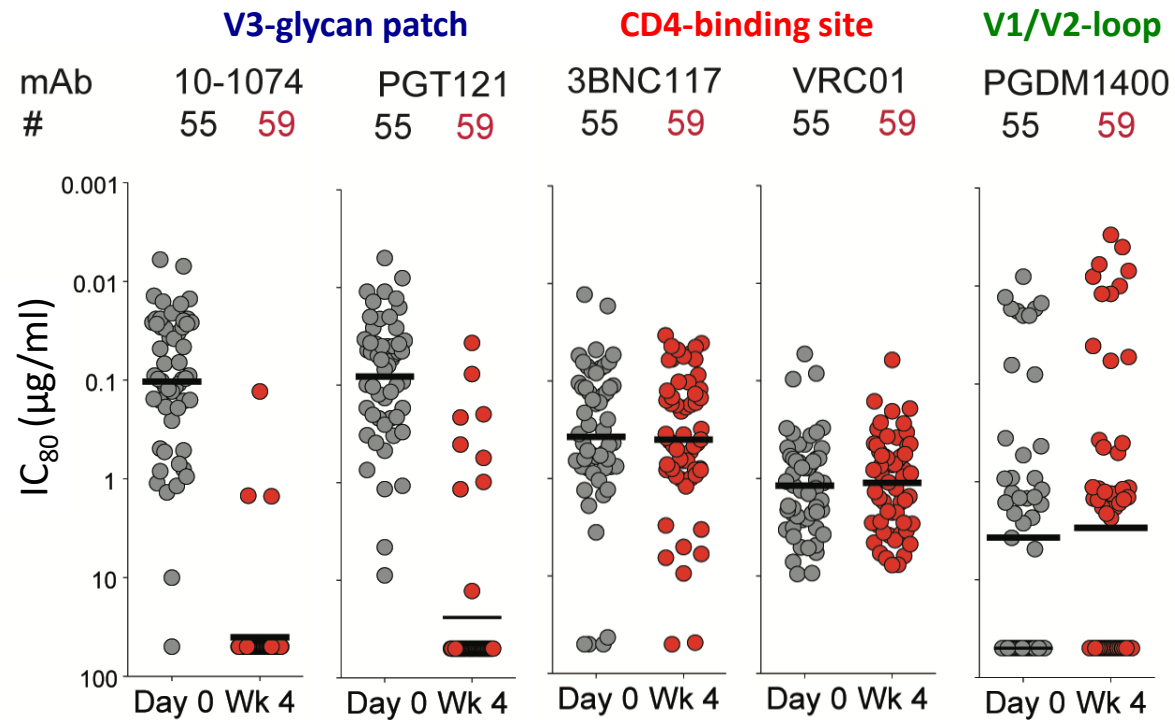
Selection of resistant viral strains

Caskey, Klein et al., Nature 2015

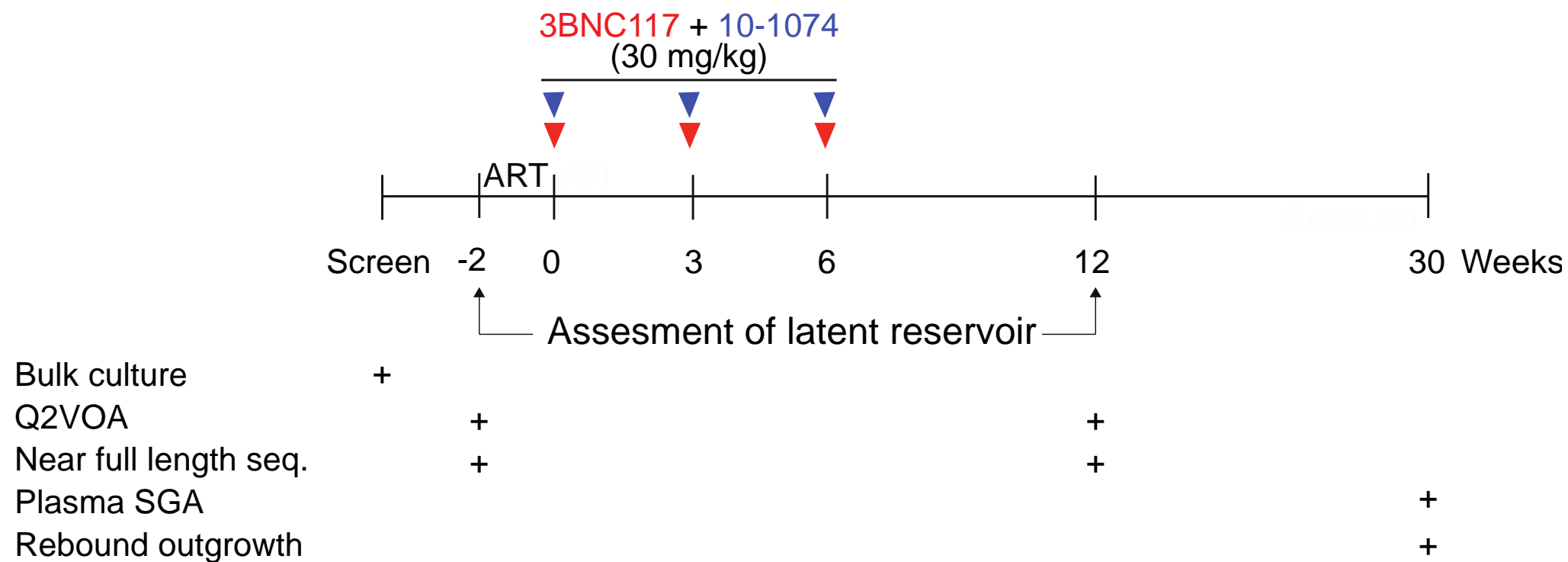
Scheid et al., Nature 2016

Caskey, Schoofs et al. Nat Med. 2017

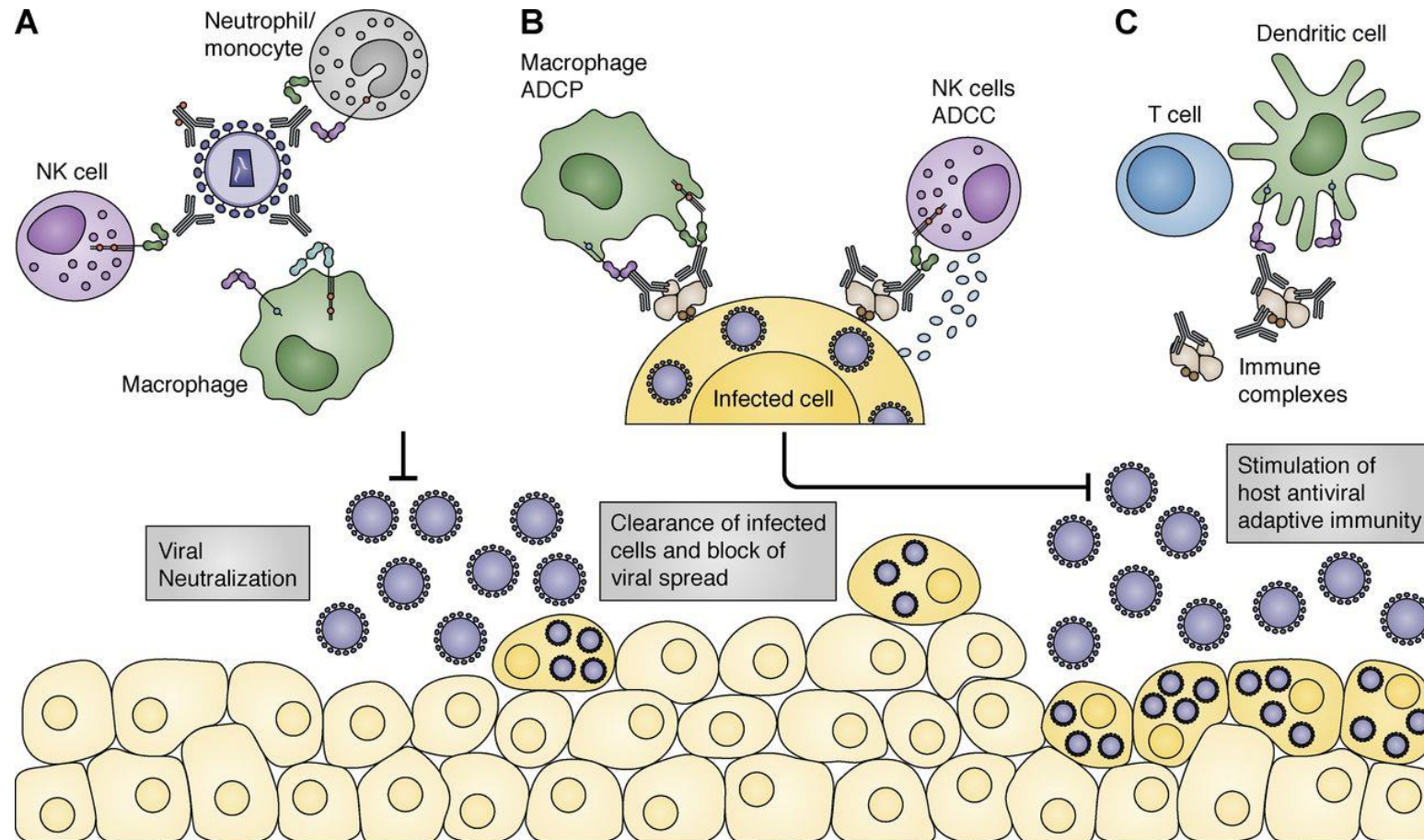
bNAb escape variants remain sensitive to antibodies targeting different Env epitopes



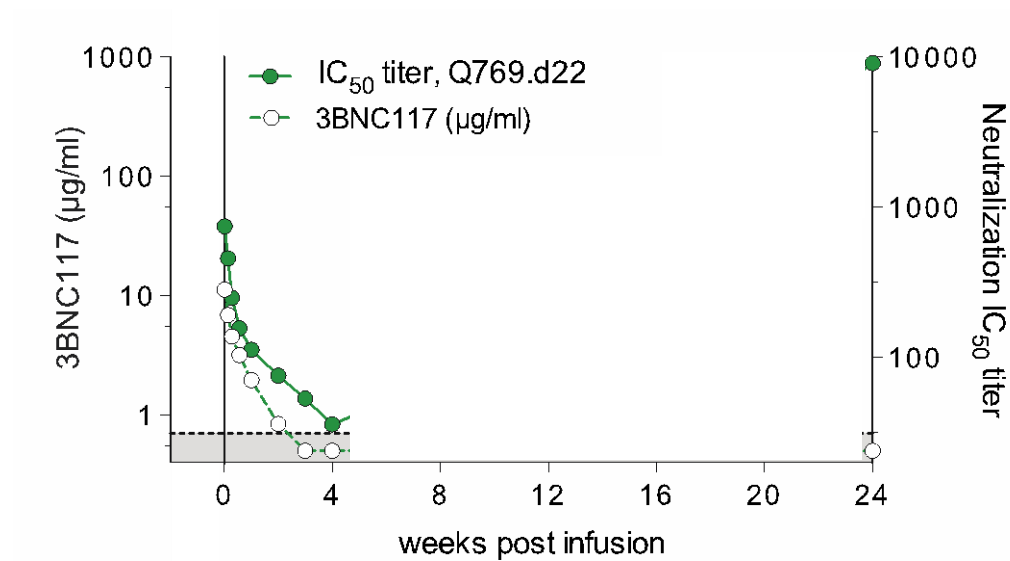
3BNC117 plus 10-1074 Combination ATI Study



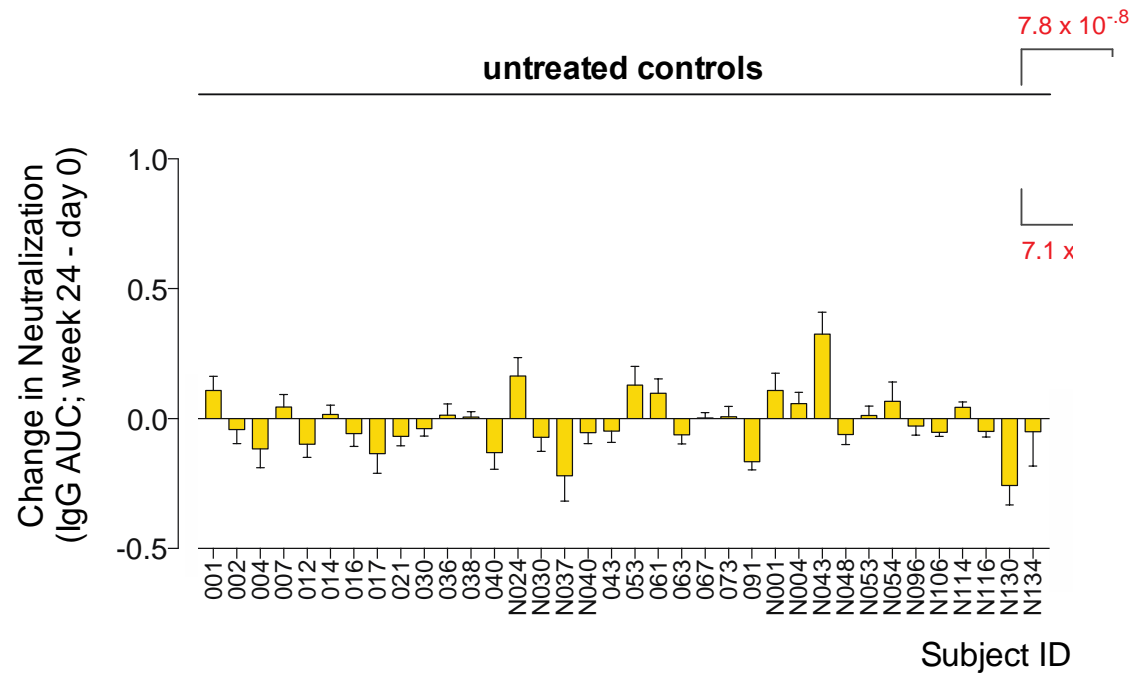
Antibodies differ from standard ART in their potential to directly eliminate HIV-infected cells and enhance host immune responses



Neutralization of tier 2 virus develop after 3BNC117 infusion in a viremic HIV-infected individual

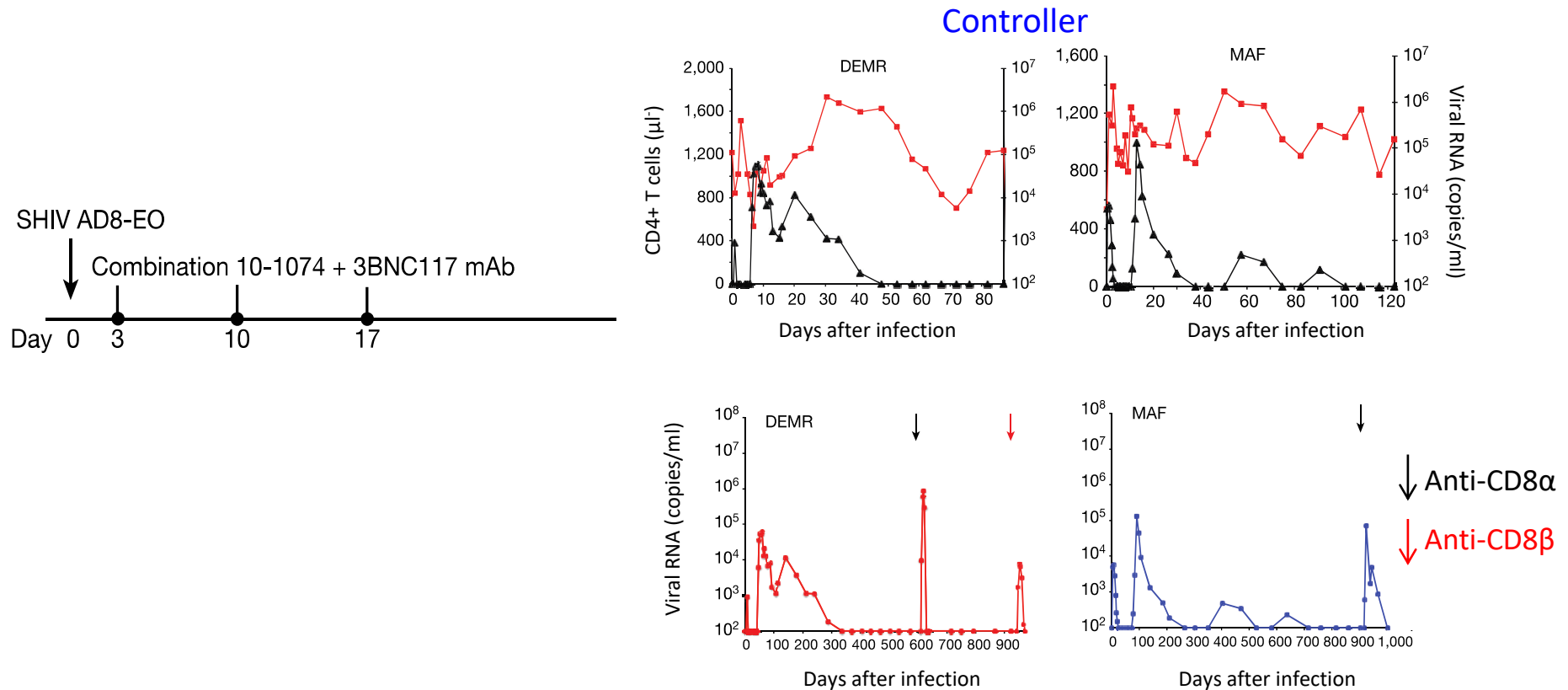


3BNC117 enhances host humoral immunity to heterologous tier 2 HIV-1 viruses

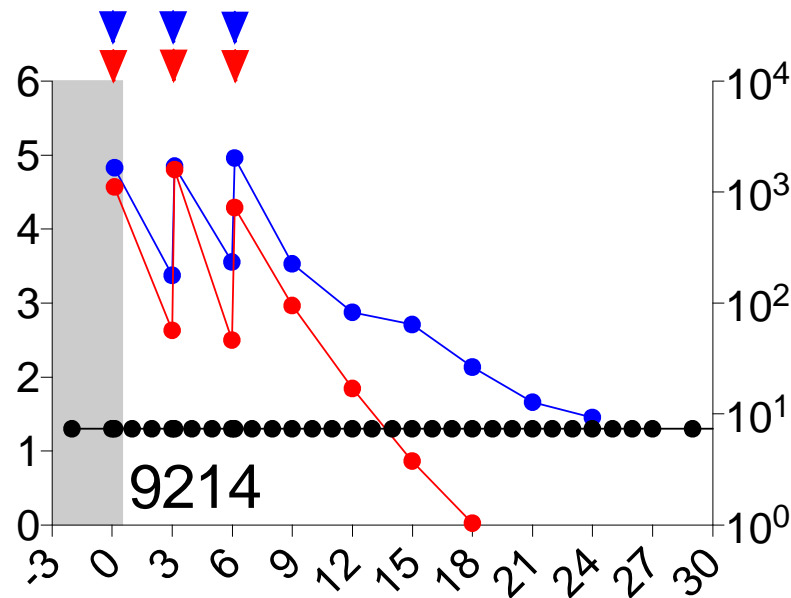


- Both a **'vaccinal effect'** and **responses to newly evolving epitopes** probably contribute to the enhancement of humoral immune responses.

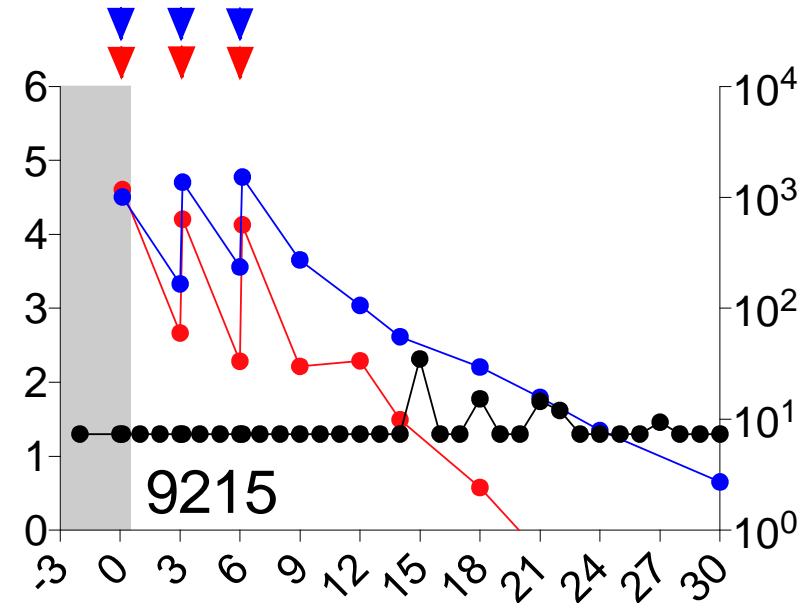
Early antibody therapy leads to CD8-mediated control of SHIV infection in NHP



Two participants continue to maintain viral suppression after both 3BNC117 and 10-1074 have been cleared



- IUPM – 0.68
- ART initiated 4-5 mo of infection
- On ART x 21 years.
- VL > 800K at start of ART
- HLA-A*1 and A*29
B*38 and B*44



- IUPM – 1.8 > 1.4
- ART initiated ~ 7 mo after Dx
- On ART x 4 years.
- VL > 80K at start of ART
- HLA-A*3 and A*25
B*18 and B*44

➤ No detectable levels of ART in blood

Summary

- **bNAbs engage the host immune system** (through ADCC and increased antigen presentation), and **enhance host humoral responses**.
 - 3BNC117 mediates direct cell killing in hu-mice (Lu et al, Science 2016)
 - Kinetics of viral suppression after 3BNC117 in viremic individuals suggested acceleration of infected cell clearance, in addition to clearance of free viruses (Lu et al, Science 2016).
 - 3BNC117 enhanced humoral immune responses in HIV-infected individuals (Schoofs et al, Science 2016).
- During early SHIV-AD8 infection, 3BNC117+10-1074 mediated long-term virologic control in a subset of animals. Long-term control was dependent on CD8+ T cells (Nishimura et al, Nature 2017).
- Two participants in the 3BNC117/10-1074 combination ATI study continue to maintain suppression after both antibodies have cleared. One of them has experienced several low level viral blips, followed by re-suppression. Evaluation of immune responses is ongoing.
- Studies combining bNAbs with LRAs (HDAC inhibitor, TLR agonists) or therapeutic vaccines are planned.

bNAb Immunotherapy - Challenges

- Pre-existing resistance in HIV-infected individuals
 - Are *in vitro* neutralization data from large pseudoviruses panels predictive?
 - Cohen, Lorenzi et al, J Virol 2018
 - How to determine antibody sensitivity in HIV-infected individuals?
 - Monogram's Pheno-Sense assay
 - What is the cut-off IC_{50} that defines "sensitivity" *in vivo*?
 - What is the optimal IC_{50} / bNAb level ratio?
- Viral escape during monotherapy.
 - Will 2 bNAbs be sufficient long-term?
- Penetration in tissues to interfere with latent reservoirs
- Immunogenicity

Modified Antibodies – Future Studies

- **Increase potency:** structure-based design (Fab region)
 - > VRC07-523-LS
- **Increase breadth:** bi-specific and tri-specific antibodies
 - > iMab/10e8v2.0
 - > SAR441236 (VRC01/10E8v4-PGDM1400-LS)
- **Increase bioavailability:** LS mutations and alternative delivery systems (AAV-vectors)
 - > VRC01-LS, VRC07-523LS, 3BNC117-LS
 - > rAAV1-PG9DP
- **Increase Fc effector functions:** Fc-mutations and multifunctional molecules
 - > BiTE, DART, VRC07-aCD3
 - > GASDALIE
- **Reduce potential for anti-drug antibody responses**

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Study participants

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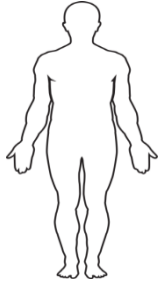
Kathy Anastos

Harris Goldstein

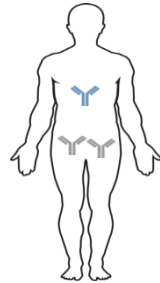
Supported by: BMGF, NIH/NIAID, RU CCTS (NCATS), Robertson Foundation, The Rockefeller University

Broadly neutralizing antibodies are generated during HIV infection

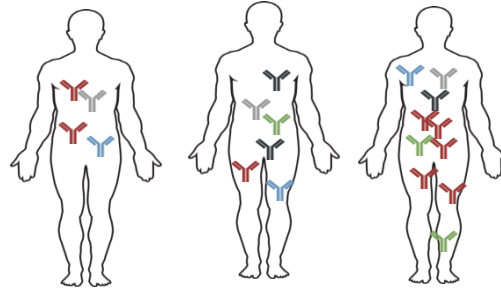
Transmission



Acute infection



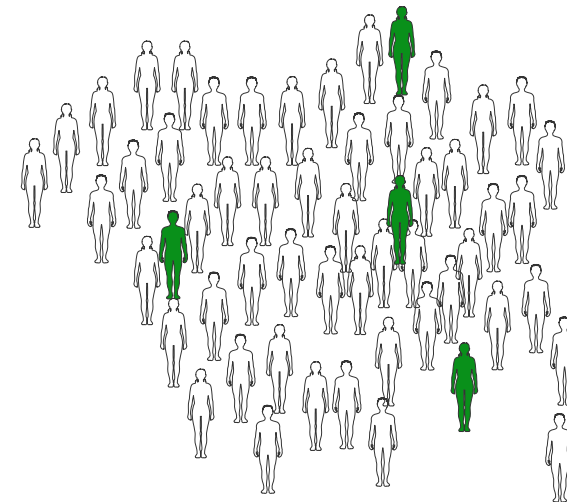
Chronic infection



Continuous interplay of autologous virus escape and antibody maturation

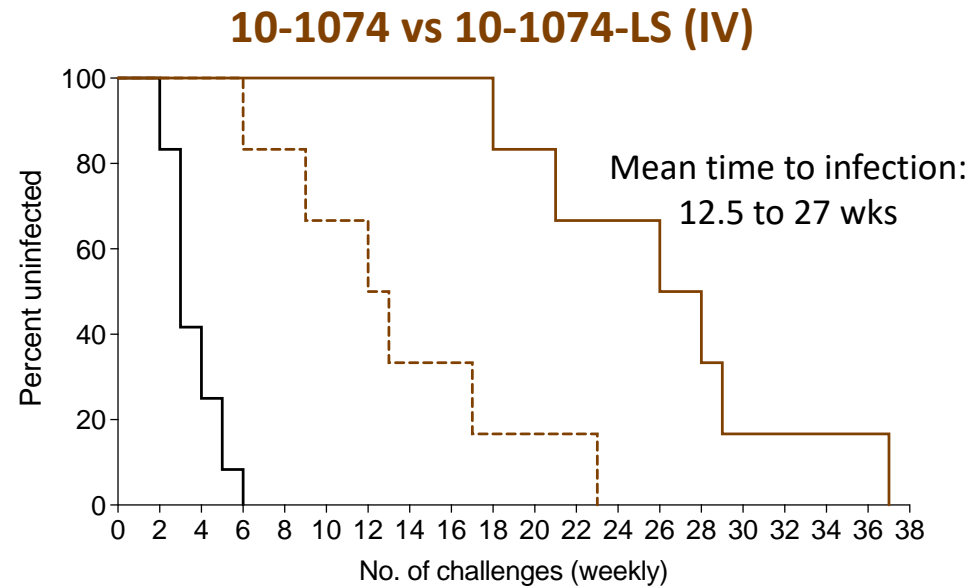
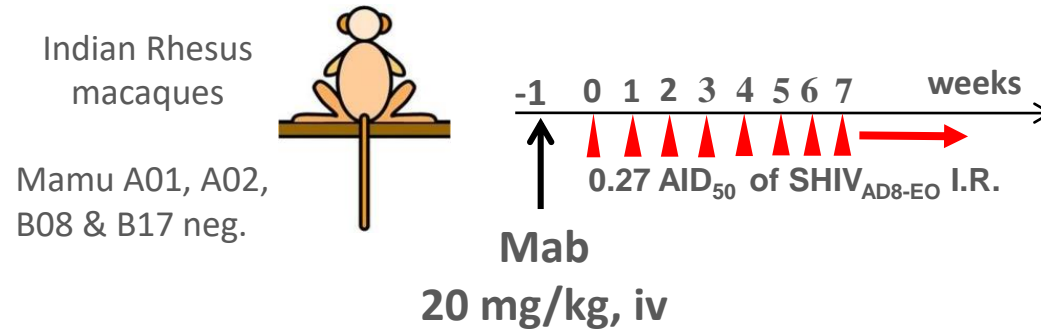
Increase in heterologous (cross) neutralization activity - breadth

10-20% of HIV+ individuals eventually develop broadly neutralizing serum antibodies



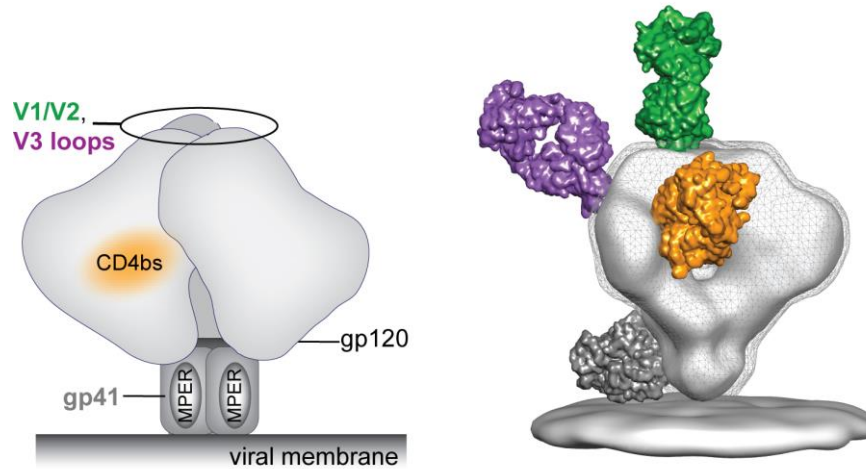
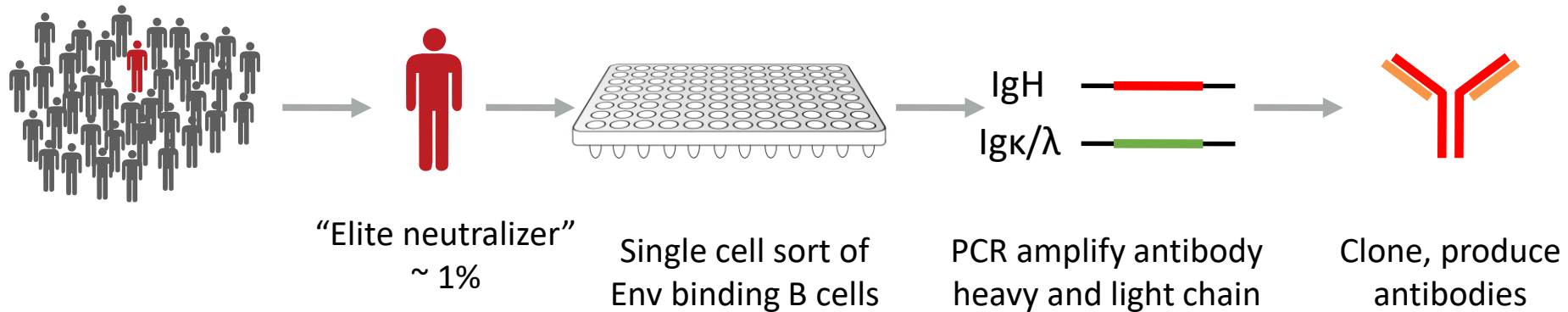
Fc modifications to prolong half-life: LS

M428L/N434S



LS-antibodies significantly delay virus acquisition in NHP during repeated low-dose rectal challenges

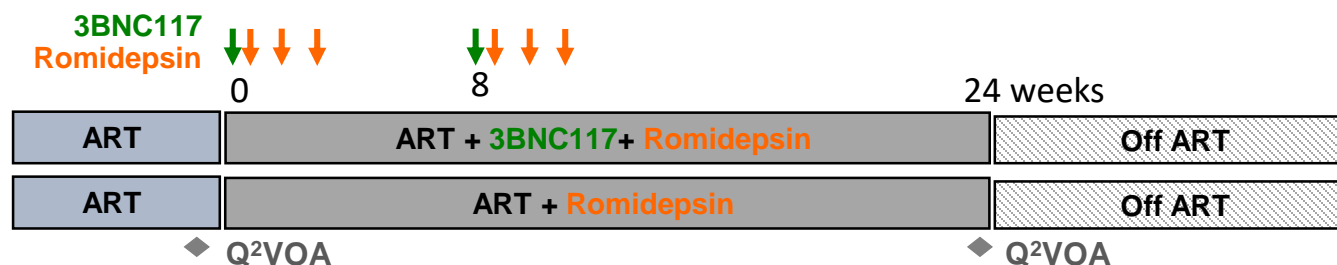
Identification of broadly neutralizing antibodies



CD4 binding site	Glycan-V3	V1/V2 loop	MPER	gp120/gp41-interface	others
b12, VRC01, 3BNC117, NIH45-46, 8ANC131, 1NC9, 12A12, CH31, CH103, PGV04, HJ16, CH235, N6	PGT121-124, 10-1074, PGT128, PGT135, VRC24, 2G12, DH270	PG9, PG16, CH01, PGT145, CAP256.VRC26, PGDM1400	4E10, 2F5, 10E8, DH511	8ANC195, 35O22, ACS202, PGT151, N123-VRC34.01	3BC176, 3BC315

Do bNAbs interfere with the latent reservoir?

- 3BNC117 plus romidepsin or romidepsin alone during ART suppression



- 3BNC117 plus 10-1074 in the presence or absence of ART suppression

