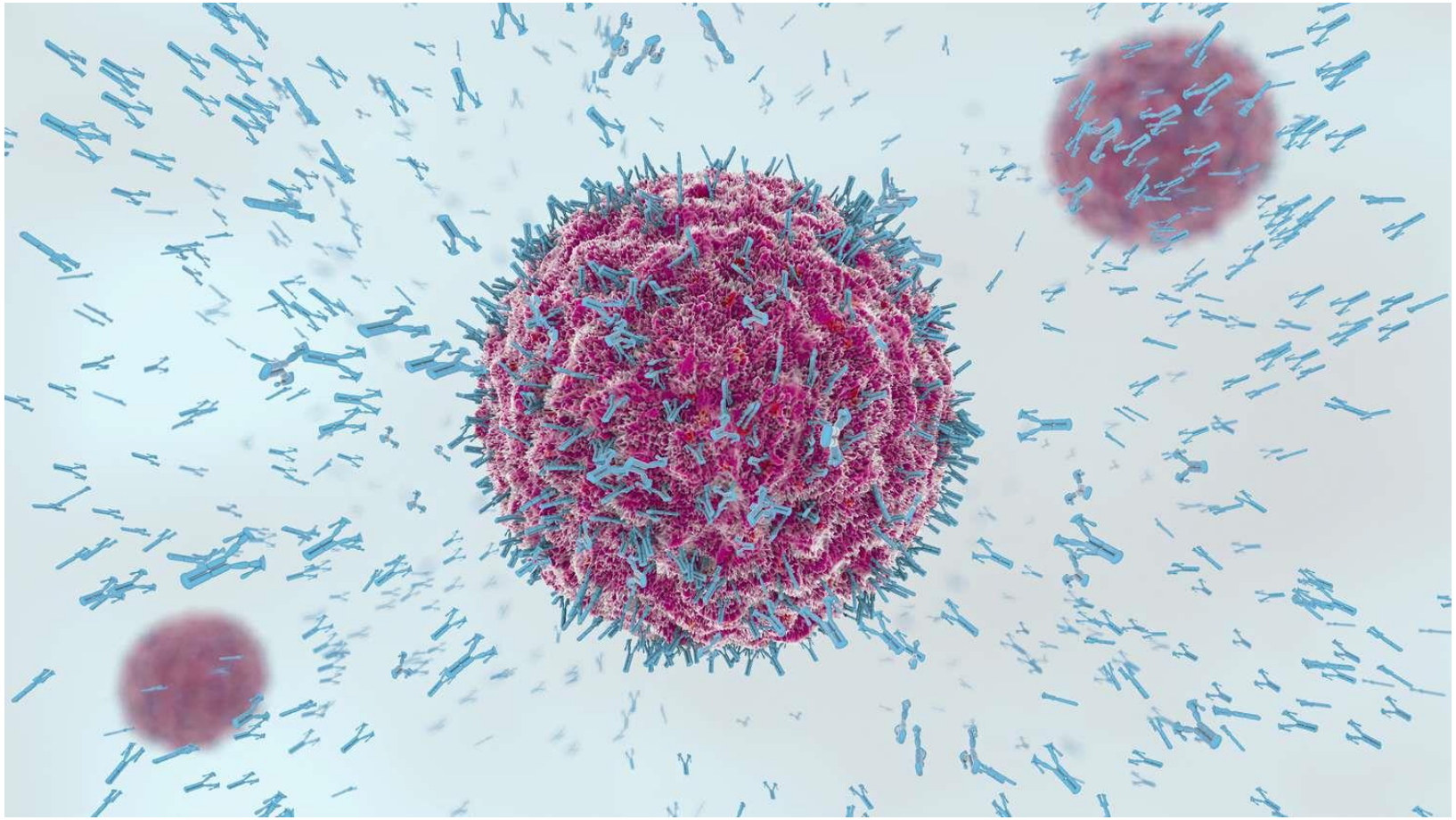
Broadly neutralizing antibodies – not prime time yet



Disclosures:

- Every HIV pharmaceutical company

- CTN, OHTN, NIH, CIHR, European funding agencies, Believe
- REACH, CanCURE,

Combination Therapy with HIV-Specific Broadly Neutralizing Antibodies

Prolonged Viral Suppression with Anti-HIV-1 Antibody Therapy

C Gaebler, L Nogueira, E Stoffel, TY Oliveira, G Breton, KG Millard, M Turroja, A Butler, V Ramos, MS Seaman, JD Reeves, CJ Petroupoulos, I Shimeliovich, A Gazumyan, CS Jiang, N Jilg, JF Scheid, R Gandhi, BD Walker, MC Sneller, AS Fauci, TW Chun, M Caskey & MC Nussenzweig

Combination Anti-HIV Antibodies Provide Sustained Virologic Suppression

MC Sneller, J Blazkova, JS Justement, V Shi, BD Kennedy, K Gittens, J Tolstendo, G McCormack, EJ Whitehead, RF Schneck, MA Proschan, E Benko, C Kovacs, C Oguz, MS Seaman, M Caskey, MC Nussenzweig, AS Fauci, S Moir & TW Chun

Combination Therapy with HIV-Specific Broadly Neutralizing Antibodies

OHTN
J Bacon

Prolonged Viral Suppression with Anti-HIV-1 Antibody Therapy

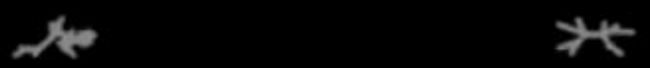
Teropavimab

Zinlirvimab

Combination Anti-HIV Antibodies Provide Sustained Virologic Suppression

MC Sneller, J Blazkova, JS Justement, V Shi, BD Kennedy, K Gittens, J Tolstendo, G McCormack, EJ Whitehead, RF Schneck, MA Proschan, E Benko, C Kovacs, C Oguz, MS Seaman, M Caskey, MC Nussenzweig, AS Fauci, S Moir & TW Chun

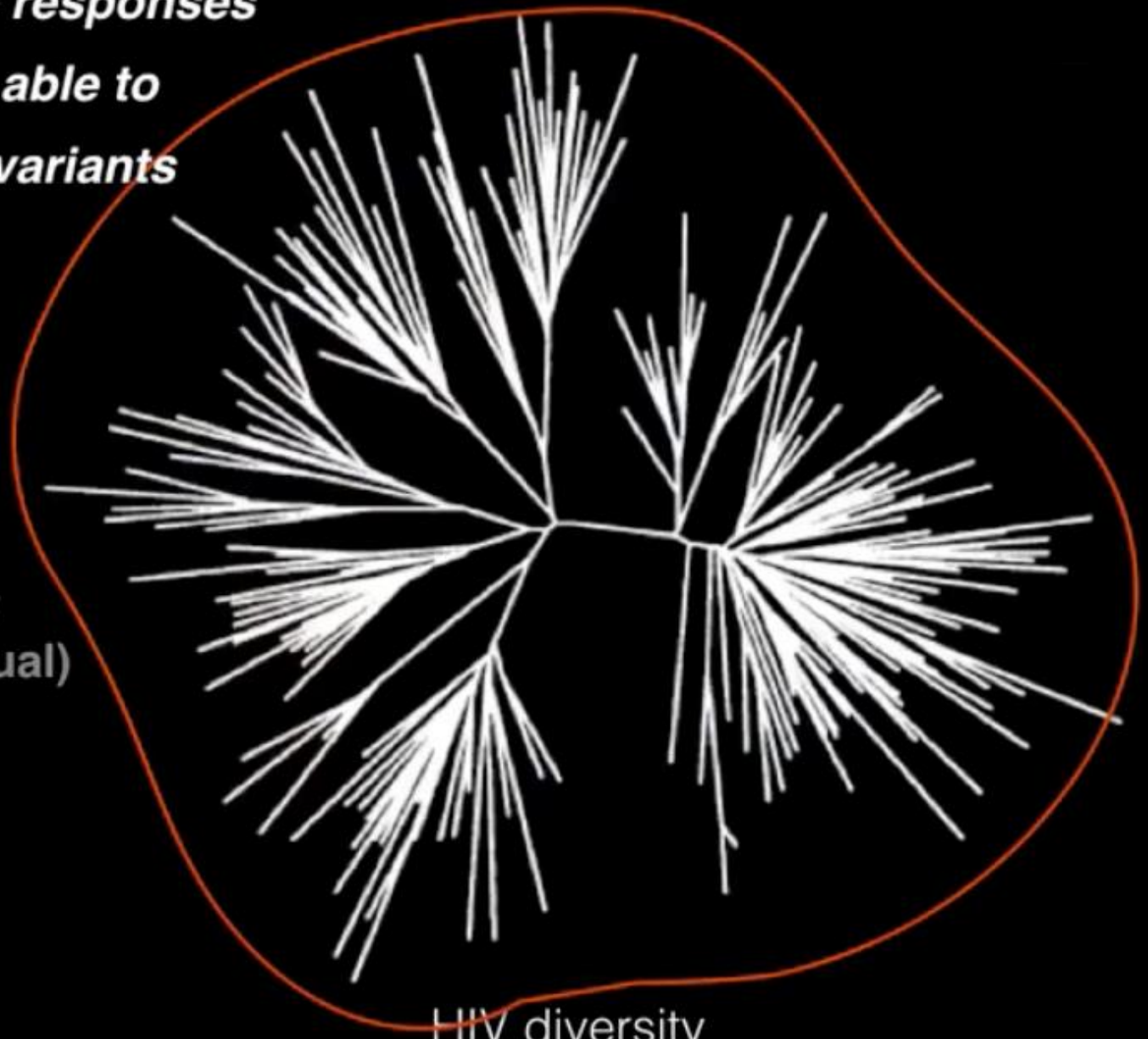
Rare individuals develop immune responses with significant "BREADTH", able to neutralize up to ~95% of viral variants



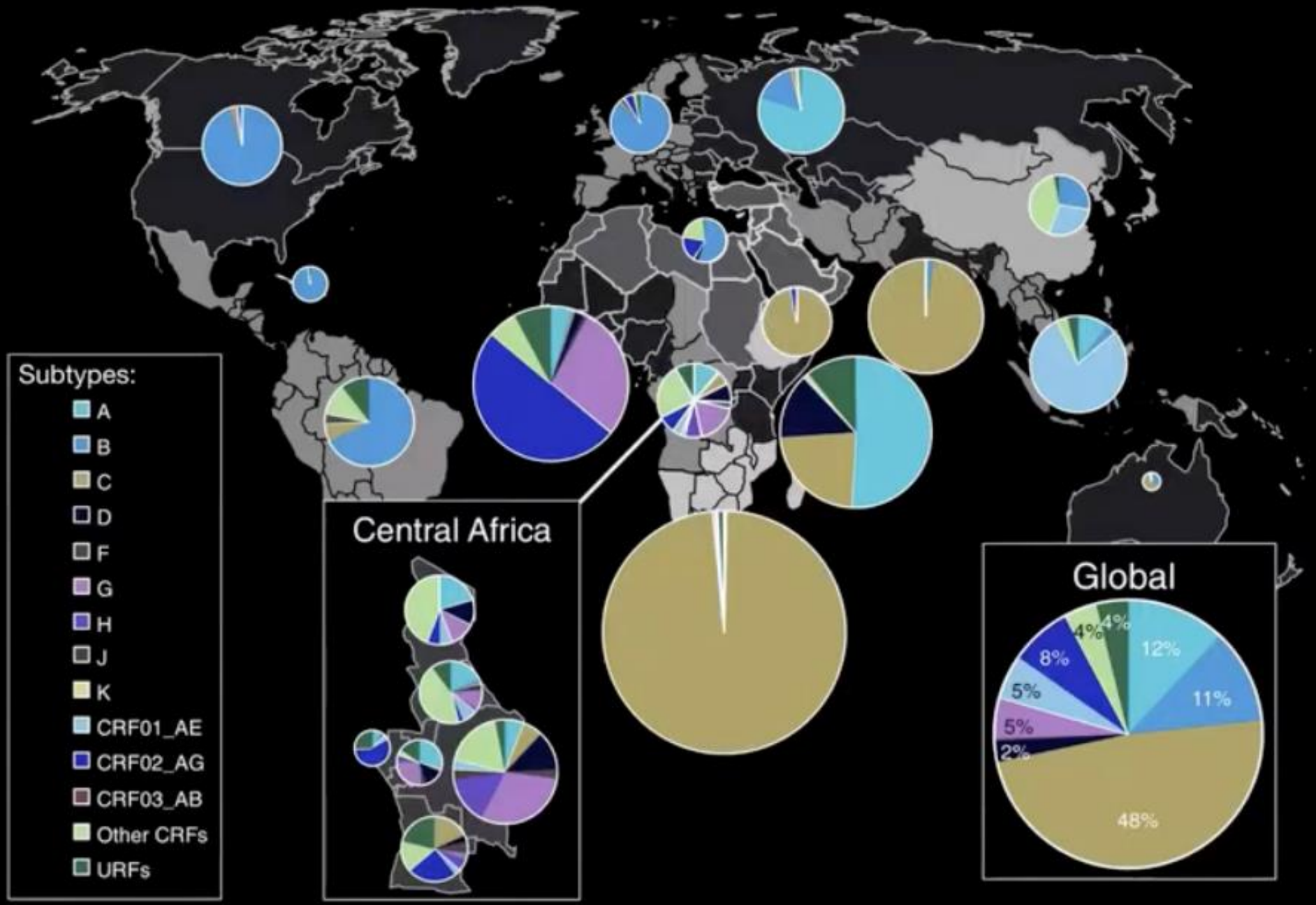
Influenza diversity in human population **(Global 1996)**

HIV diversity **(Single Individual)**

0.10



HIV diversity **(Democratic Republic of Congo 1996)**


Subtypes:
A
B
C
D
F
G
H
J
K
CRF01_AE
CRF02_AG
CRF03_AB
Other CRFs
URFs
Central Africa
Global
12%
11%
48%
2%
5%
5%
8%
4%
4%

Key Sites of Neutralization-Sensitivity on HIV-1 gp160

What immune systems sees -- Env

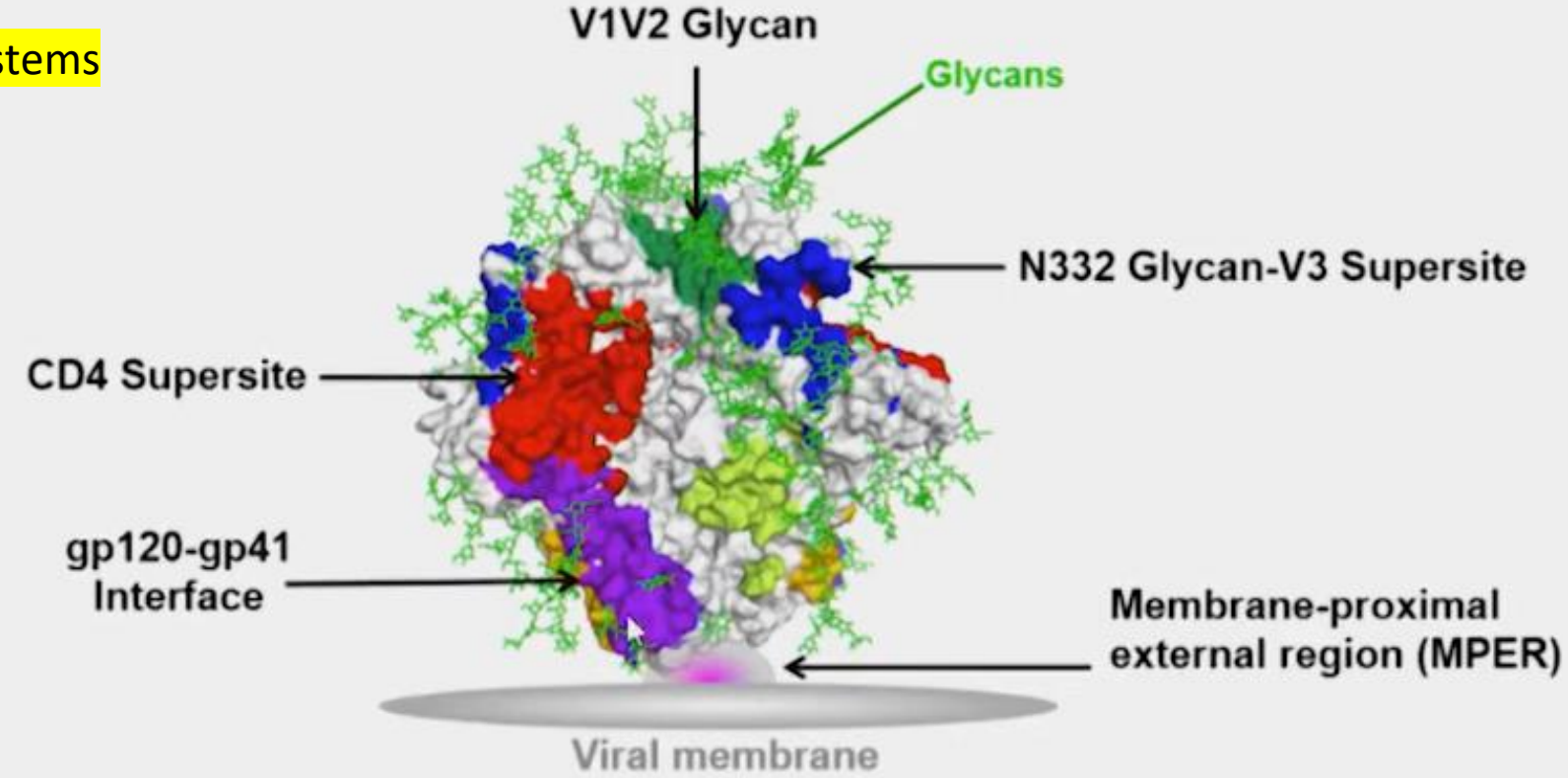
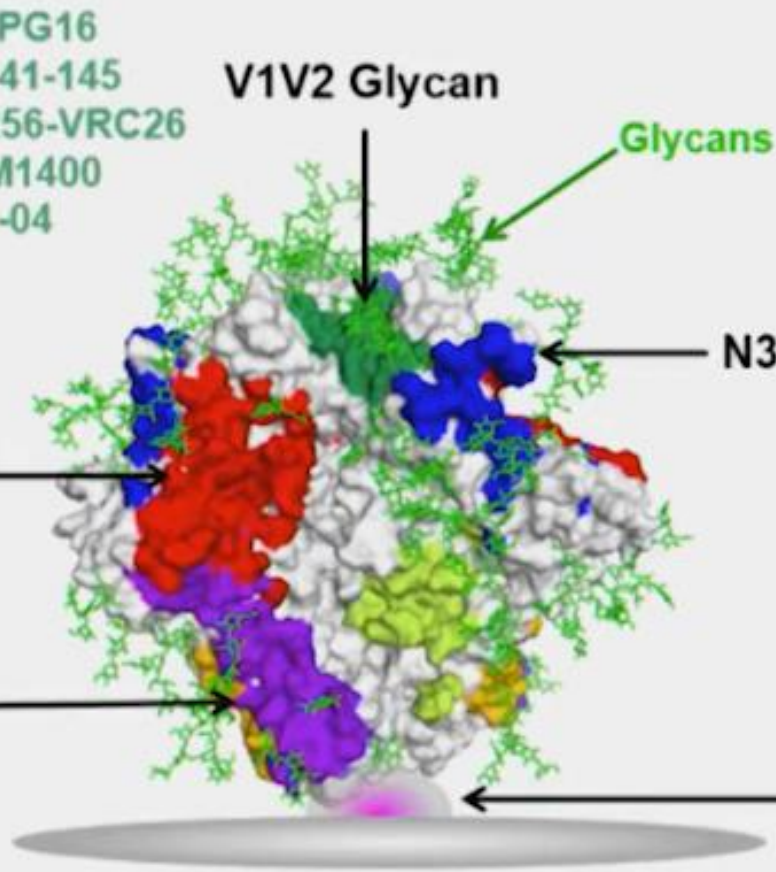
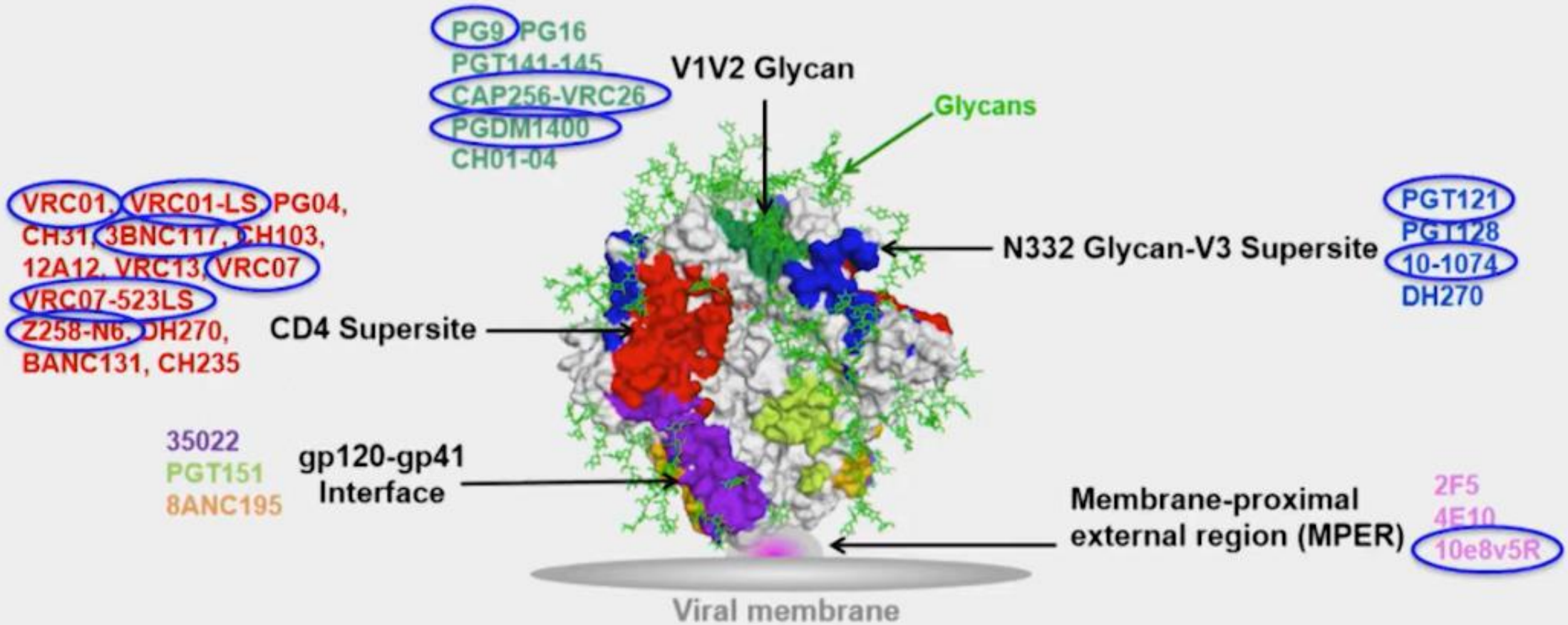


Image by Stewart-Jones, Doria-Rose, Stuckey

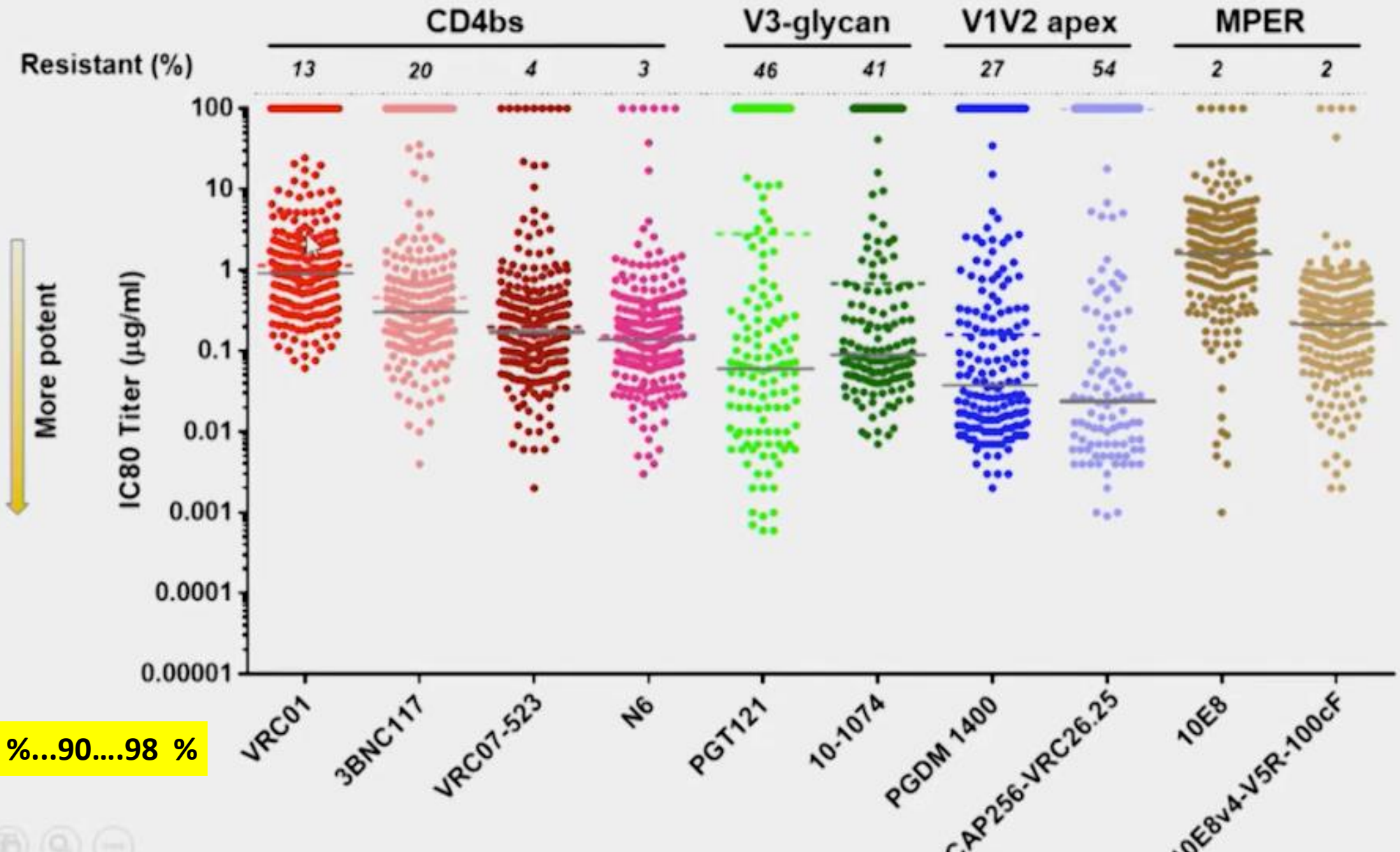
Broadly Neutralizing mAbs in Development



Broadly Neutralizing mAbs in Development



Antibodies with Improved Potency/Breadth

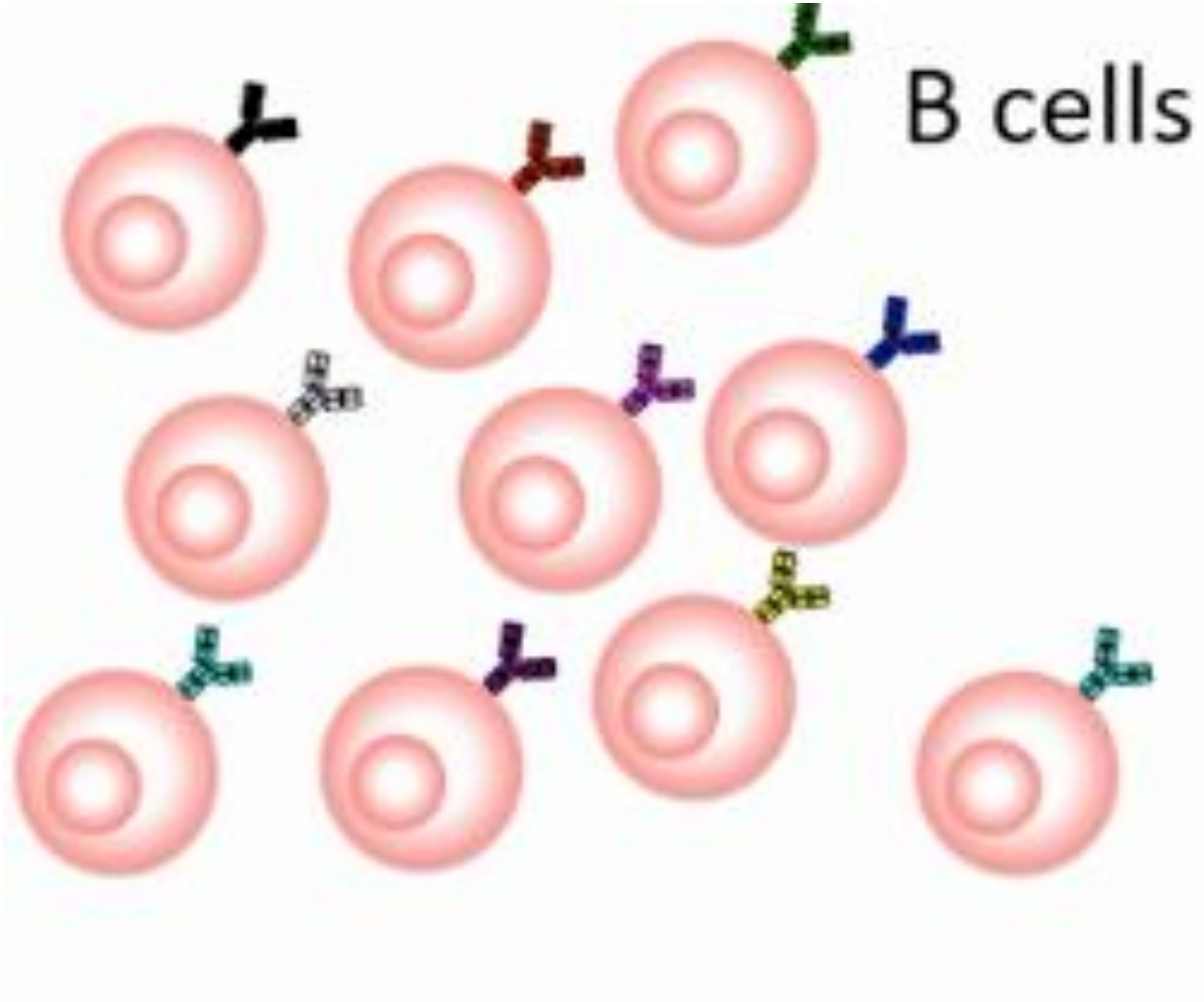


80 %...90....98 %

Naïve B cells

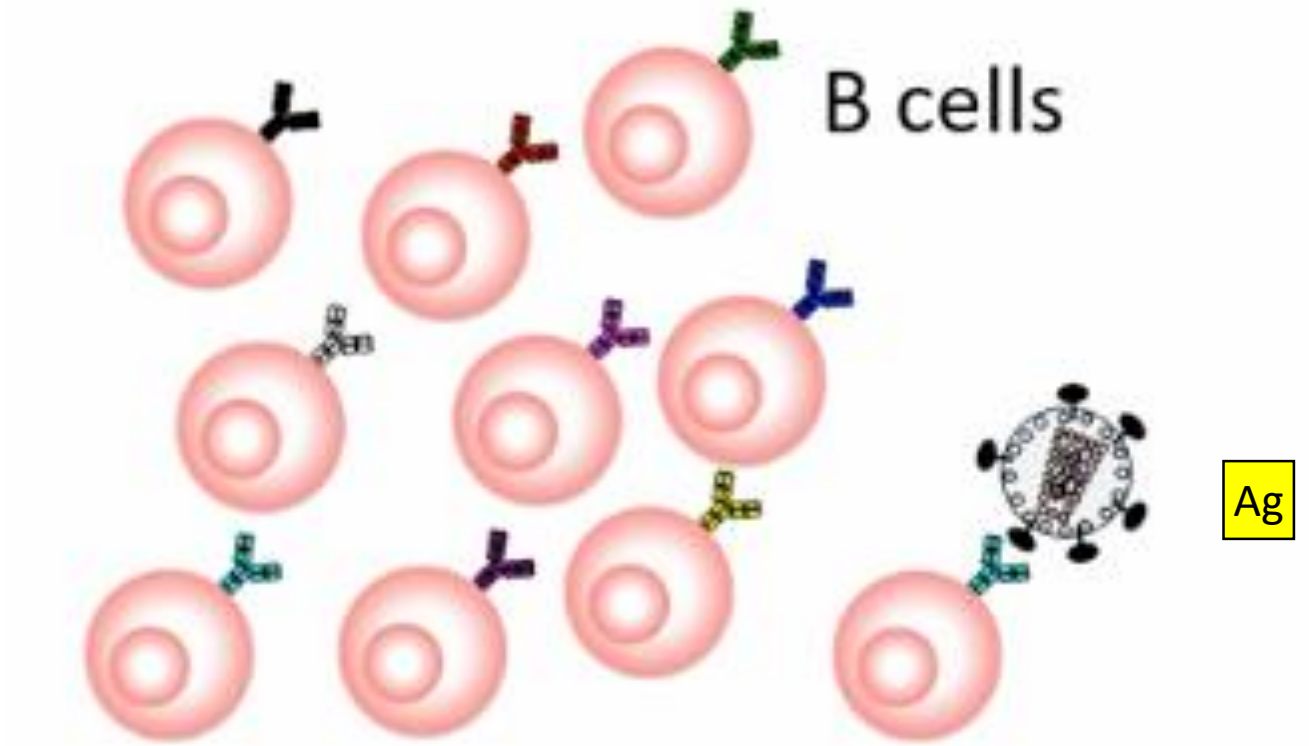
Repertoire: 10_{18}

total # B cells: 10_{11}



- encounters Ag

- Initially low affinity IgM
- Less specific

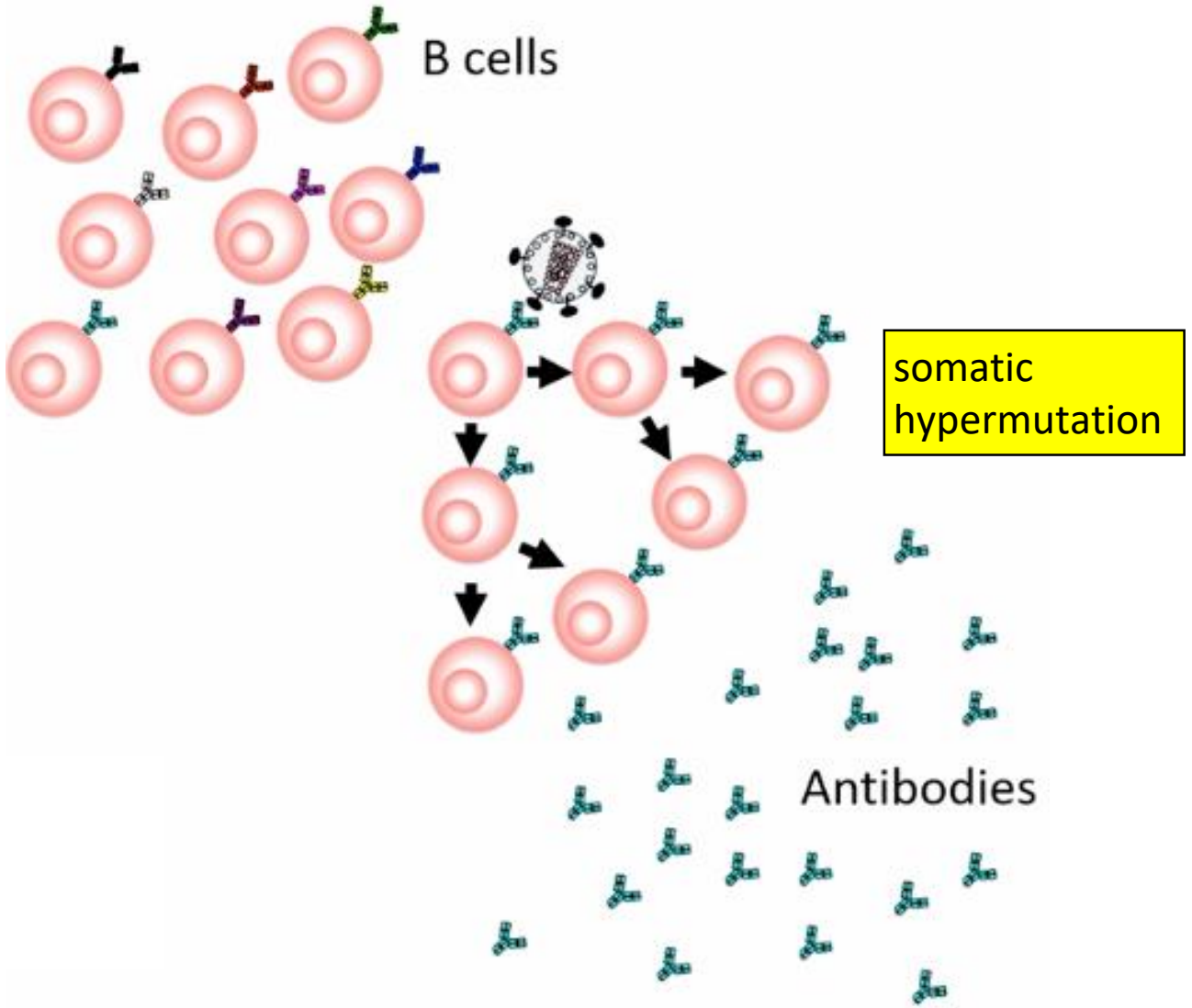


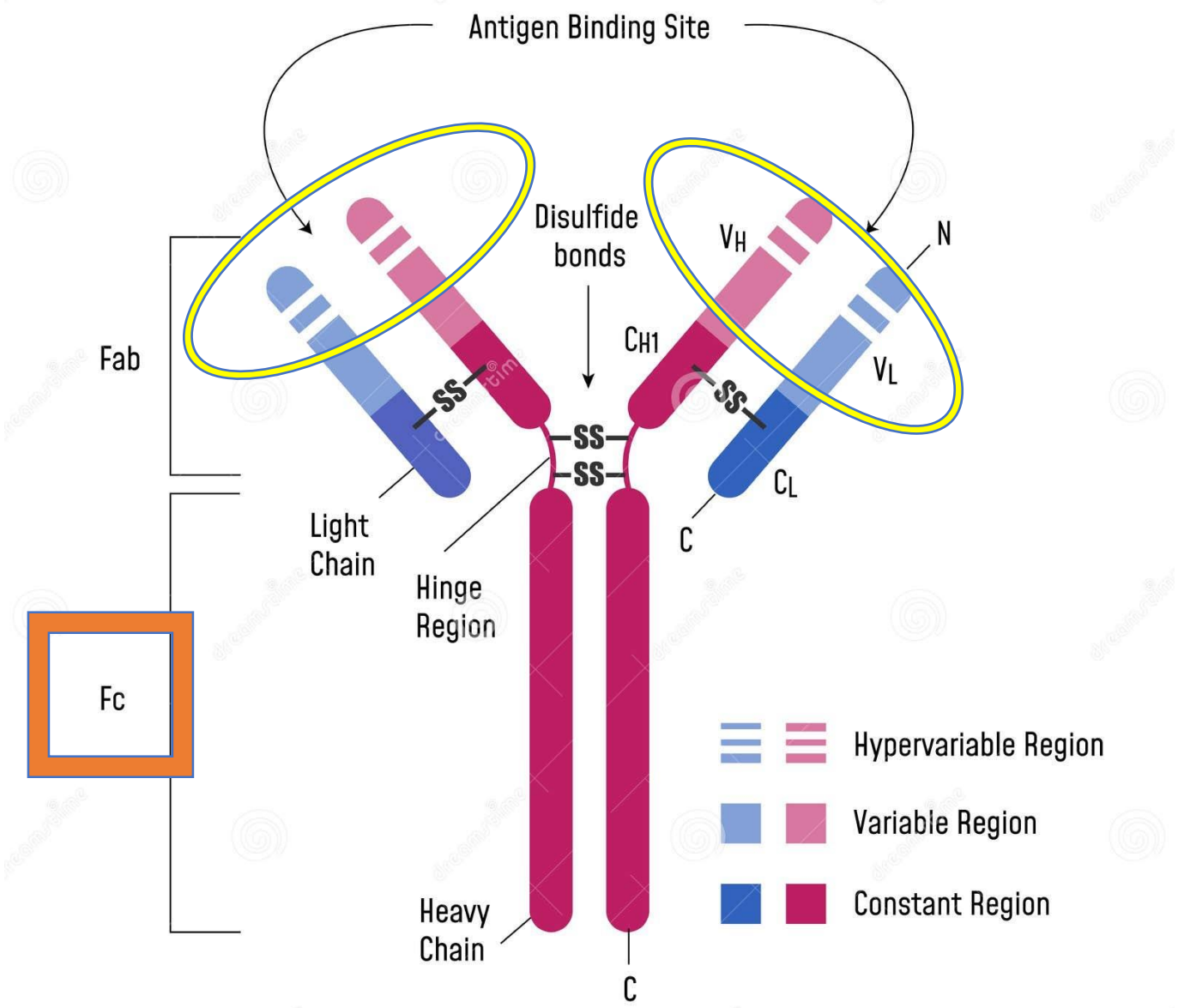
- Somatic mutation

  mutations B cell genome

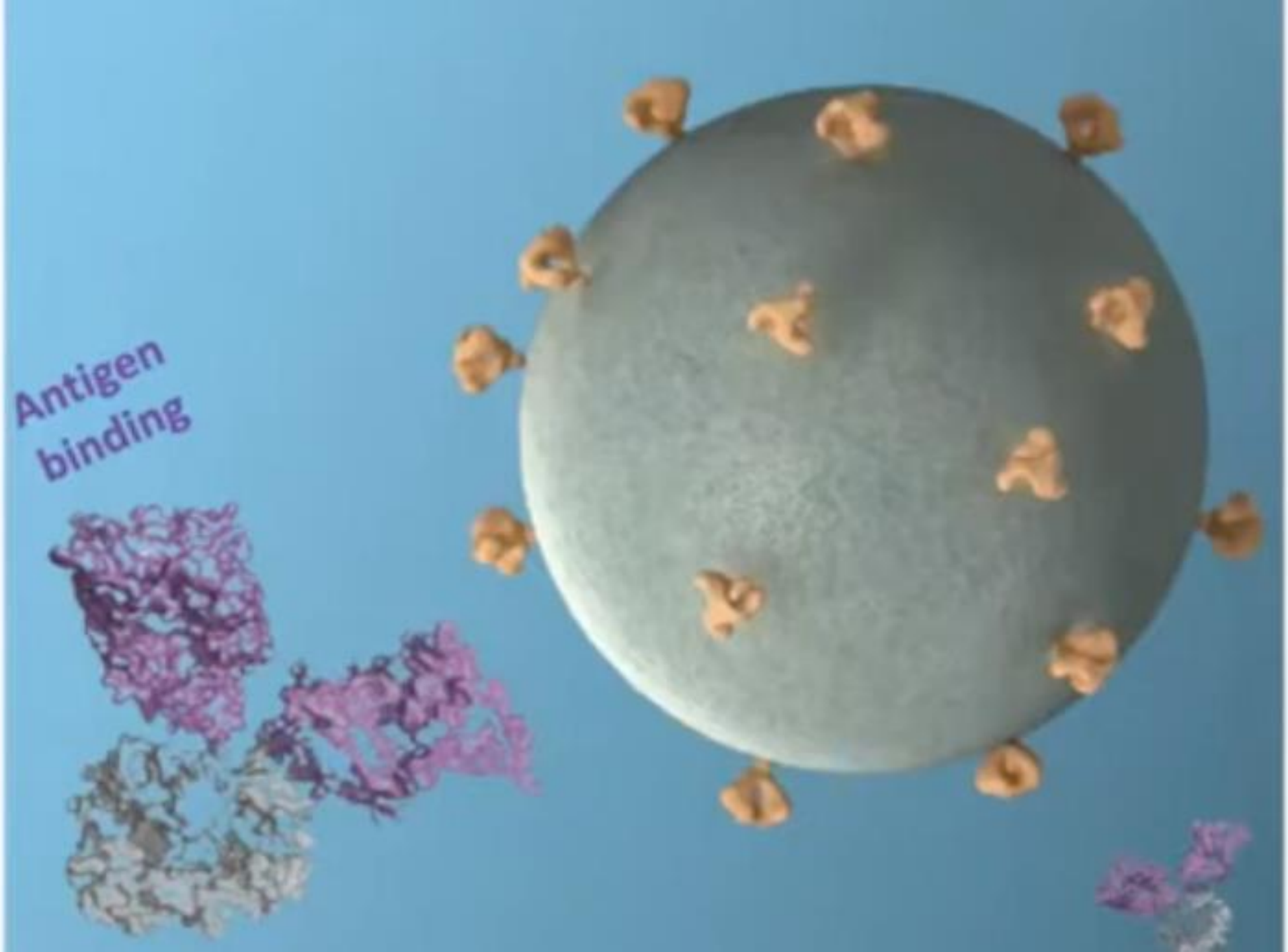
- > affinity ….> breath

- Form. bNAb

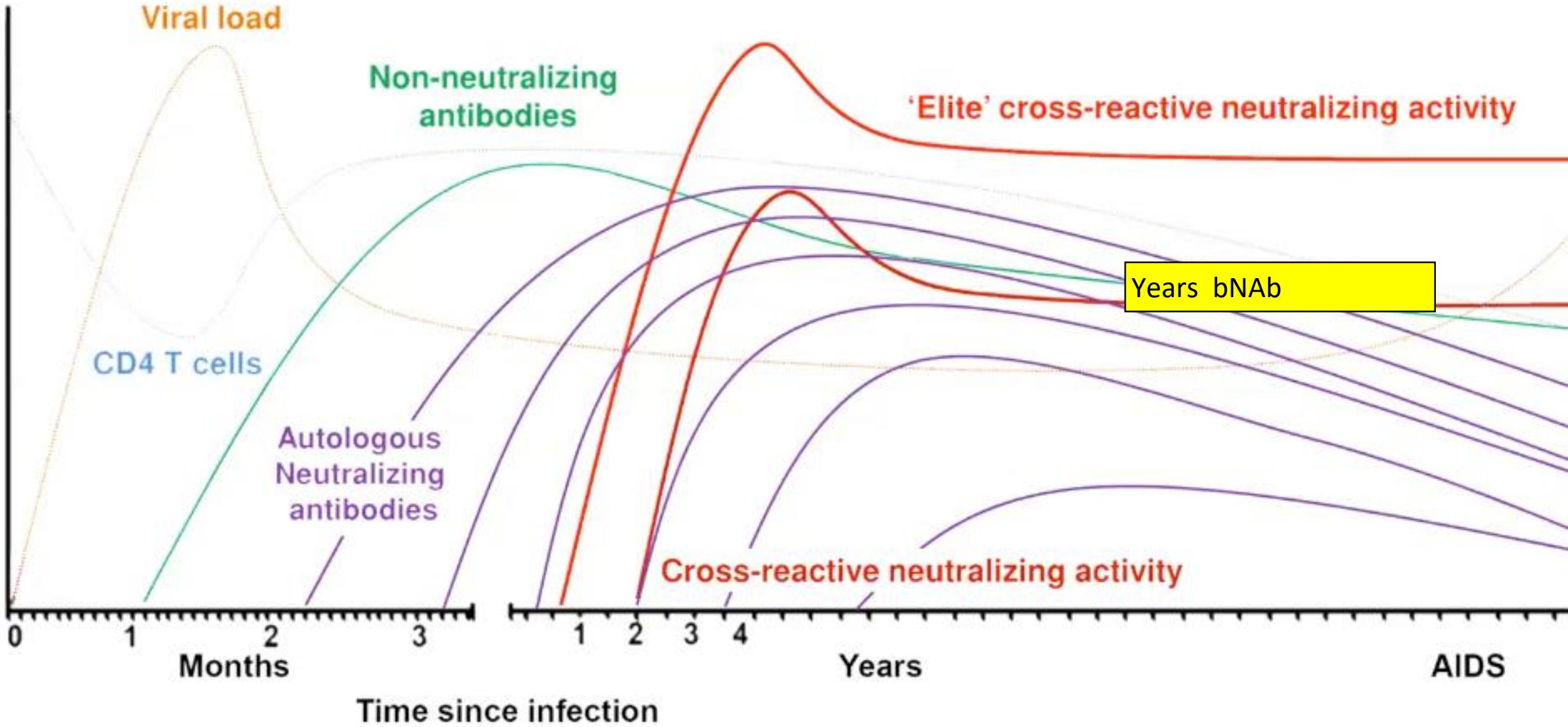




Selection
improved affinity


Antigen
binding

Autologous nAb response to HIV-1 infection



REVIEW Open Access

Development of broadly neutralizing antibodies in HIV-1 infected elite neutralizers

Elise Landais[1,2,3] and Penny L. Moore[4,5,6*]

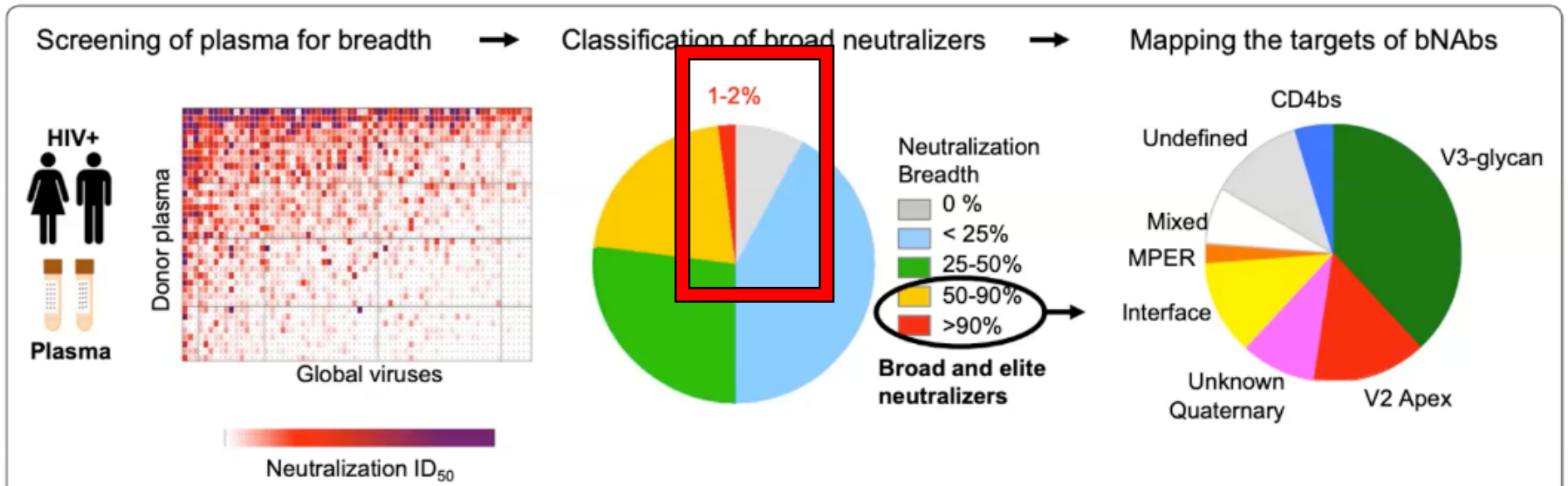
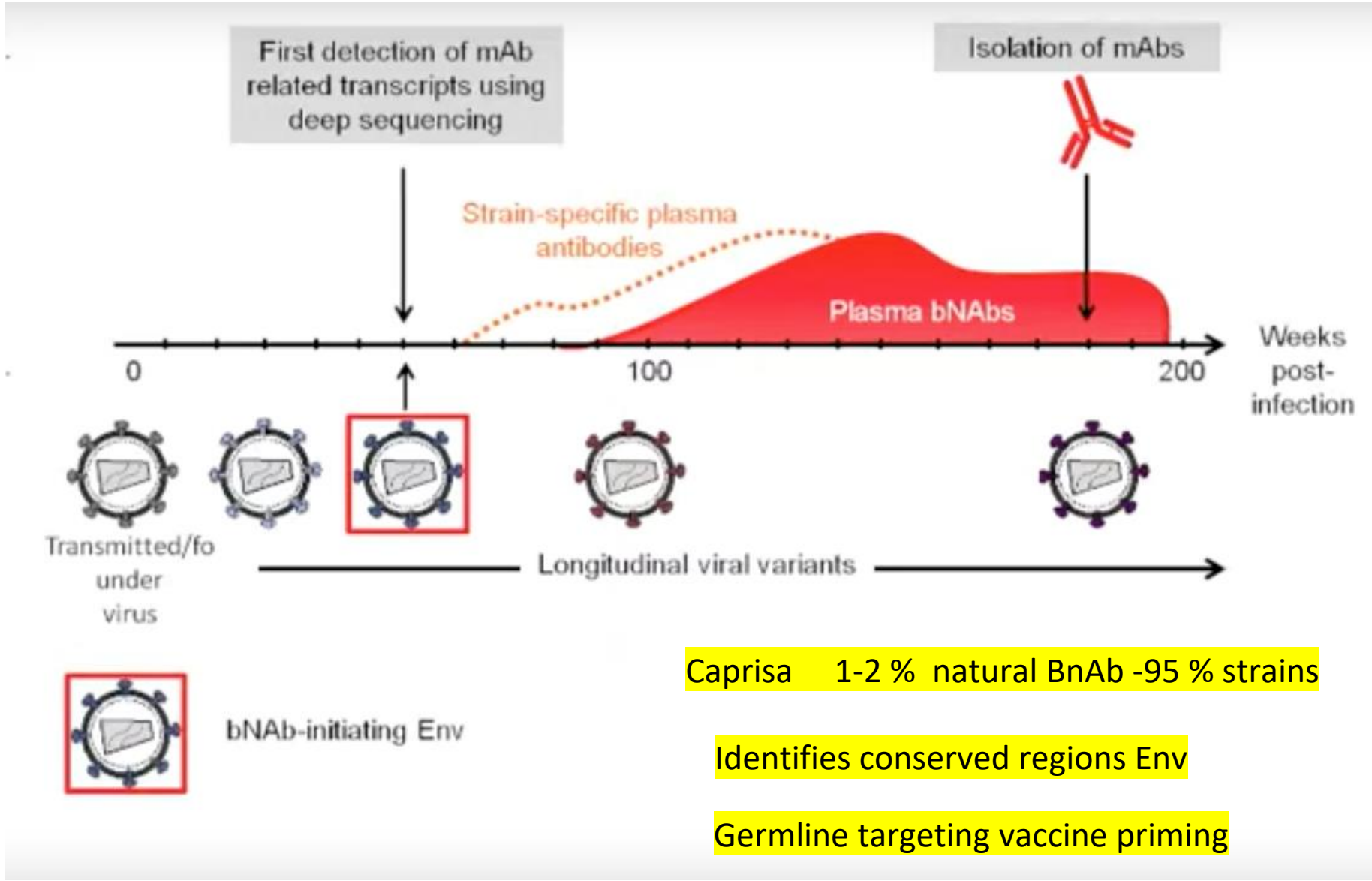


Fig. 1 Identification of HIV-1 elite neutralizers and epitope mapping. Typically, plasma samples collected from HIV-1 infected individuals are tested for neutralization against panels of global env-pseudotyped viruses. Volunteers are ranked based on a their neutralization breadth and potency. The broad neutralizing activity in the top neutralizers is then mapped for epitope specificity using mutant viruses, and peptide and protein adsorptions. Reproduced with permission from [21]



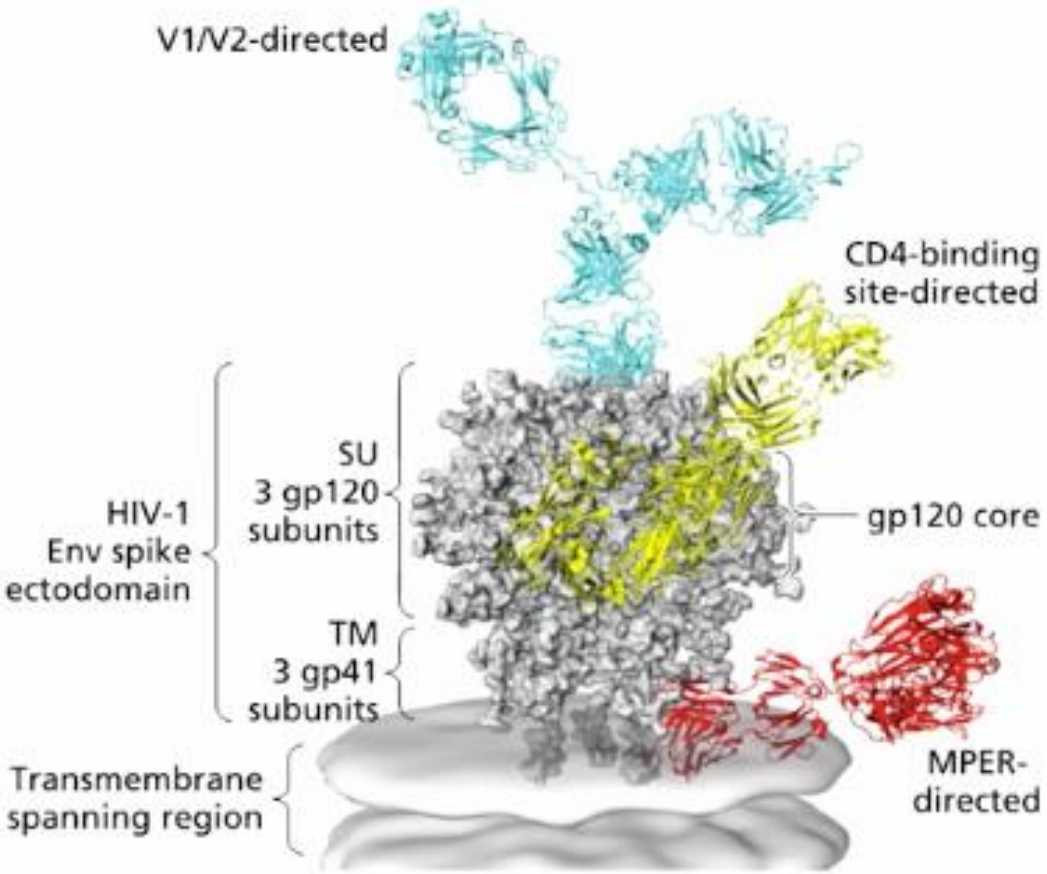
Caprisa 1-2 % natural BnAb -95 % strains

Identifies conserved regions Env

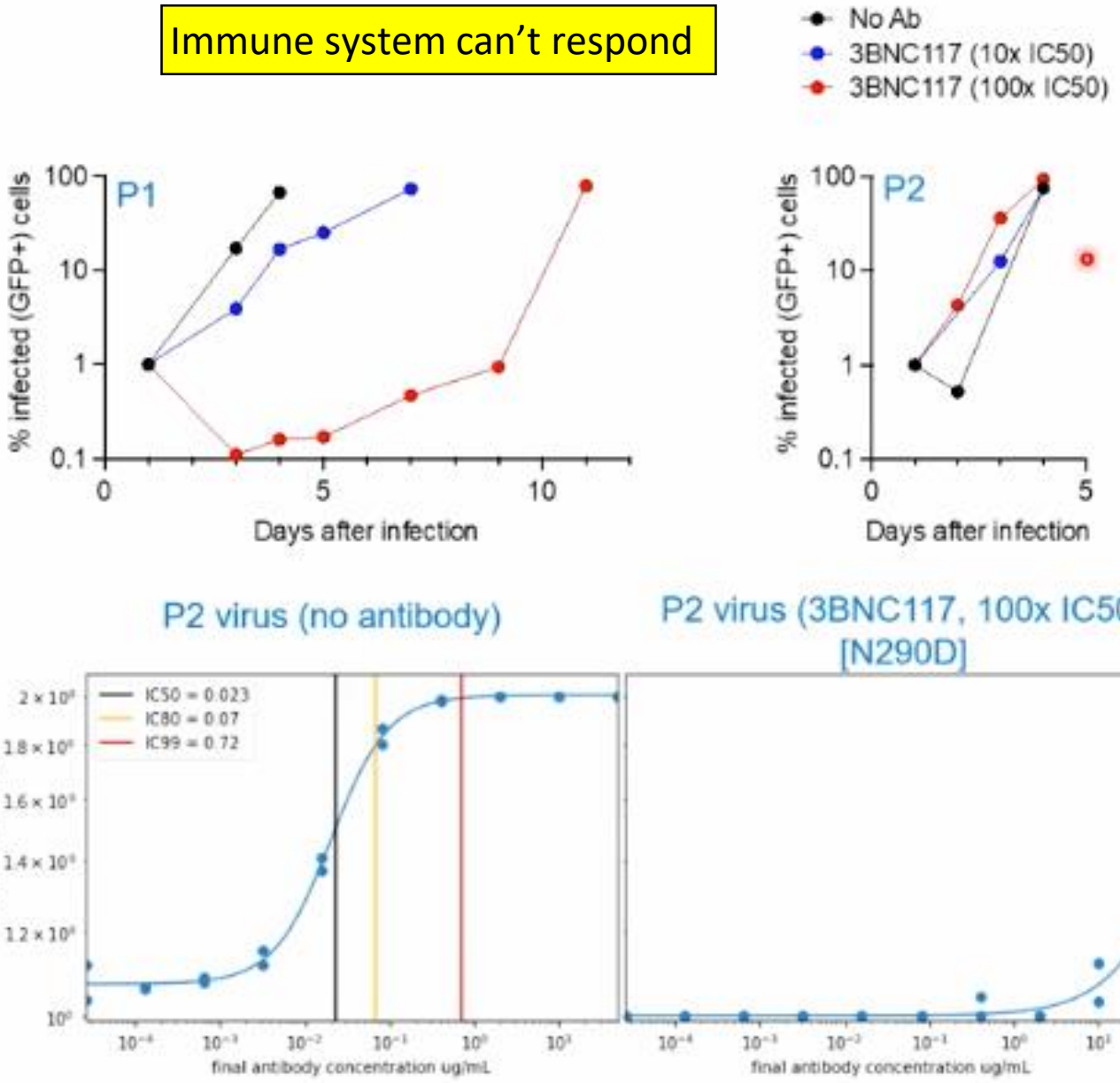
Germline targeting vaccine priming

Neutralizing antibodies and acquisition of resistance (HIV-1)

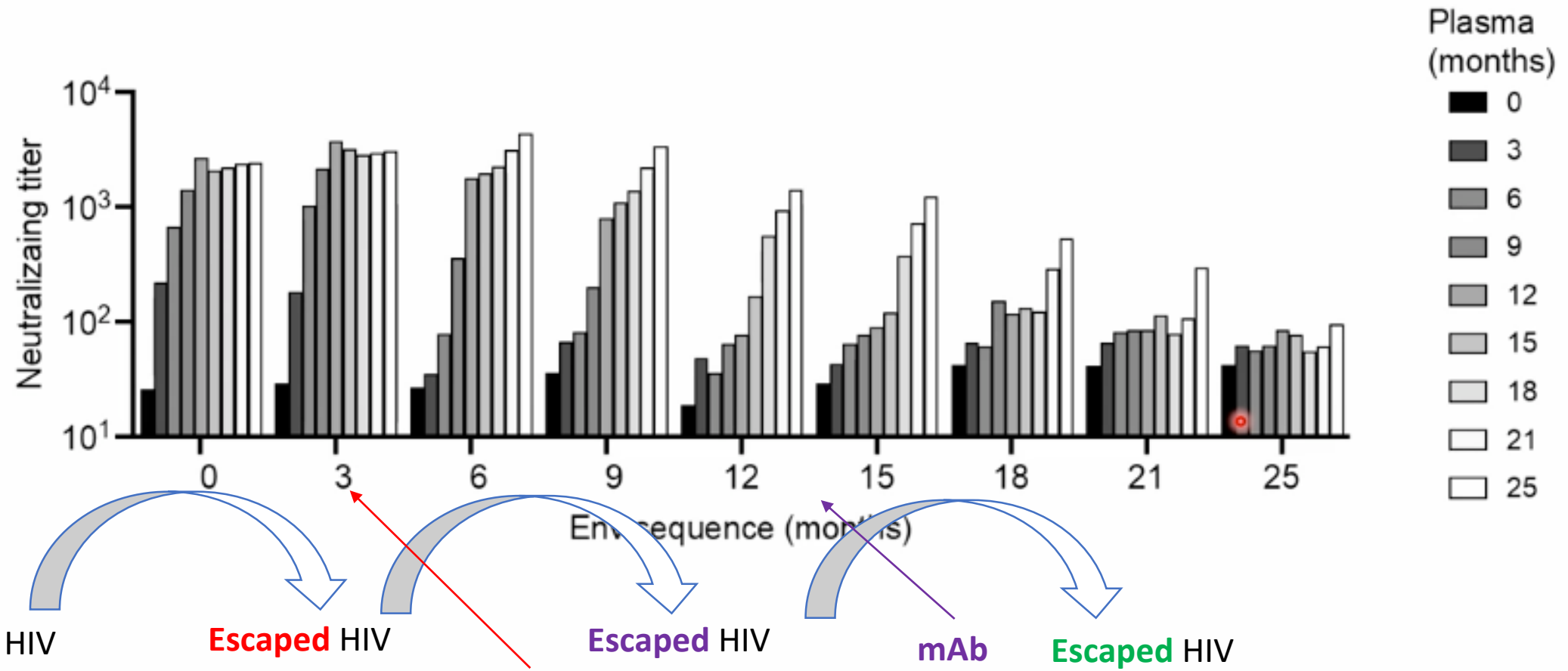
One replication cycle-1 aa change- resistance



Immune system can't respond

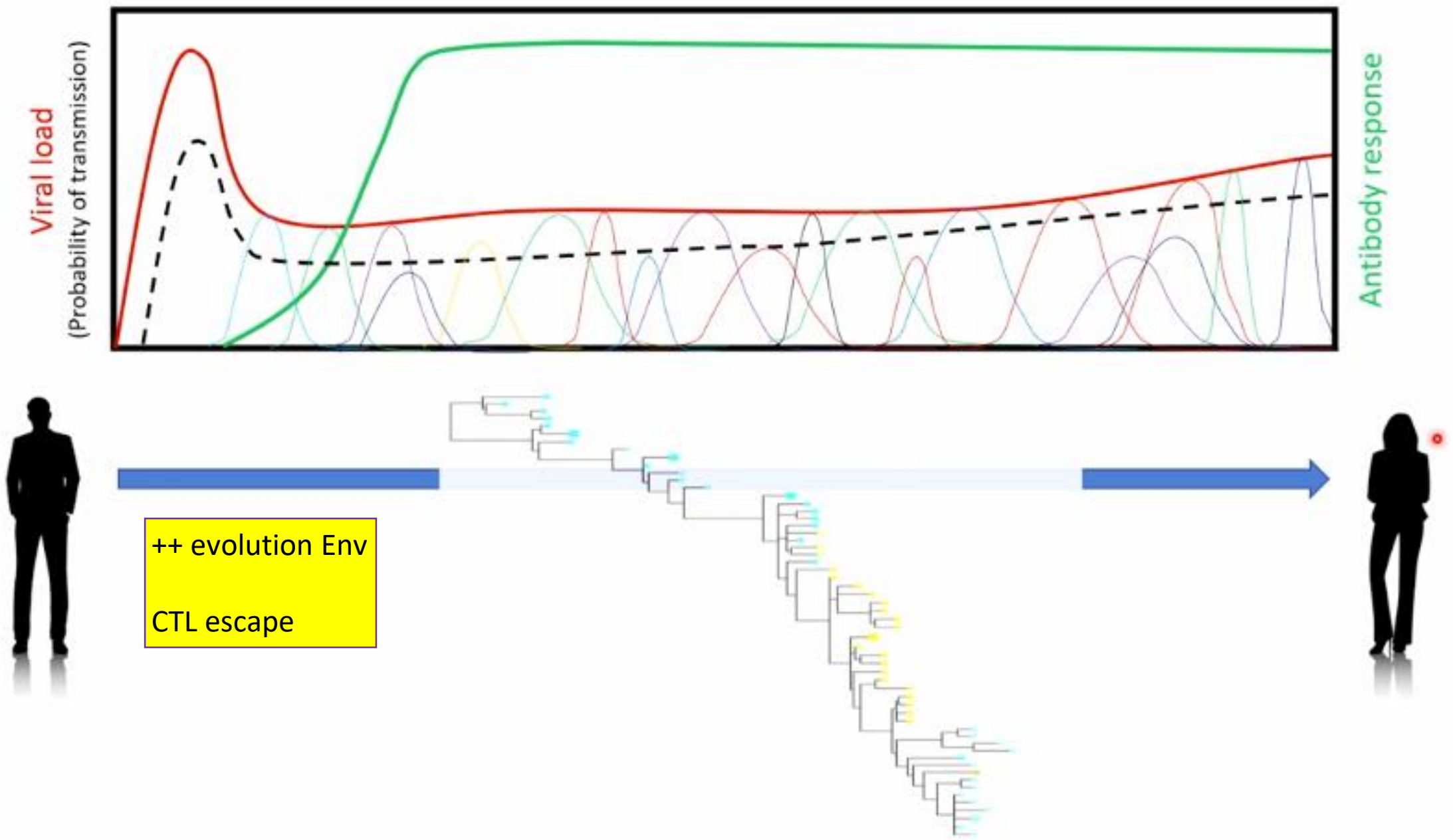


Neutralizing antibodies and acquisition of resistance (HIV-1)

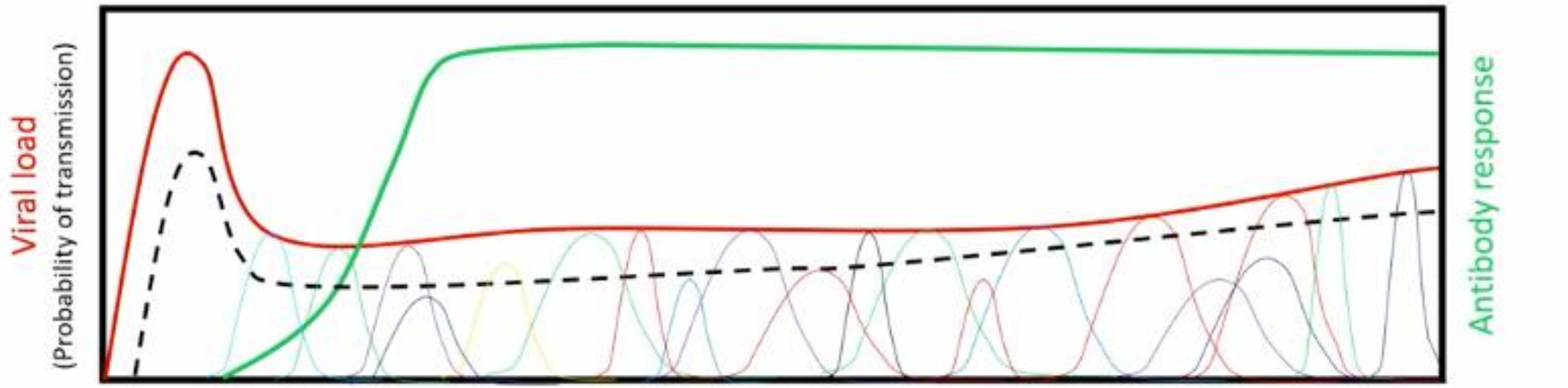


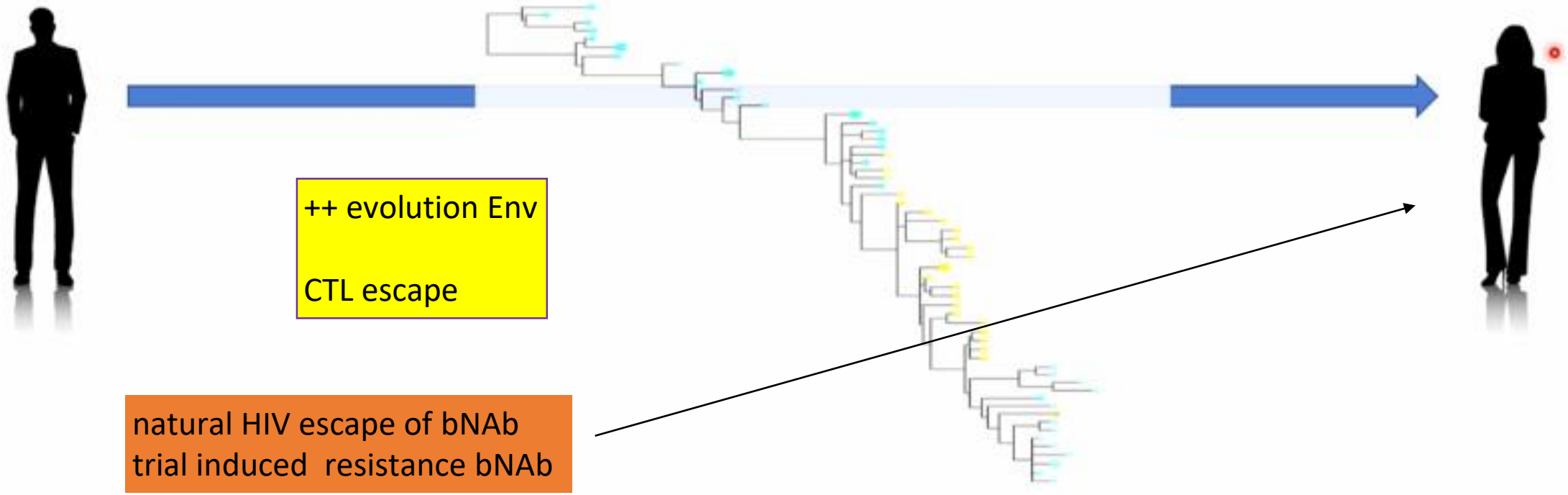
Data from: Richman et al *PNAS* 2003 100 (7) 4144-4149
See also: Wei et al. *Nature* 2003 422(6929):307-12

Neutralizing antibodies and acquisition of resistance (HIV-1)



Neutralizing antibodies and acquisition of resistance (HIV-1)





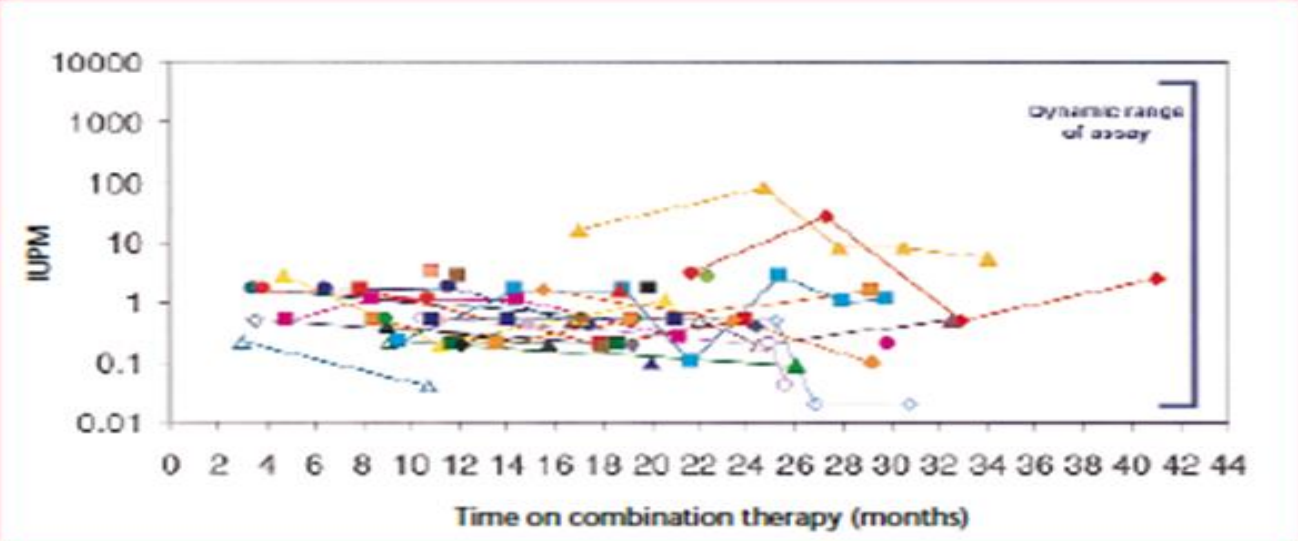
++ evolution Env

CTL escape

natural HIV escape of bNAb
trial induced resistance bNAb

Cell associated infectivity

Treatment in acute and early infection results in more rapid clearance of infected cell reservoir and smaller residual reservoir size.



Finzi et al *Nat Med* 1999

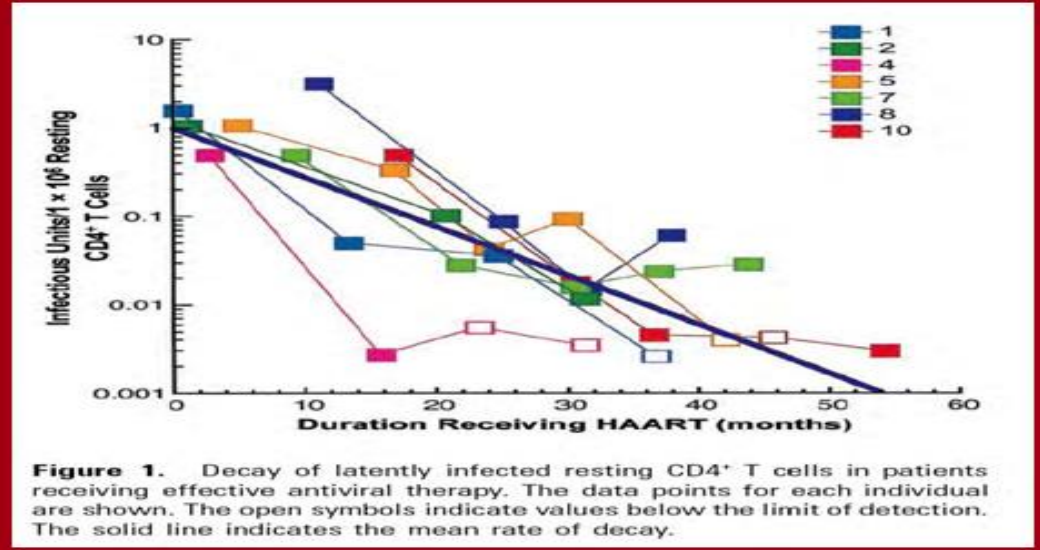
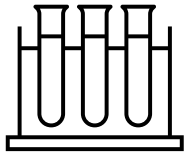


Figure 1. Decay of latently infected resting CD4⁺ T cells in patients receiving effective antiviral therapy. The data points for each individual are shown. The open symbols indicate values below the limit of detection. The solid line indicates the mean rate of decay.

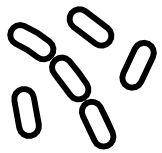
Chun et al *JID* 2007

< 20

Initial studies: pos VL



PMBC



Remove integrated HIV
- take **Env**

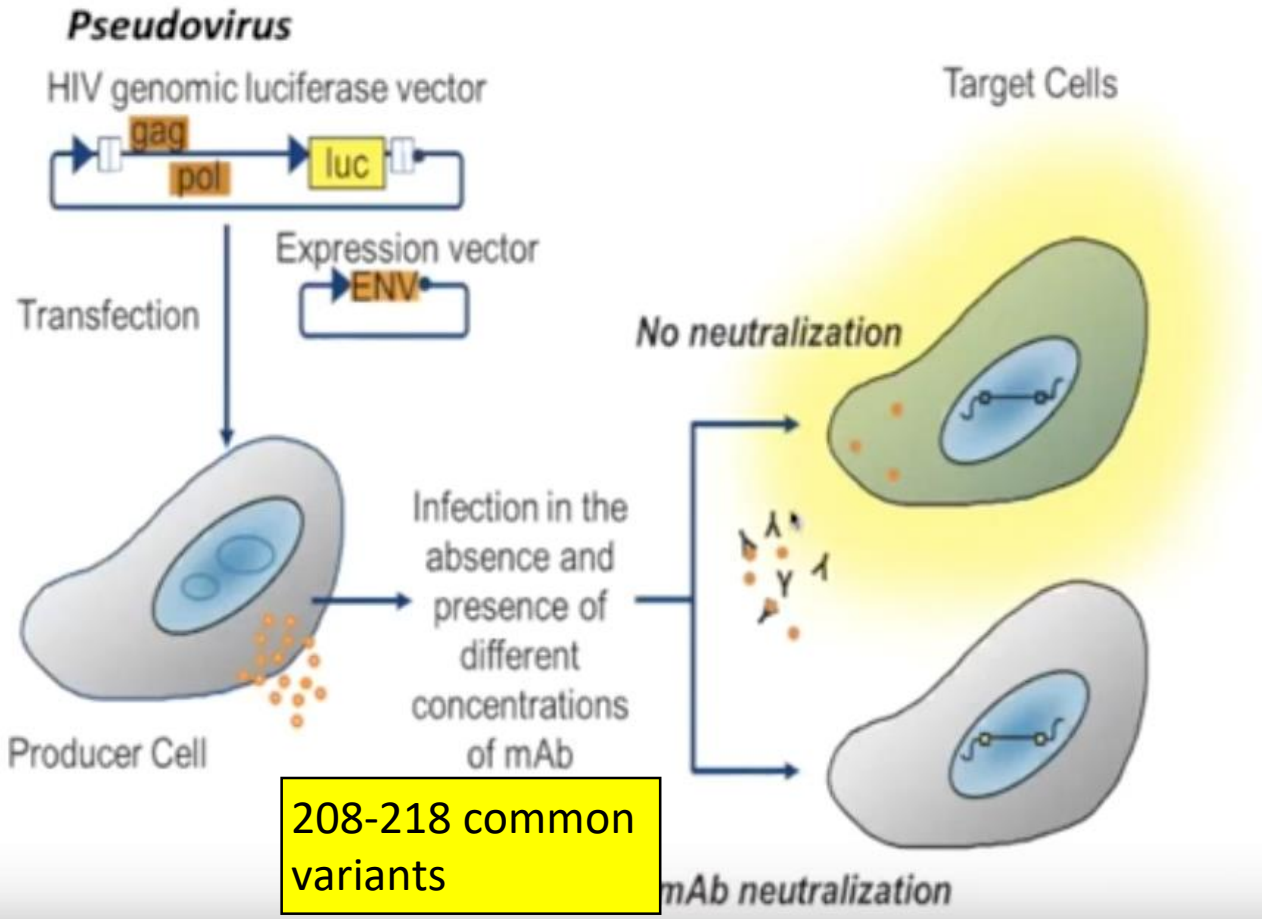
phenotype

genotype

2 %

Screening for bNAb Sensitivity

PhenoSense Monoclonal Antibody (mAb) Assay



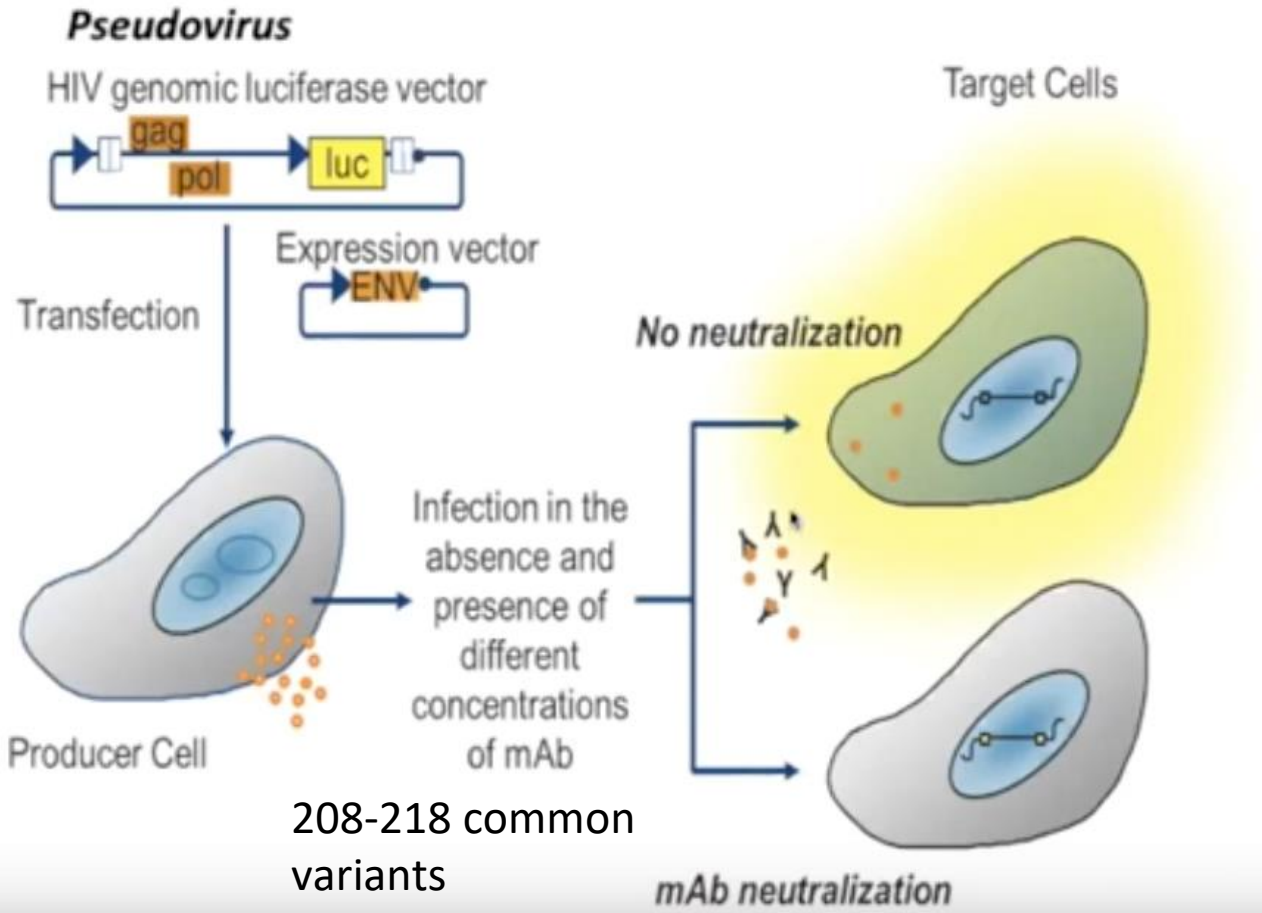
208-218 common variants

80…90….98 %

20 weeks …2 weeks

Screening for bNAb Sensitivity

PhenoSense Monoclonal Antibody (mAb) Assay



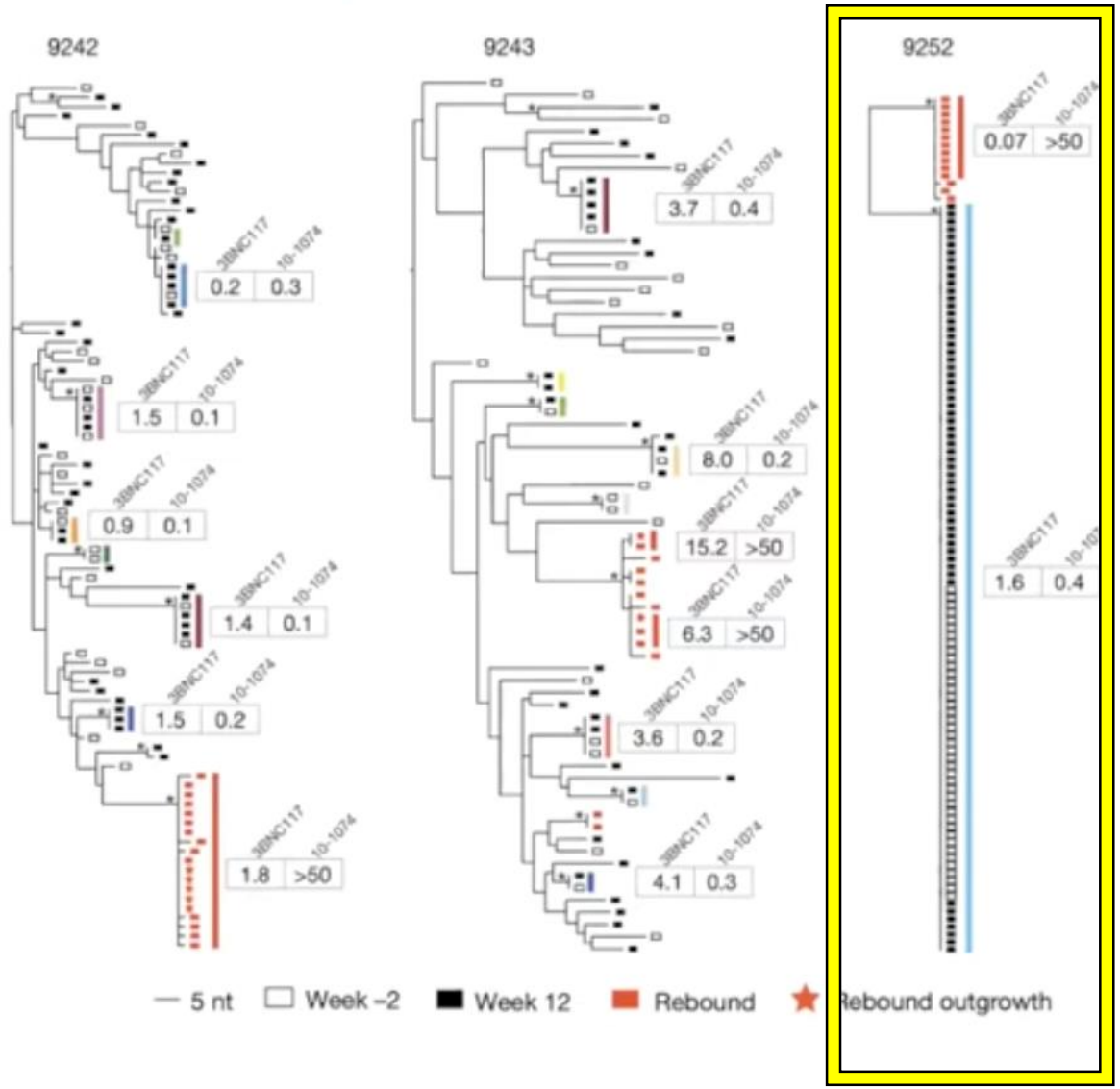
208-218 common variants

Assays don't always agree

Assays don't always predict

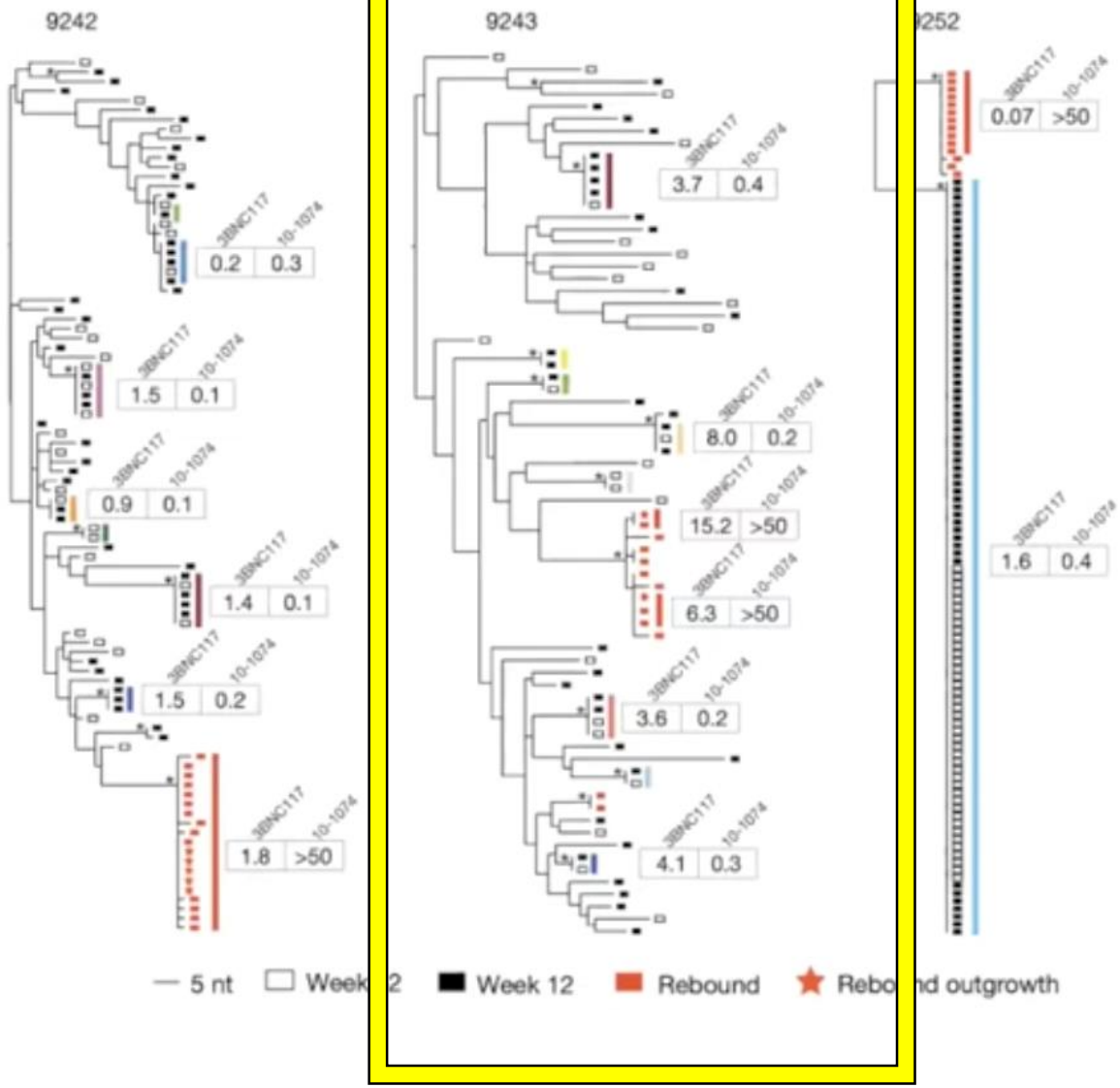
Assays don't always amplify

Viral Diversity in the Reservoir of PLWH



treated acutes

Viral Diversity in the Reservoir of PLWH



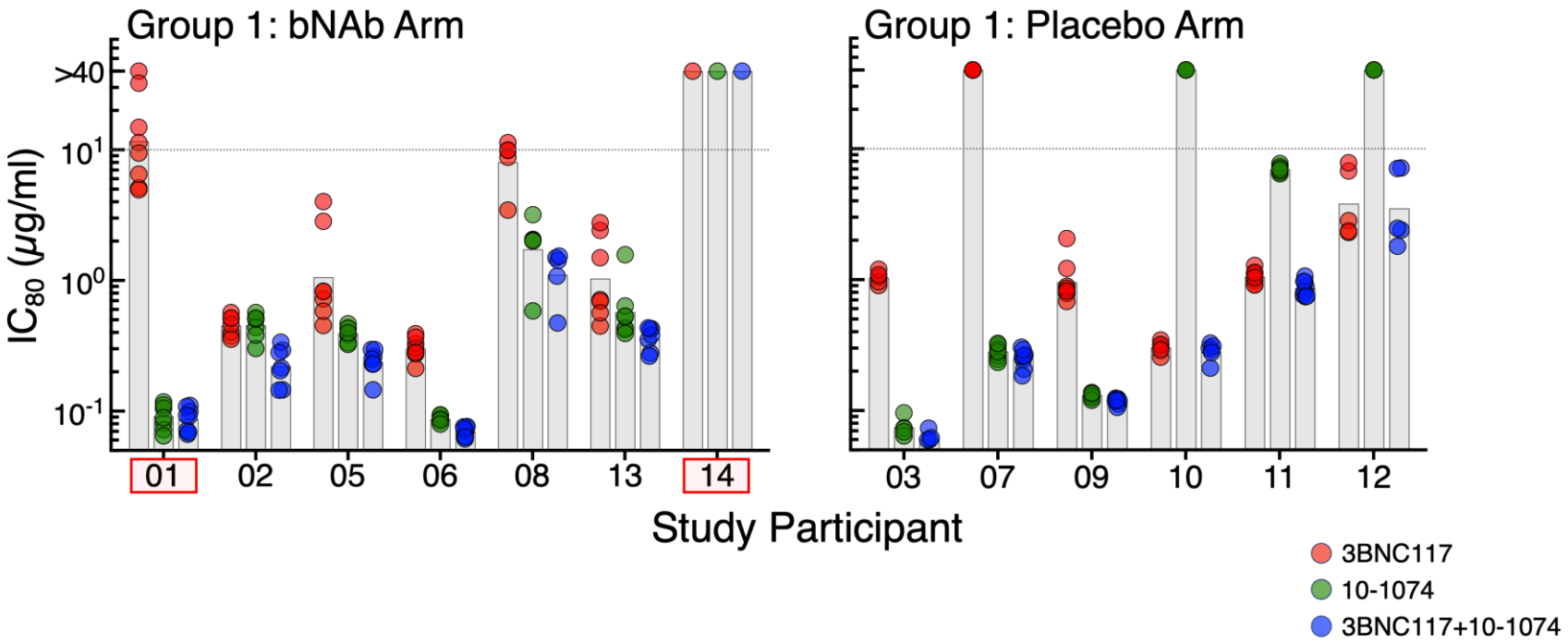
chronic treated

Baseline Sensitivity of Replication-Competent HIV to bNAbs

Nadir >350 entry > 500

Frequency of pre-existing resistant HIV at screening (Group 1)

1. Resistance to either 3NBC117 or 10-1074: **38**%
2. Resistance to 3BNC117: **23**%
3. Resistance to 10-1074: **23**% Long term treated acutes
4. Resistance to both antibodies: **8**%



MS Sneller, T-W. Chun, et al, *Nature*, 606:375-381, 2022

activated

+ transcription

no full length HIV

- *Short abortive* HIV

- ***? rare HIV epitopes***

No sig RV

Latency: ? Lack production

large deletions

++ and NOT activated

+++transcription HIV RNA

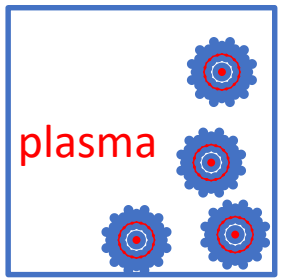
MINOR defective HIV

defective HIV

+ HIV protein produced

+ HIV epitopes

+ RV ? infectious

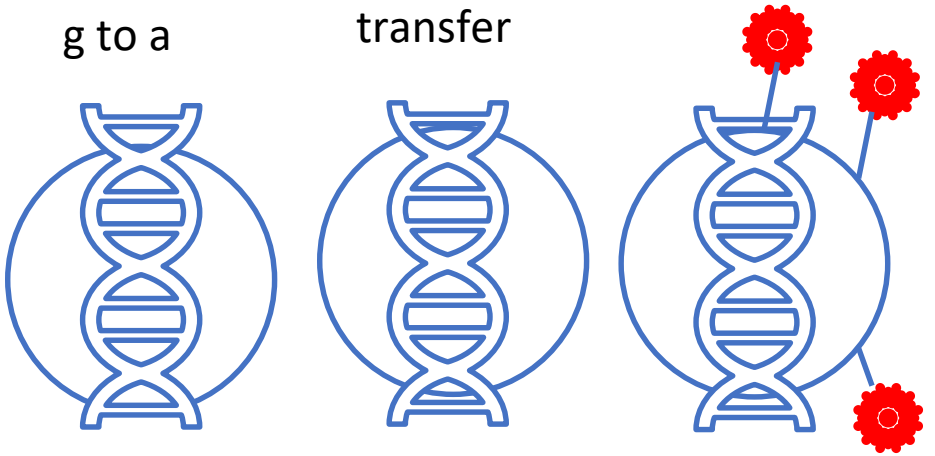


minor deletions

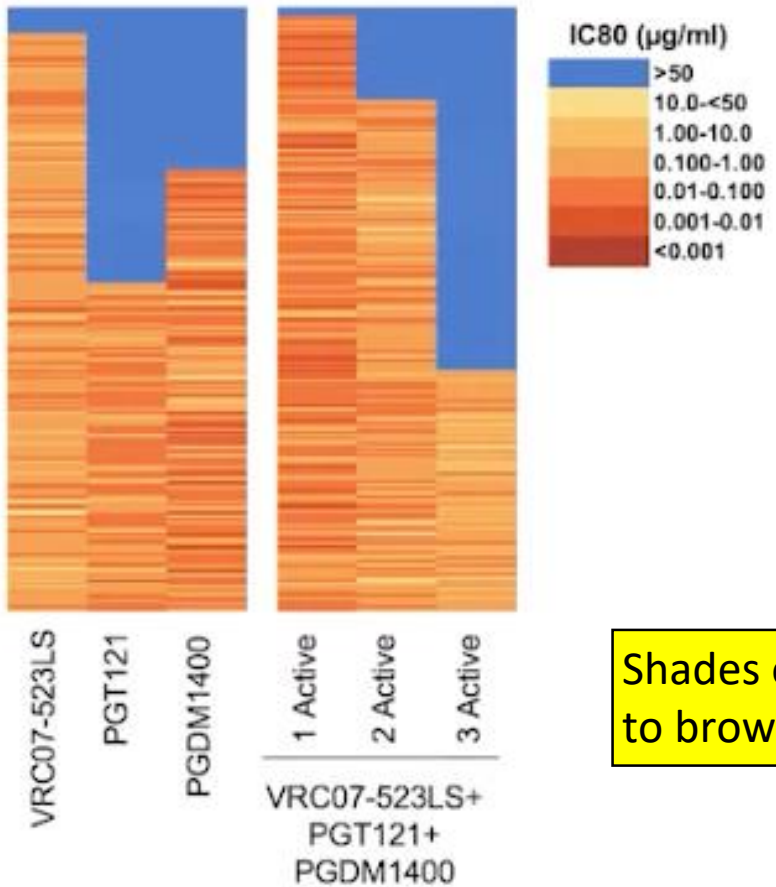
APOBEC

g to a

5 ‘ strand transfer

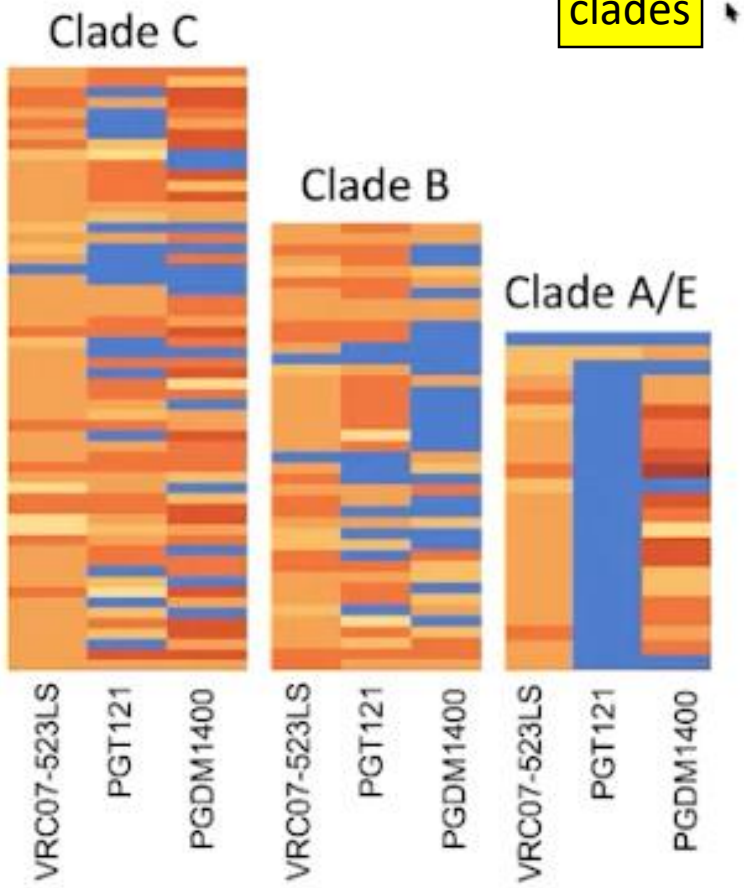


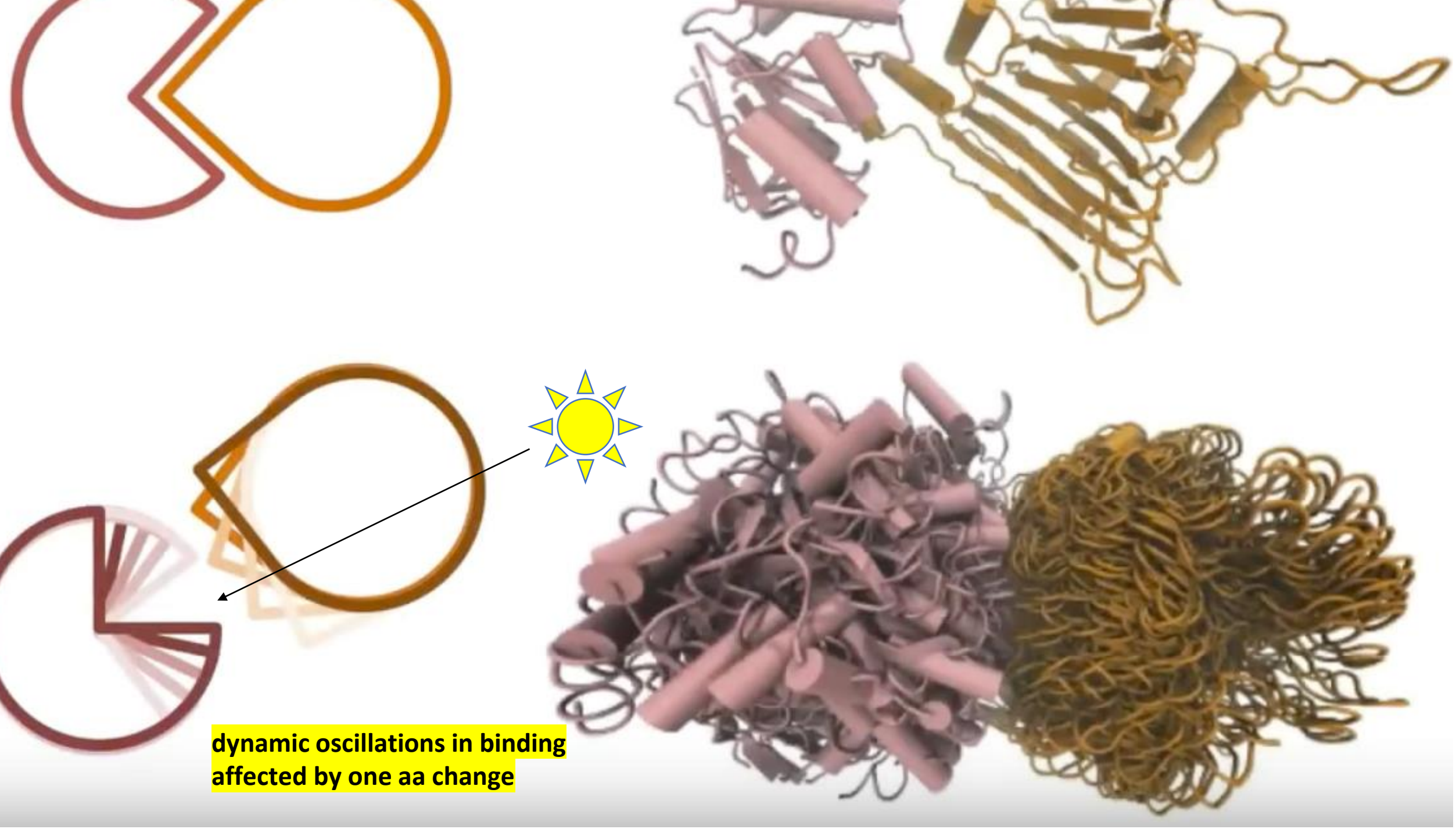
Improving bNAbs - combinations

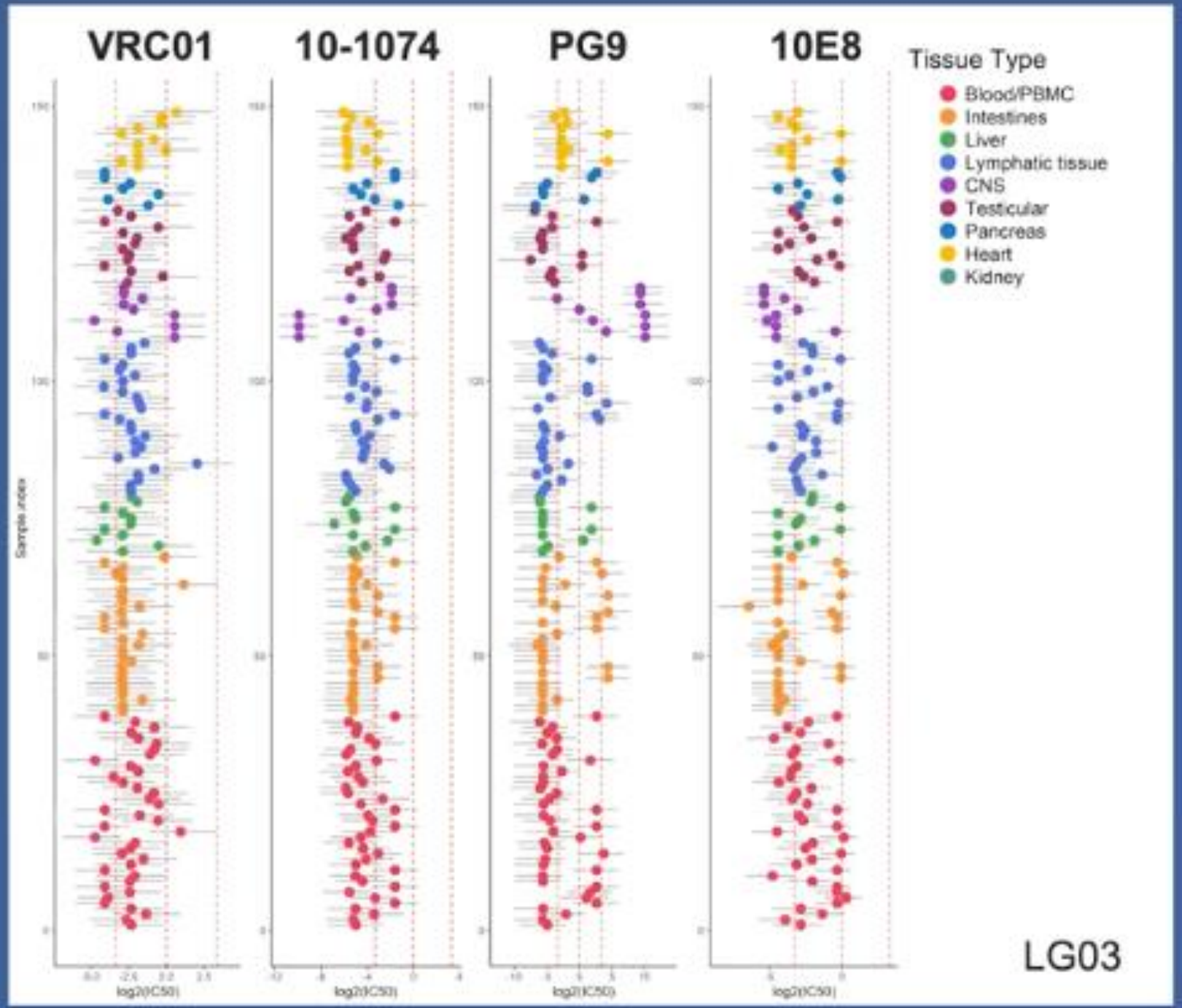


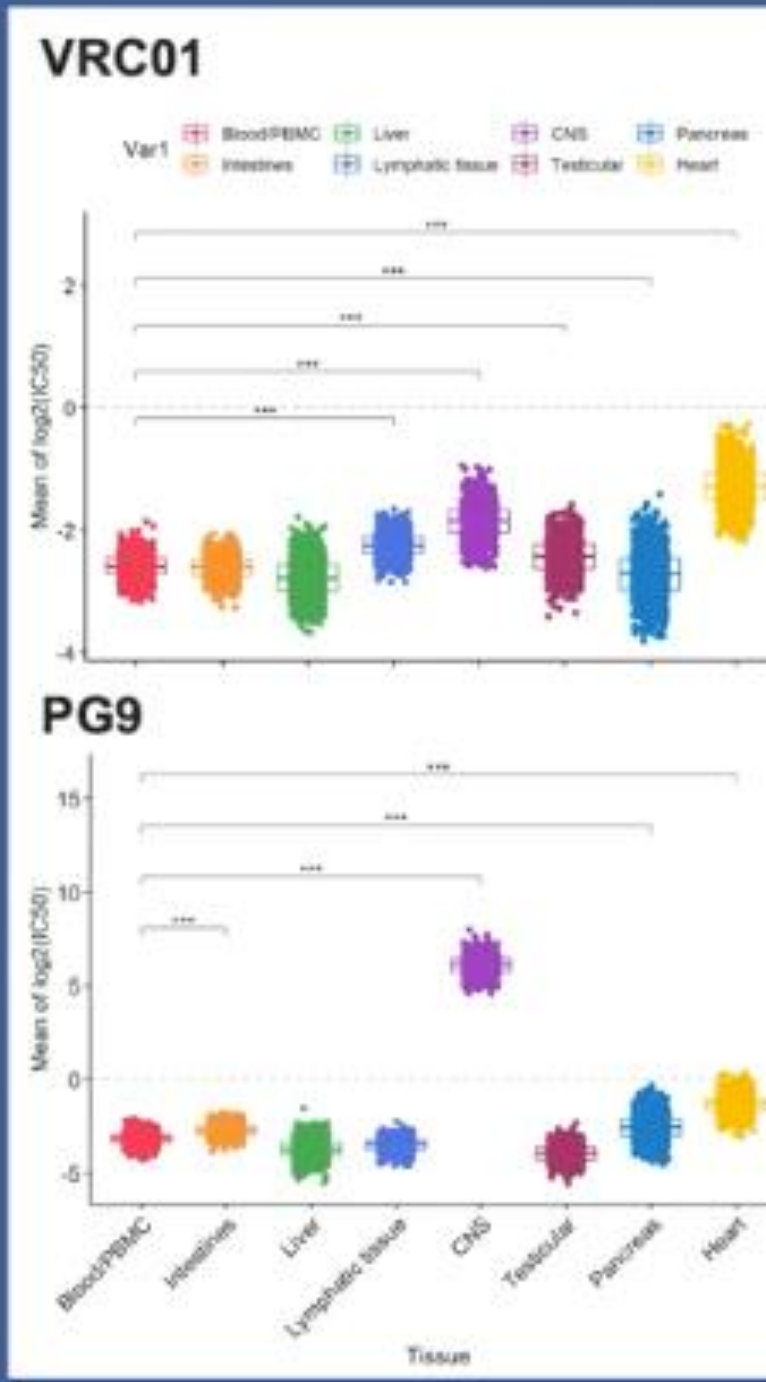
Shades of orange to brown

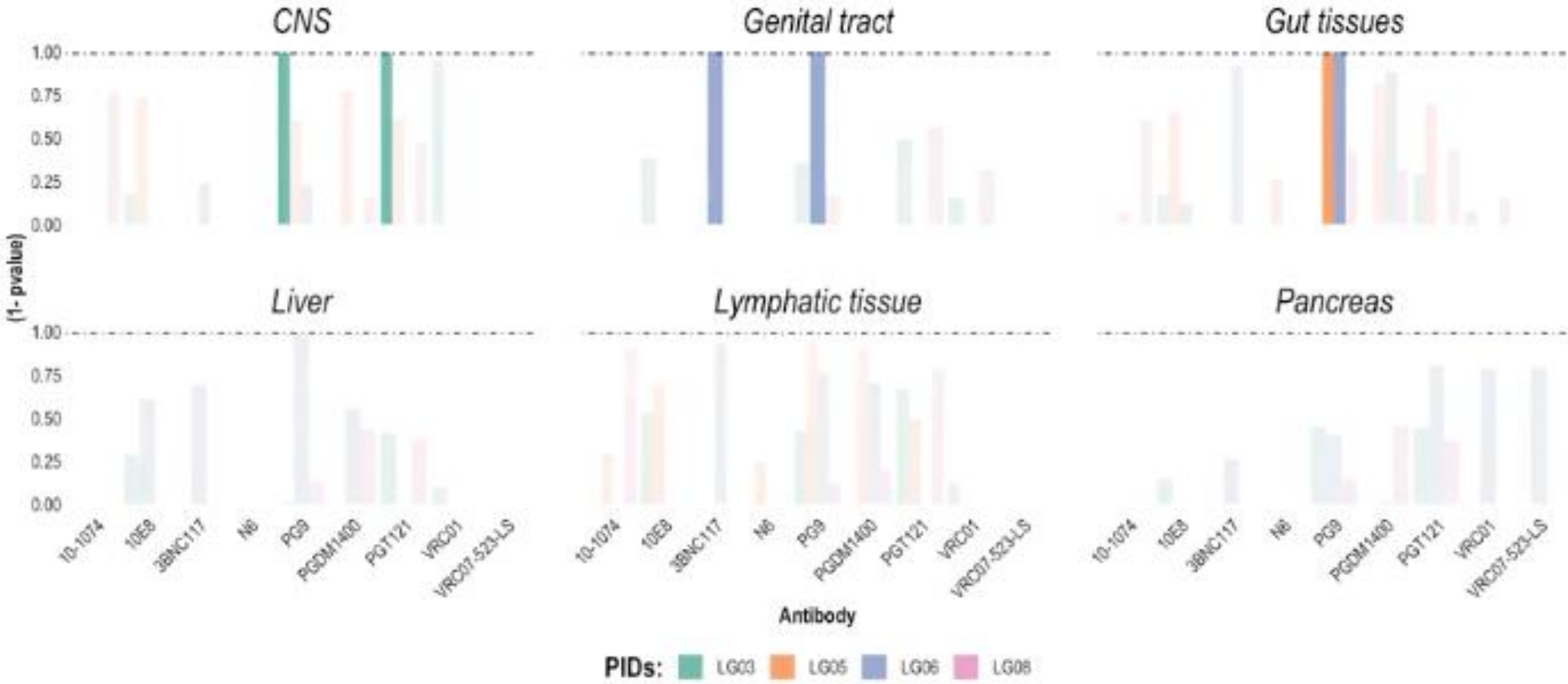
clades




dynamic oscillations in binding
affected by one aa change

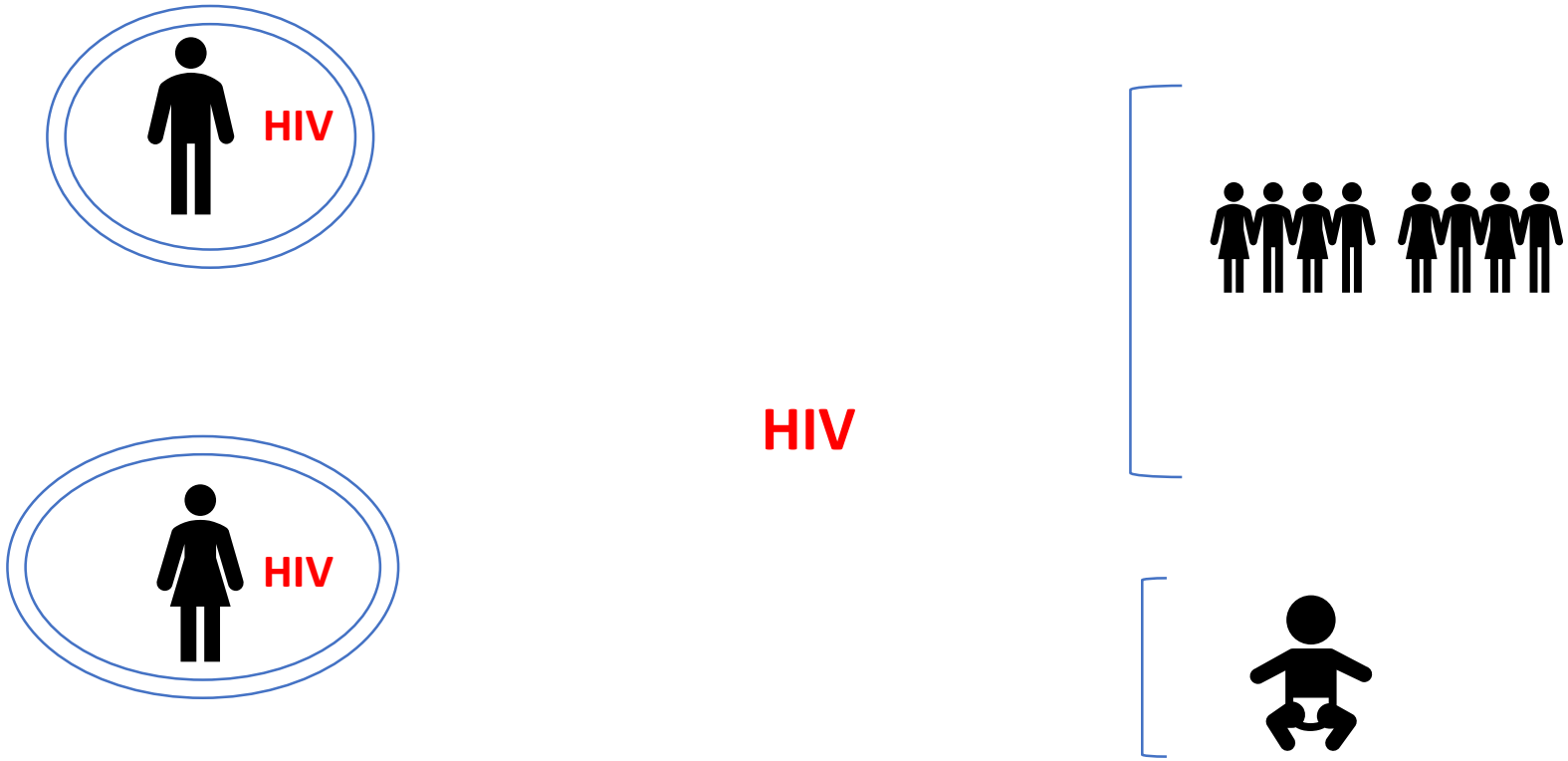

VRC01
10-1074
PG9
10E8
Tissue Type
Blood/PBMC
Intestines
Liver
Lymphatic tissue
CNS
Testicular
Pancreas
Heart
Kidney
Sample index
log2(IC50)
LG03


VRC01
Var1
Blood/PBMC
Intestines
Liver
Lymphatic tissue
CNS
Testicular
Pancreas
Heart
Mean of log2(IC50)
PG9
Mean of log2(IC50)
Blood/PBMC
Intestines
Liver
Lymphatic tissue
CNS
Testicular
Pancreas
Heart
Tissue



ut-off IC50 value = 1ug/ml, P-value cut-off = 0.01 associated with a False Discovery Rate of 29%

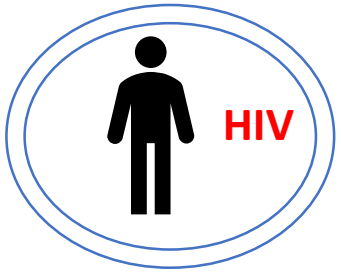
???? ……Possible uses bNAb:



> 200 development only Env target for immune system

Treatment

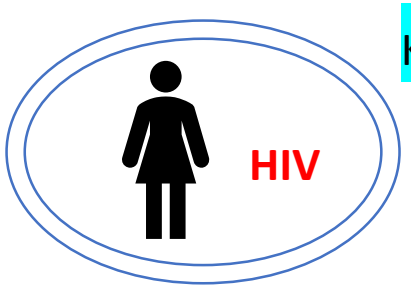
replace ART
adjunct ART



CURE

Rinse / drain

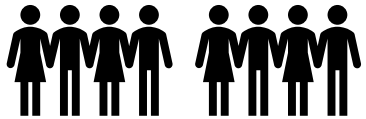
Kick and **kill**



vaccine
Reverse iteration

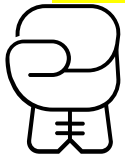
HIV

prevent



AMP

PEP



IMPAACT

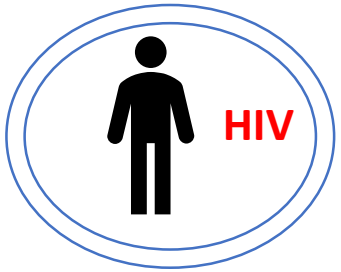
Potential pitfalls

Potency
Breath
Cost
equity

Treatment

Pre-test phenotype / genotype

vaccine
Reverse iteration



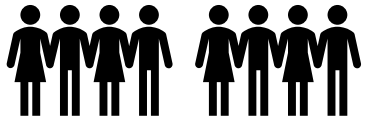
Post use: RESISTANCE

Permanent
Immune dysfunction

Pt spec. reservoir

Tissue levels

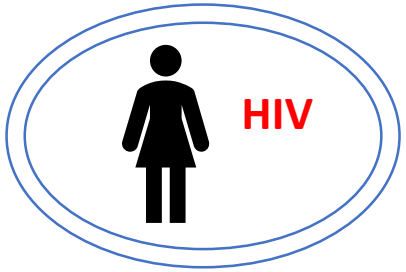
prevent



HIV

claide
Transmitted Species
equity- cost
Tissue levels

CURE



Pt spec. reservoir
defective clonal

PEP

ADCC

N= small number of patients in trials phase 2b

short duration of trial - varying bNAb arms - variable entry sensitivity testing Ab susceptibility

different outcome measures: immune based control-time to rebound- first phase slope- set point …….
……

- ***Titan trial:*** ***impact of TLR9 agonist [leftitolimod] and bNAbs on HIV persistence: the randomized phase 2a***

Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial

- **Effect of 3BNC117 and romidepsin on the HIV-1 reservoir in people taking suppressive antiretroviral therapy**
- **(ROADMAP): a randomised, open-label, phase 2A trial**

- **Combination therapy with anti-HIV-1 antibodies maintains viral suppression**

Rio trial and more……..enrolling …..Cab + VRC07-LS ACTG5357 ……LEN- + 2bNAb ……

Fig. 1: TITAN trial design (a) and abbreviated CONSORT flow diagram (b).

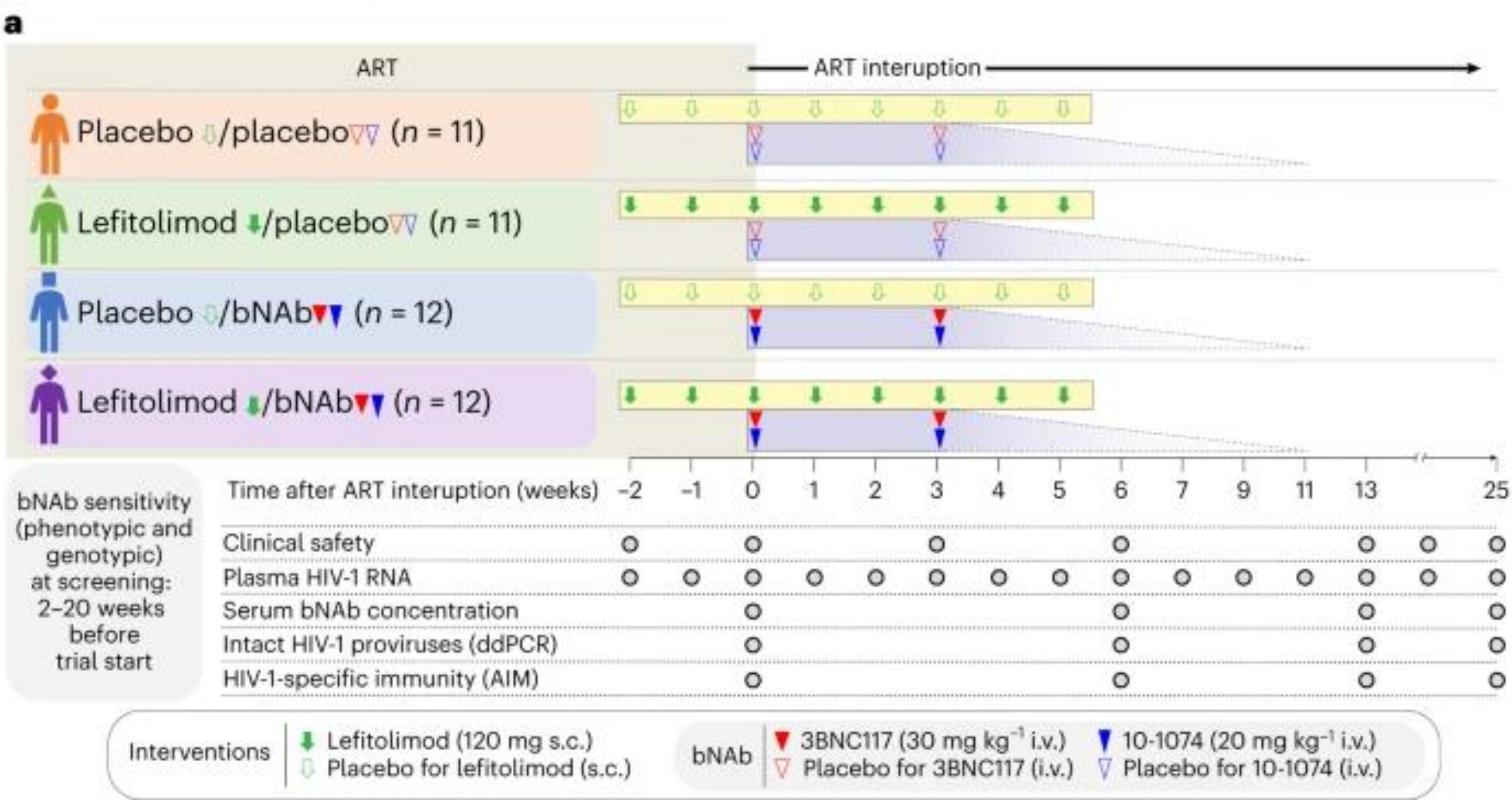
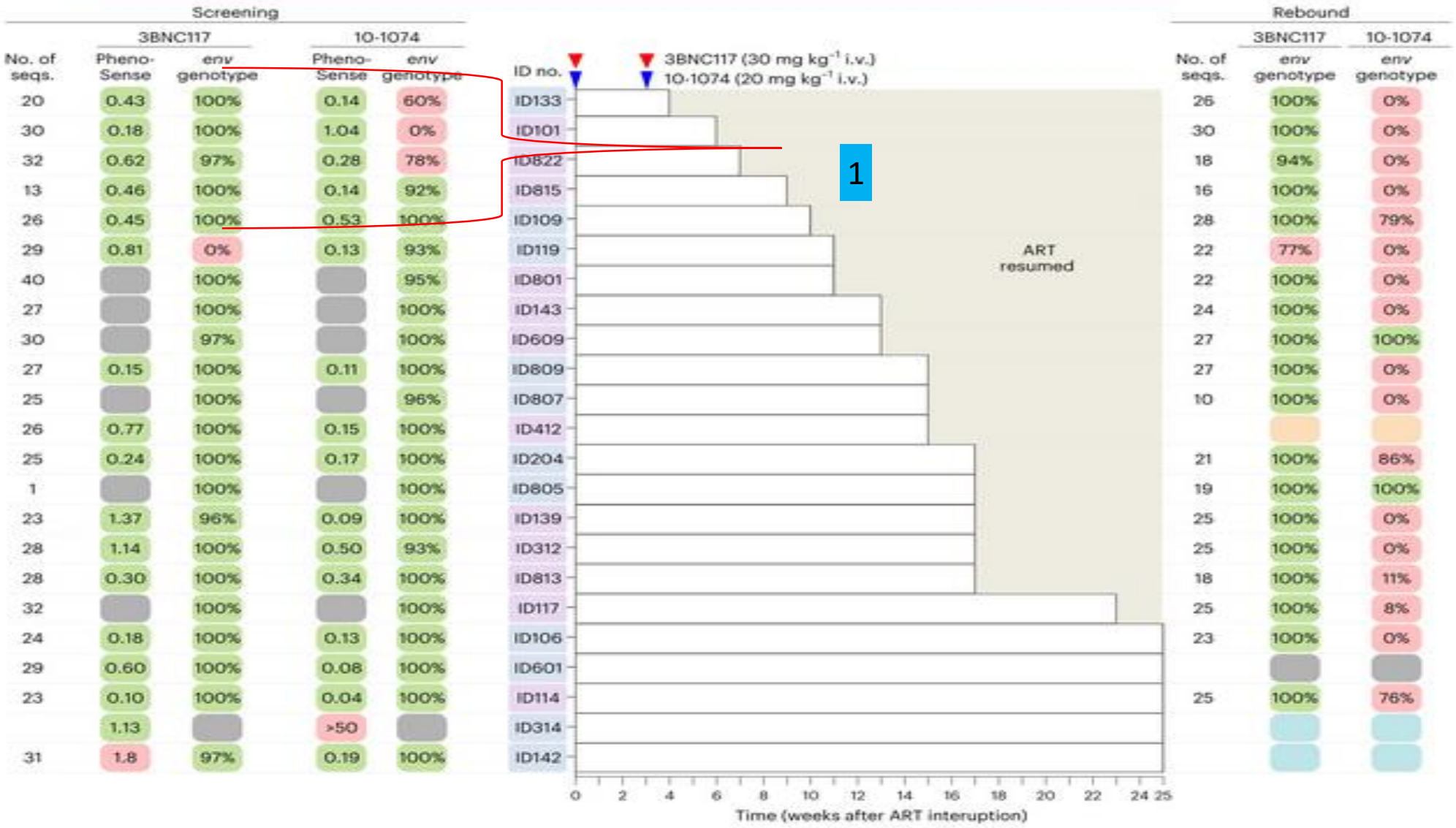


Fig. 3: bNAb sensitivity at screening and viral rebound.

From: Impact of a TLR9 agonist and broadly neutralizing antibodies on HIV-1 persistence: the randomized phase 2a TITAN trial



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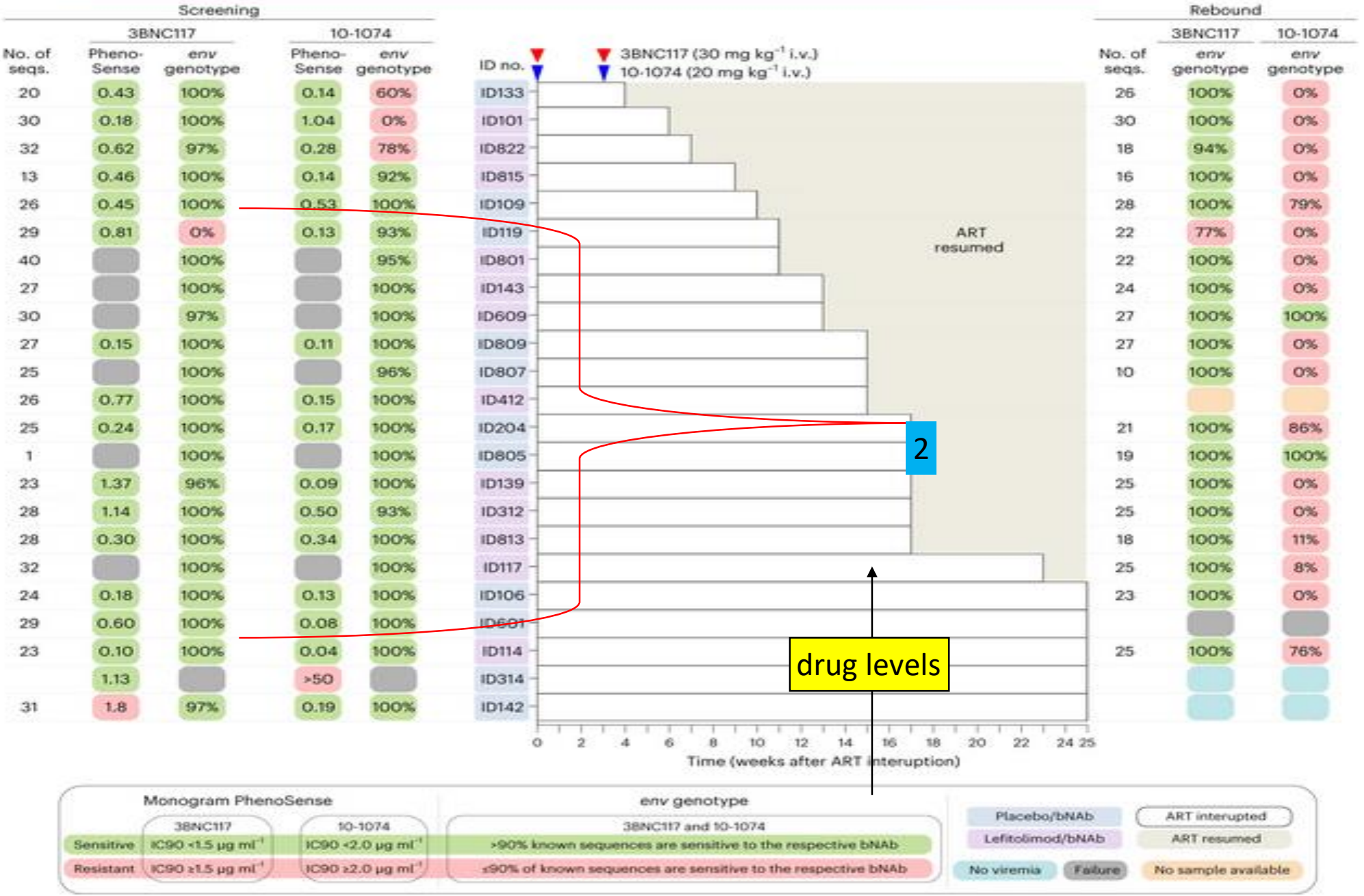

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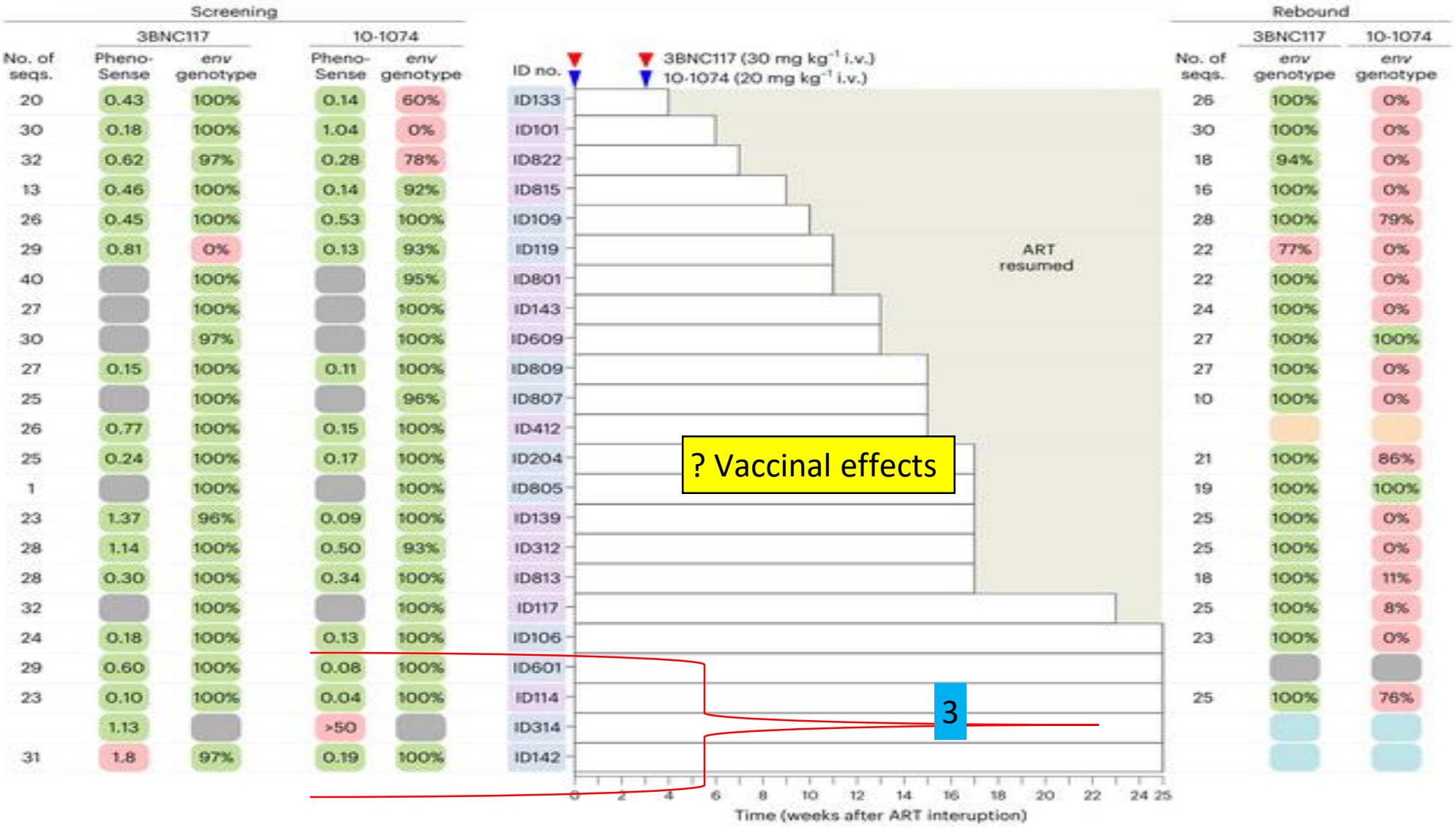

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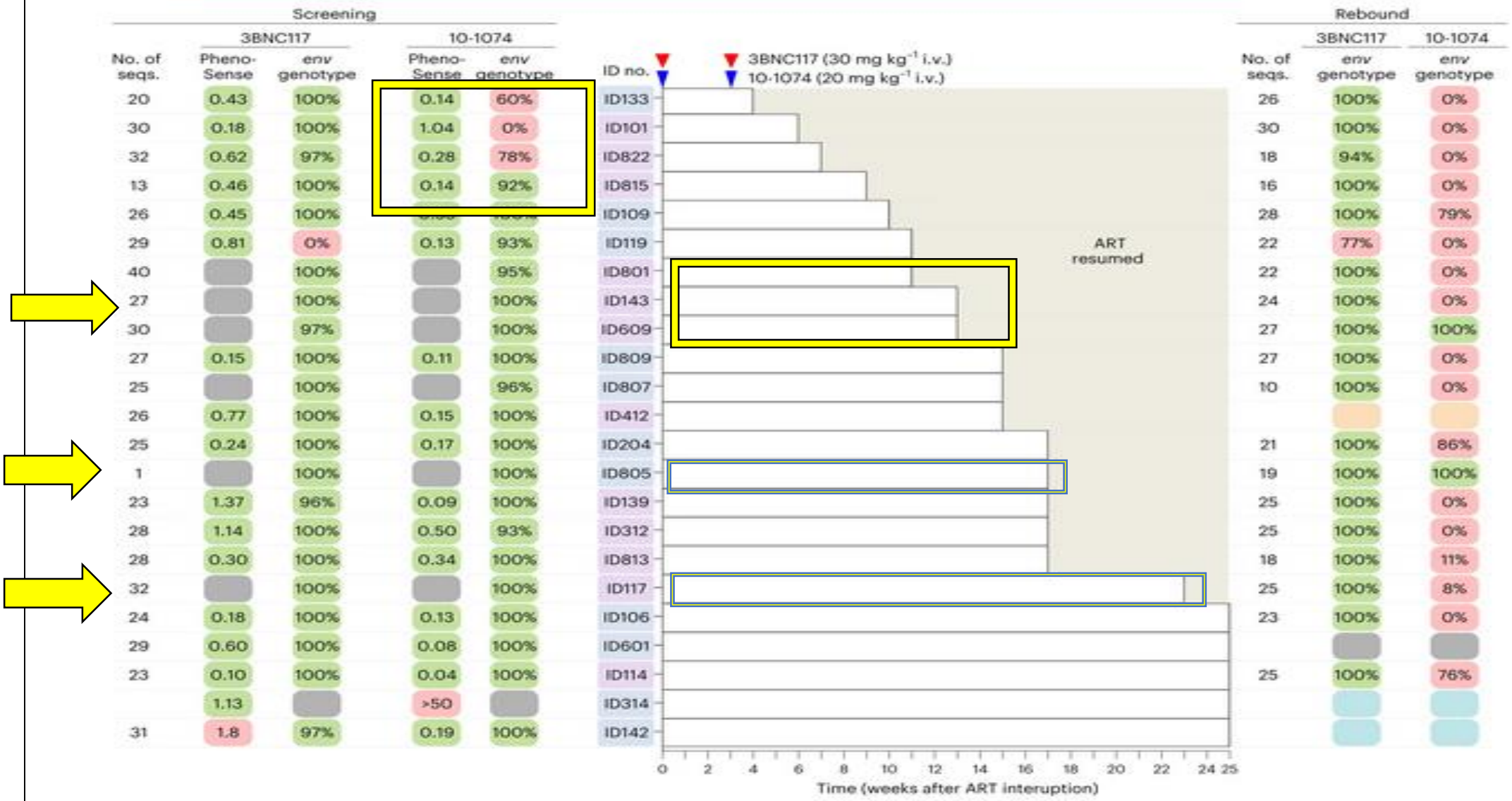
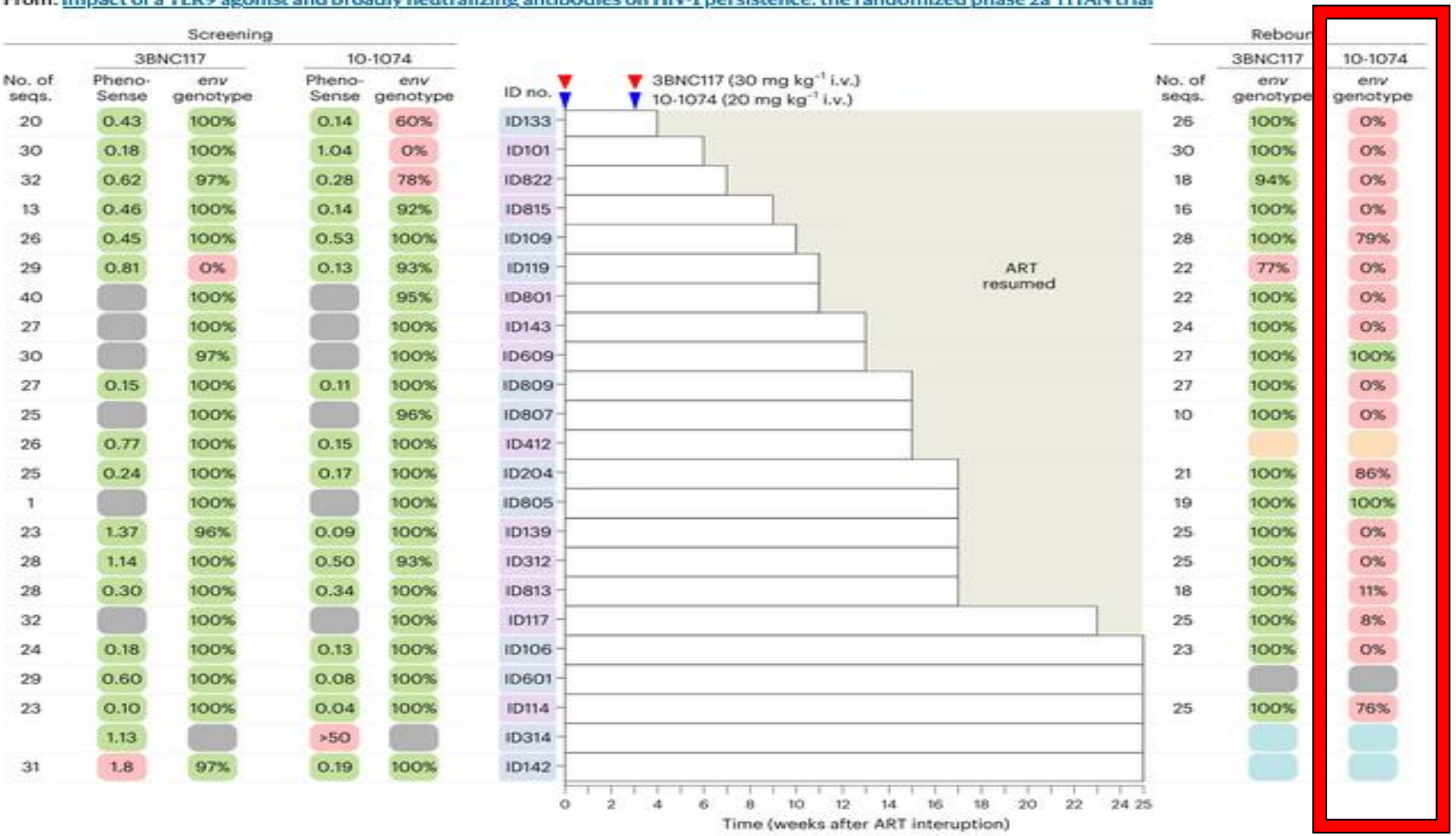


80 -98 %

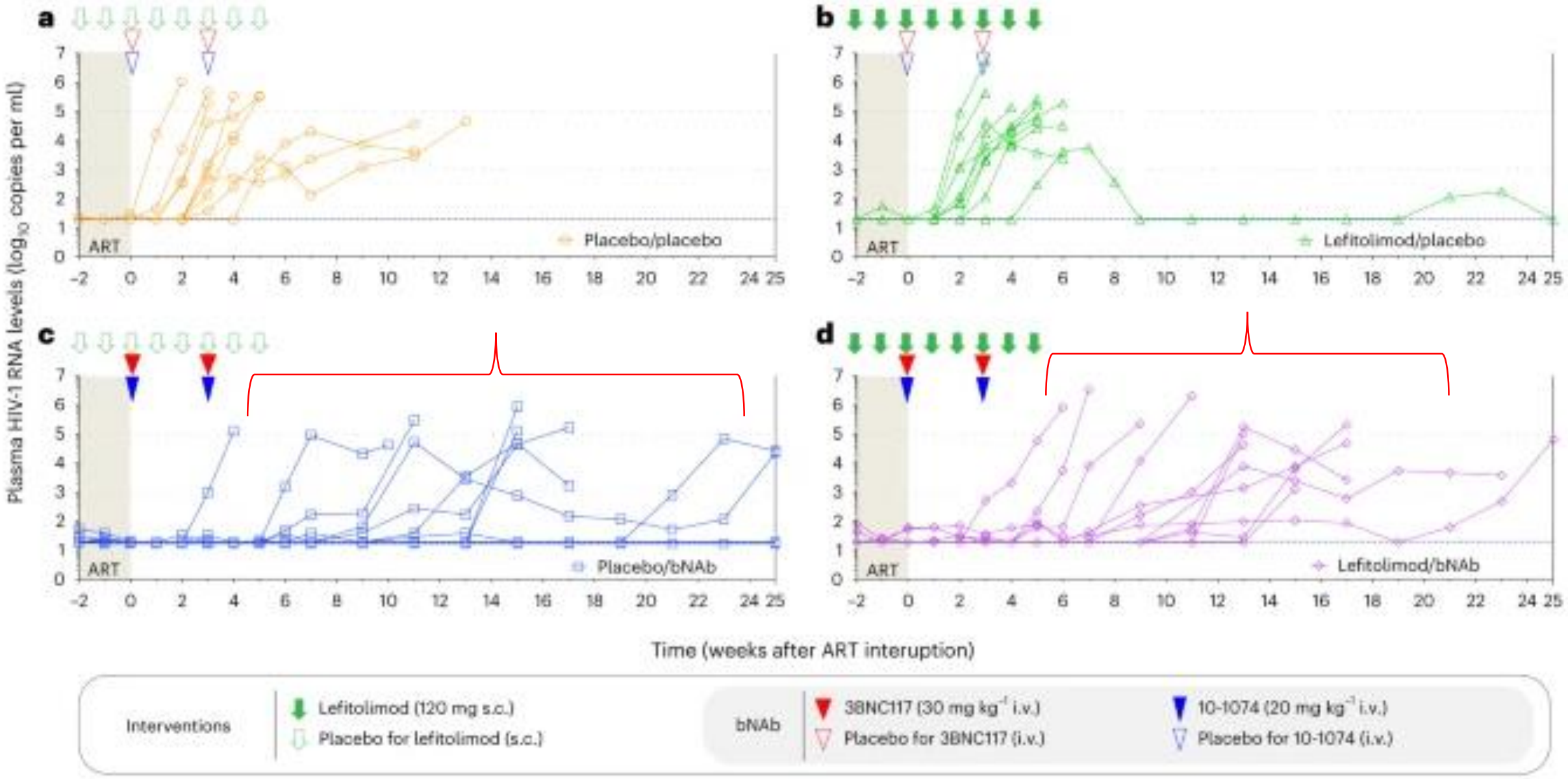
Fig. 3: bNAb sensitivity at screening and viral rebound.

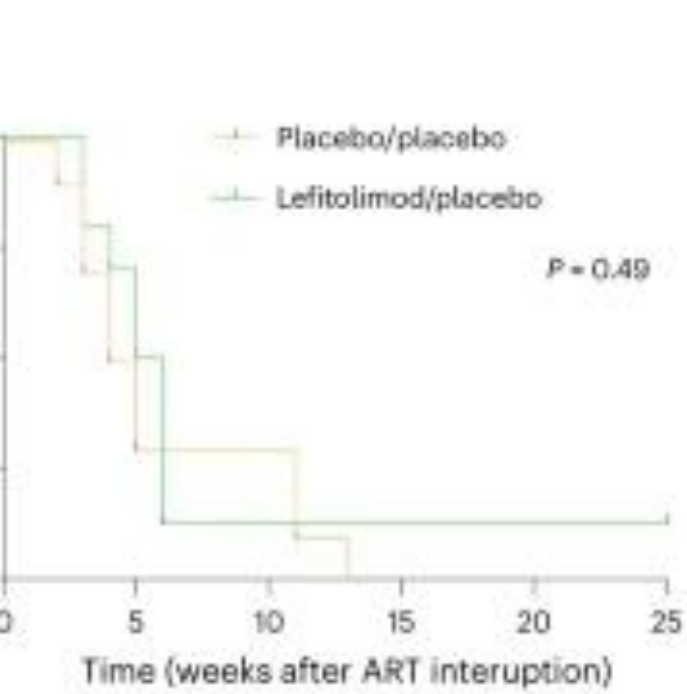
From: Impact of a TLR9 agonist and broadly neutralizing antibodies on HIV-1 persistence: the randomized phase 2a TITAN trial

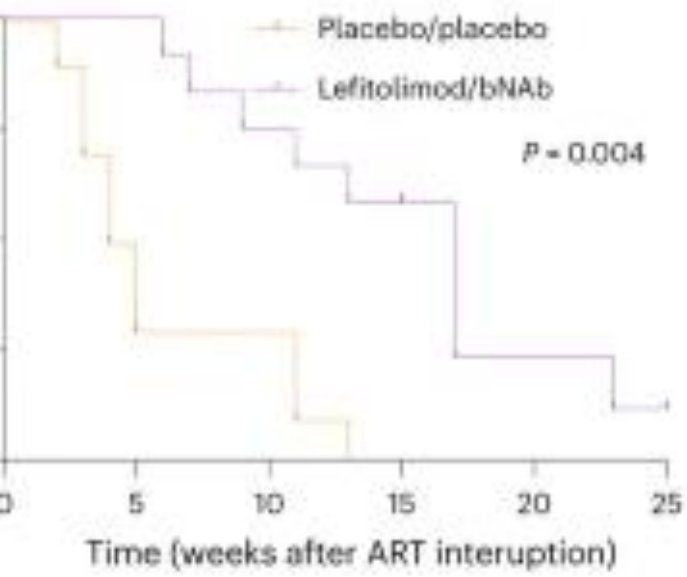


? future

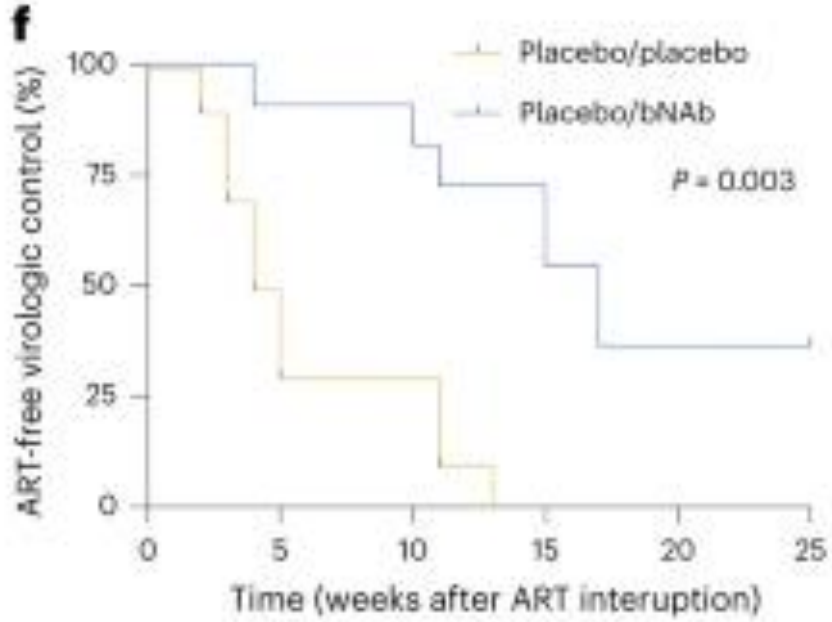
Fig. 2: Viral kinetics and time to loss of virologic control during 25 weeks of ATI.



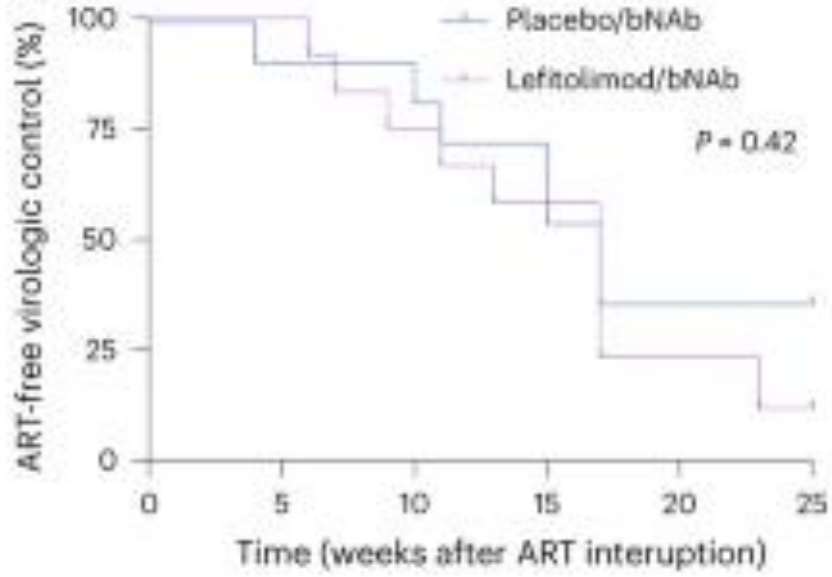

Placebo/placebo
Lefitolimod/placebo
P = 0.49
0
5
10
15
20
25
Time (weeks after ART interuption)


Placebo/placebo
Lefitolimod/bNAb
P = 0.004
0
5
10
15
20
25
Time (weeks after ART interuption)

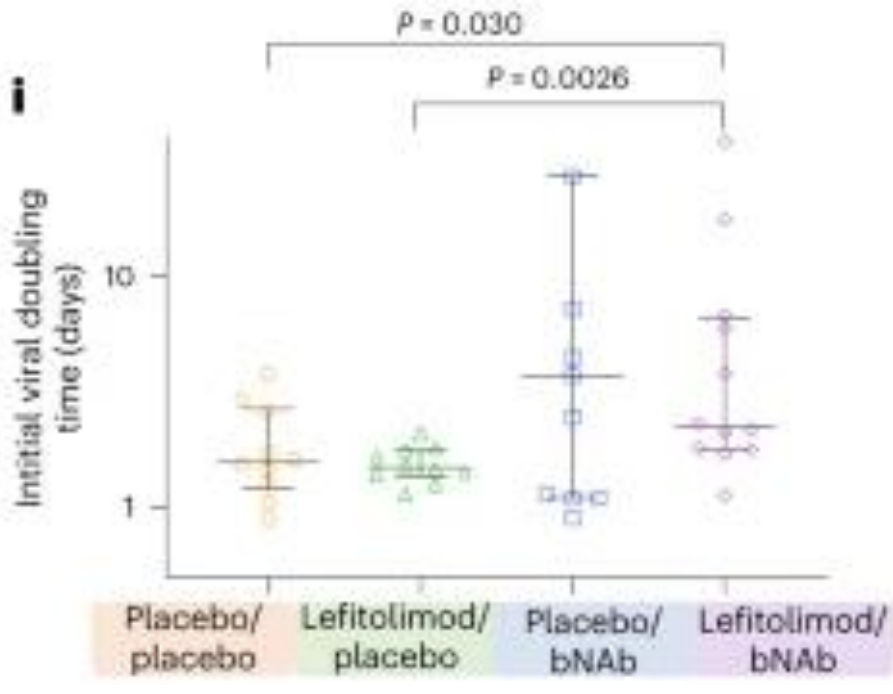
f


ART-free virologic control (%)
100
75
50
25
0
Placebo/placebo
Placebo/bNAb
P = 0.003
0
5
10
15
20
25
Time (weeks after ART interuption)

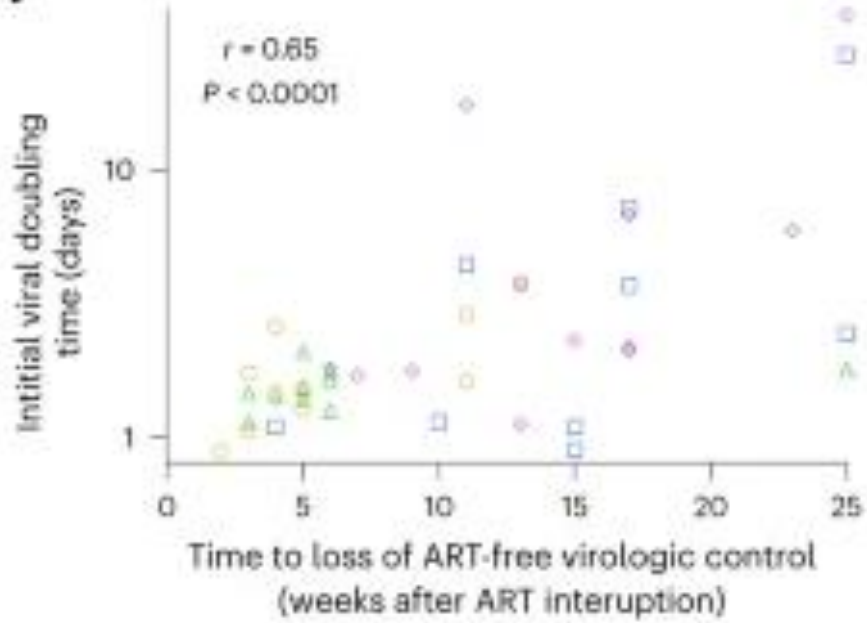
h


ART-free virologic control (%)
100
75
50
25
0
Placebo/bNAb
Lefitolimod/bNAb
P = 0.42
0
5
10
15
20
25
Time (weeks after ART interuption)

i


P = 0.030
P = 0.0026
Intitial viral doubling time (days)
10
1
Placebo/ placebo
Lefitolimod/ placebo
Placebo/ bNAb
Lefitolimod/ bNAb

j


r = 0.65
P < 0.0001
Intitial viral doubling time (days)
10
1
0
5
10
15
20
25
Time to loss of ART-free virologic control
(weeks after ART interuption)

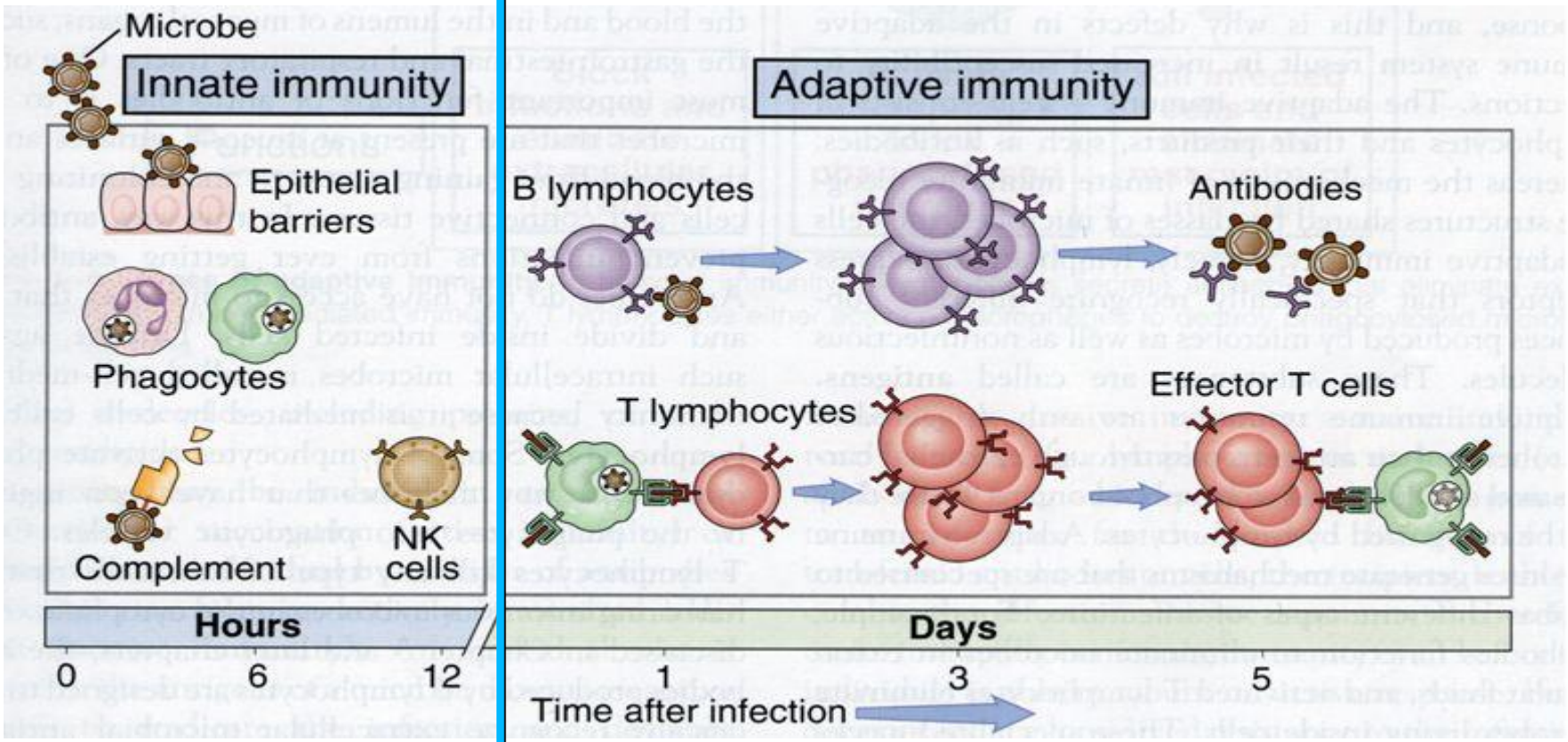
Conclusions

- Not yet " prime time " clinic …….hold promise !
- bNAbs can lead to transient decline in viremia
- Long term trials – [small molecules combination] underway as treatment option
- emerging evidence that combination bNAbs can maintain viral suppression during ATI in some individuals with sensitive viruses
- Viral reservoir , pre-existing resistance and selecting for sensitivity to bNAbs remains challenge to widespread adoption currently
- Emerging evidence that ADCC may play central role in CURE strategies
- ? bNAbs may impact proviral DNA landscape and modify anti-HIV immune responses

Audience !!

Fail to control infection

HIV infection



1

2

HSC

BONE MARROW

MPP

CLP

SPLEEN

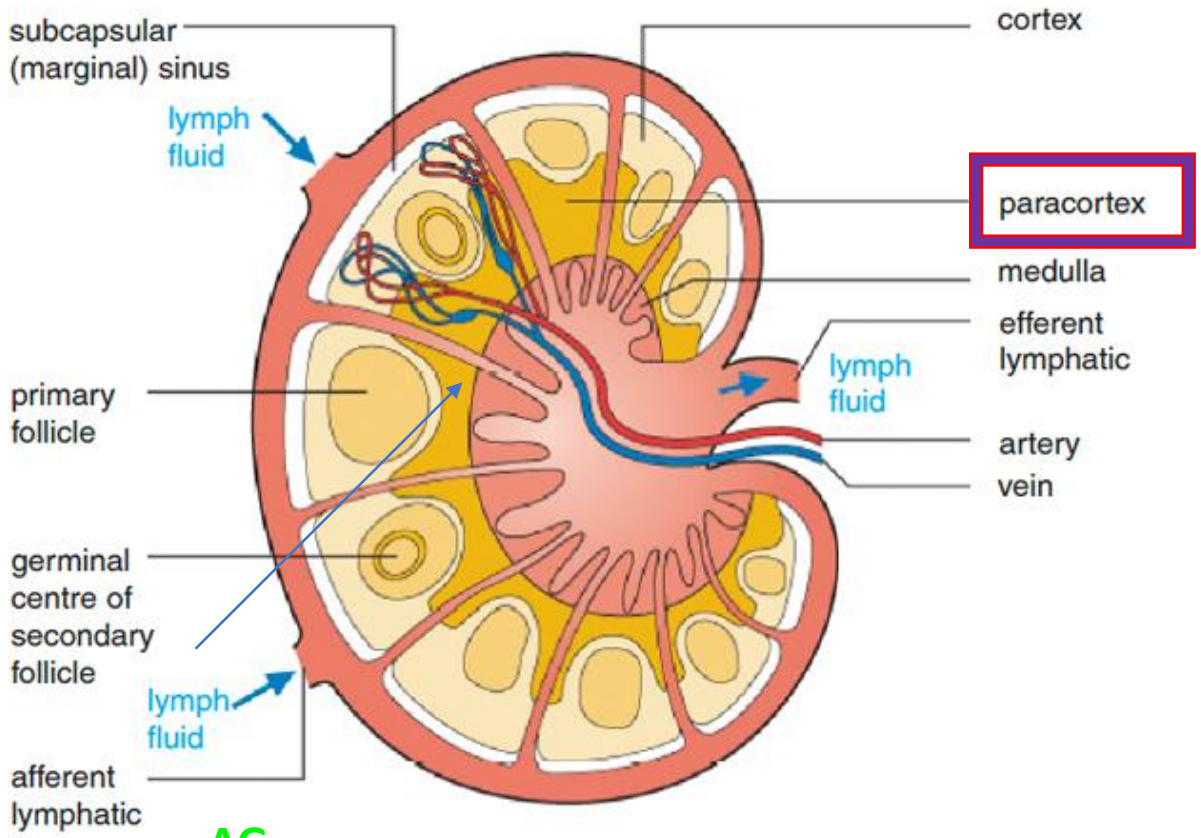
T1

T2

BLOOD

naive /mature plasma cells

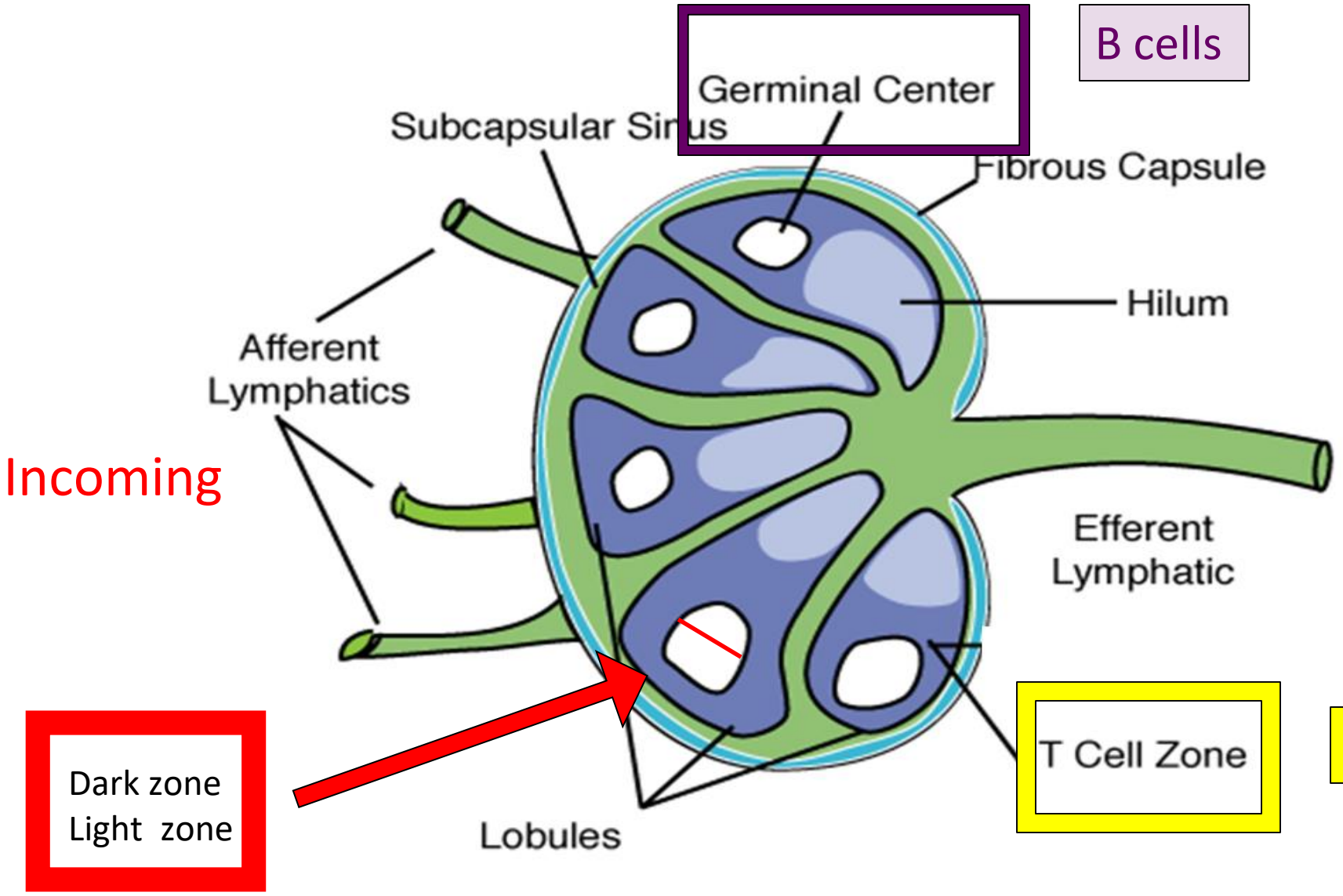
FO OR MZ



AG

PLASMABLAST

in lymphatic tissues



B cells

Incoming

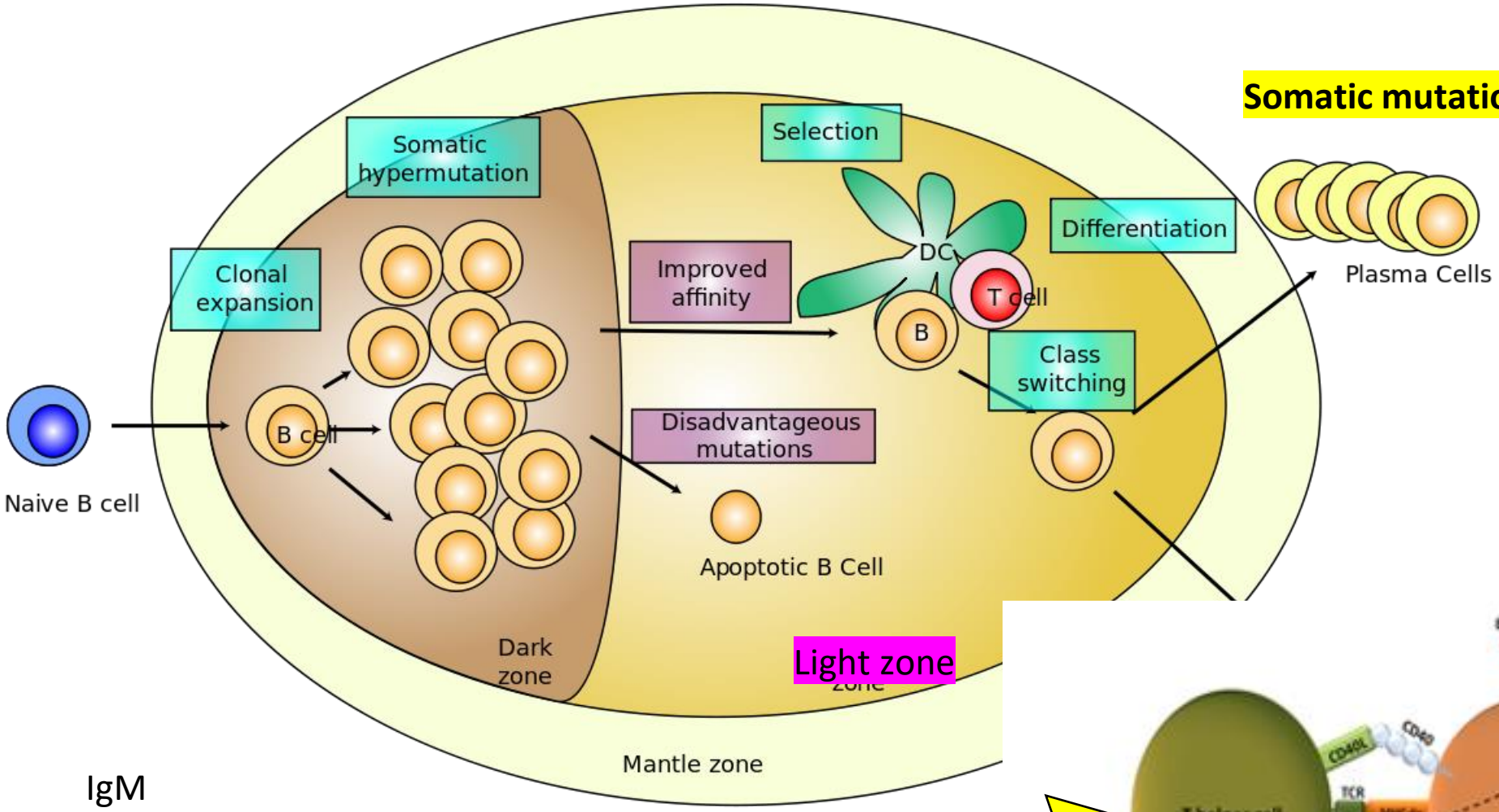
outgoing

CD8

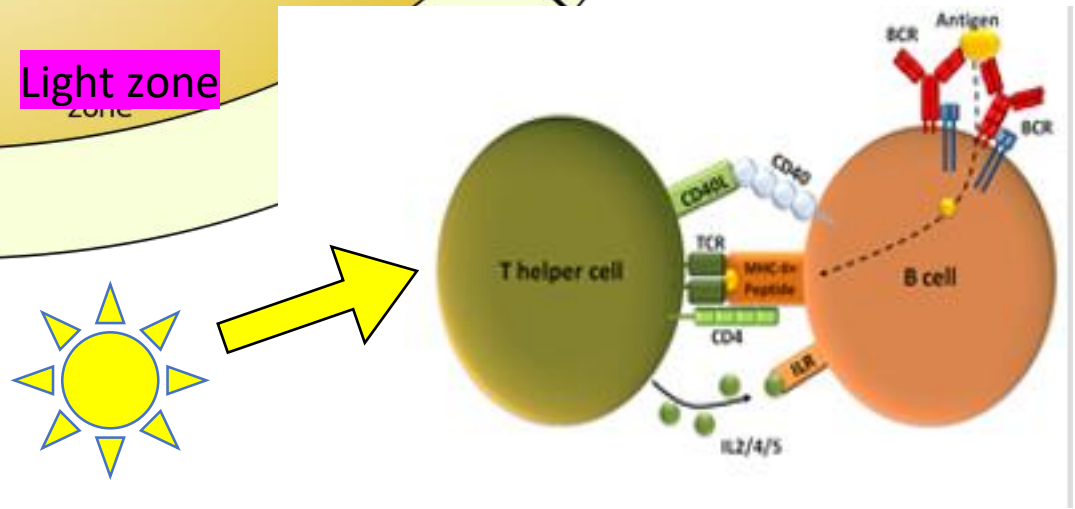
MHC-II

B cell FOLLICLE

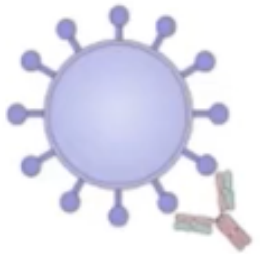
Somatic mutations



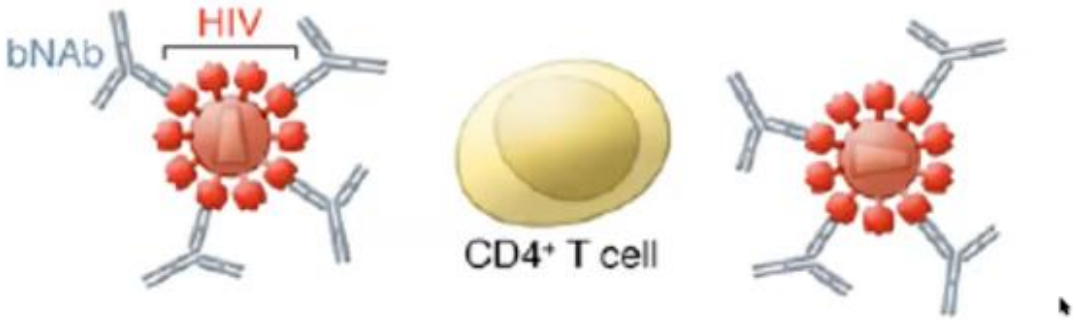
IgM
less affinity
Immed.



Improving effector functions

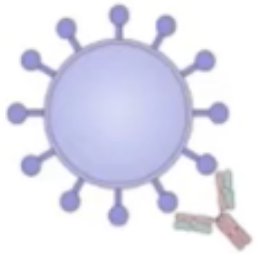


Virus neutralization



Neutralization of cell-free virus

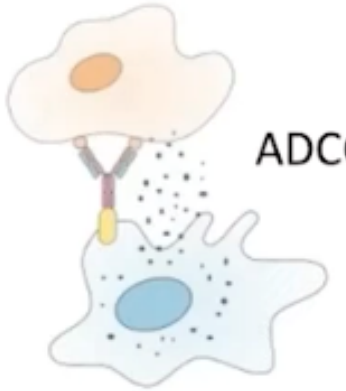
Improving effector functions



Virus neutralization

Activation of complement

CDC

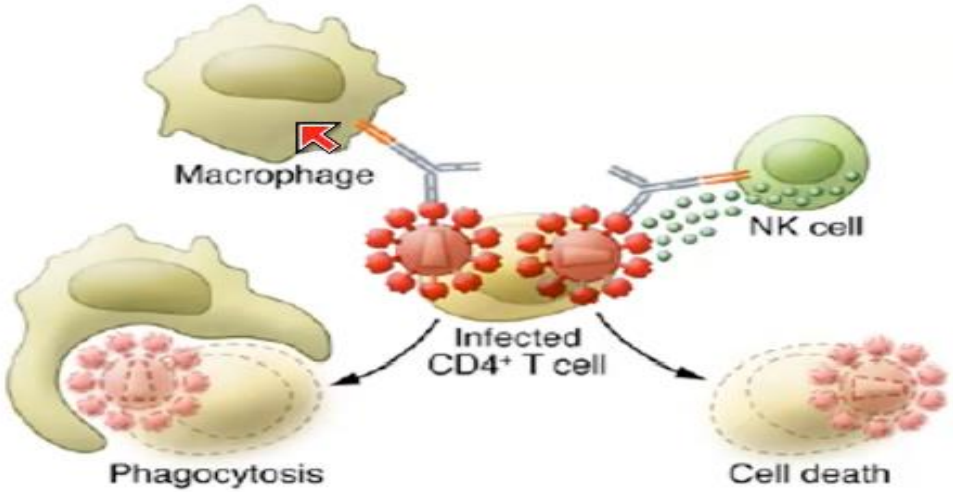


ADCC

Antibody-mediated cell cytotoxicity

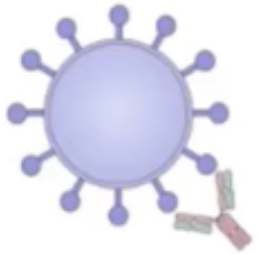
Phagocytosis

Auto-immune
Cancer
HIV- ATI- early/acute



Binding of virus-infected cells:
ADCC via NK cells or ADCP
Phagocytosis via macrophages,
CDC via complement

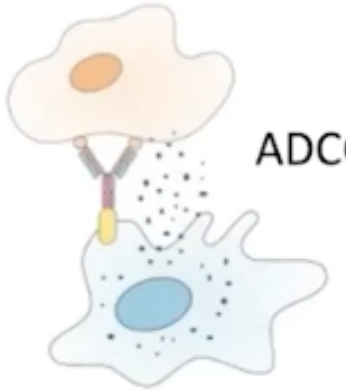
Improving effector functions



Virus neutralization

Activation of complement

CDC

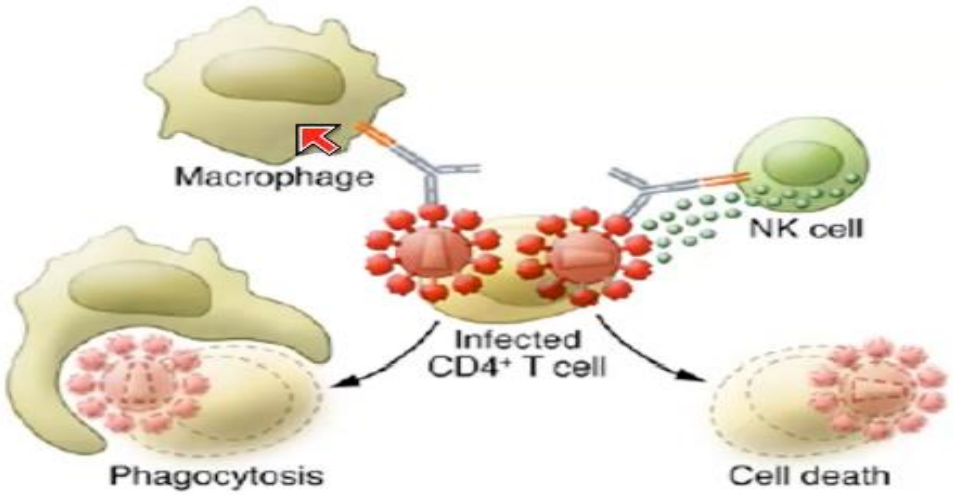


ADCC

Antibody-mediated cell cytotoxicity

Phagocytosis

VACCINAL EFFECT



Binding of virus-infected cells:
ADCC via NK cells or ADCP
Phagocytosis via macrophages,
CDC via complement

nature COMMUNICATIONS

eClear

Nat Commun. 2022; 13: 6473.
Published online 2022 Oct 29. doi: 10.1038/s41467-022-34171-2

PMCID: PMC9617872
PMID: 36309514

Administration of broadly neutralizing anti-HIV-1 antibodies at ART initiation maintains long-term CD8+ T cell immunity

Miriam Rosás-Umbert,[1] Jesper D. Gunst,[1,2] Marie H. Pahus,[1] Rikke Olesen,[1] Mariane Schleimann,[2] Paul W. Denton,[3] Victor Ramos,[4] Adam Ward,[5,6] Natalie N. Kinloch,[7,8] Dennis C. Copertino,[5,6] Tuixent Escribà,[9] Anuska Llano,[9] Zabrina L. Brumme,[7,8] R. Brad Jones,[5,6] Beatriz Mothe,[9,10,11] Christian Brander,[9,11,12] Julie Fox,[13,14] Michel C. Nussenzweig,[4,15] Sarah Fidler,[16,17] Marina Caskey,[4] Martin Tolstrup,[1,2] and Ole S. Søgaard[1,2]

cellular immunity were directly correlated to pre-treatment 3BNC117-sensitivity. Notably, increased HIV-1-specific immunity is associated with partial or complete ART-free virologic control during treatment interruption for up to 4 years. Our findings suggest that bNAb treatment at the time of ART initiation maintains HIV-1-specific CD8+ T cell responses that are associated with ART-free virologic control.

nature COMMUNICATIONS

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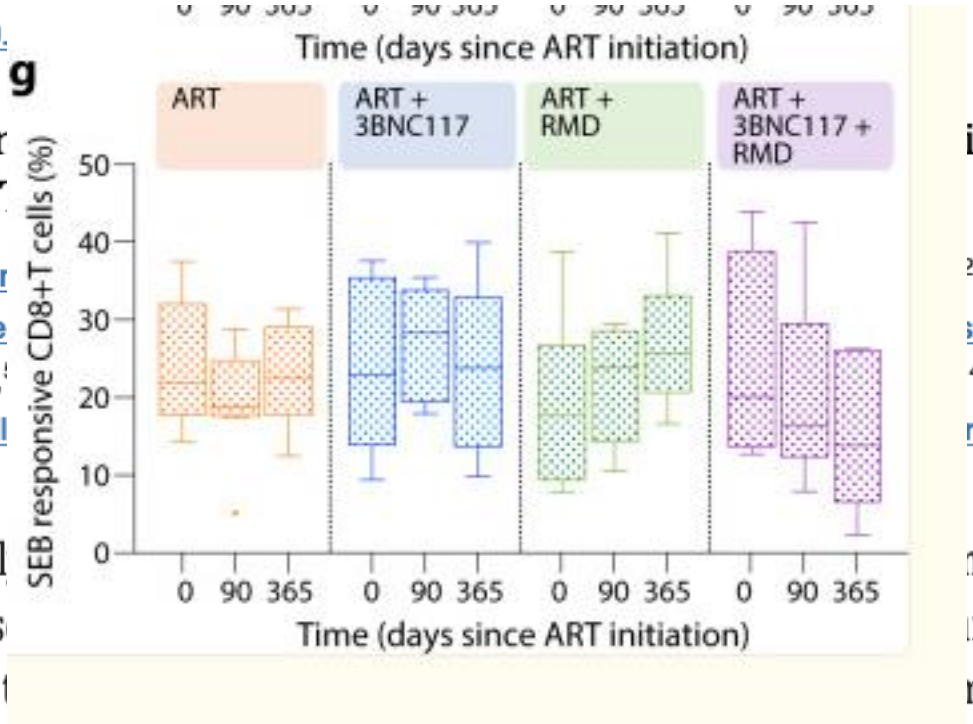

cellular immunity were directl ncreased
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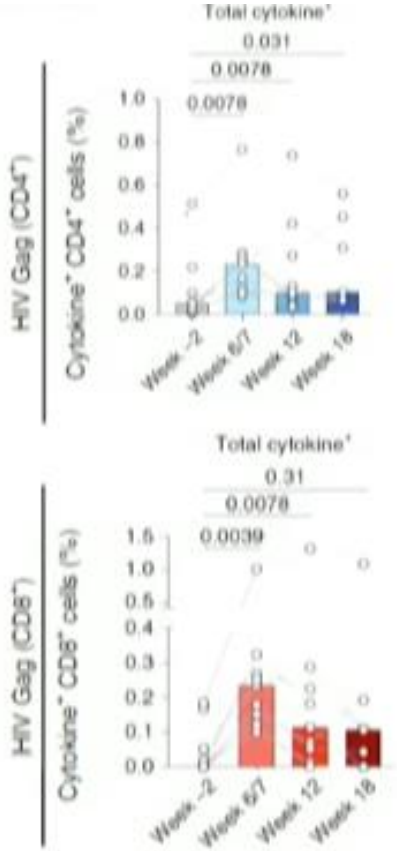
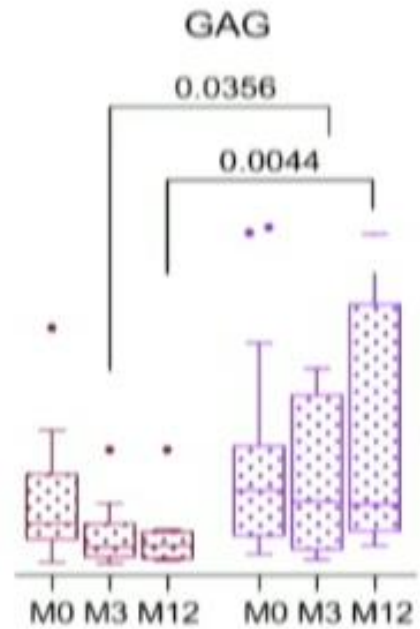


Niessl; Nat Med 2020

Increase in multiple cytokines after bNAbs

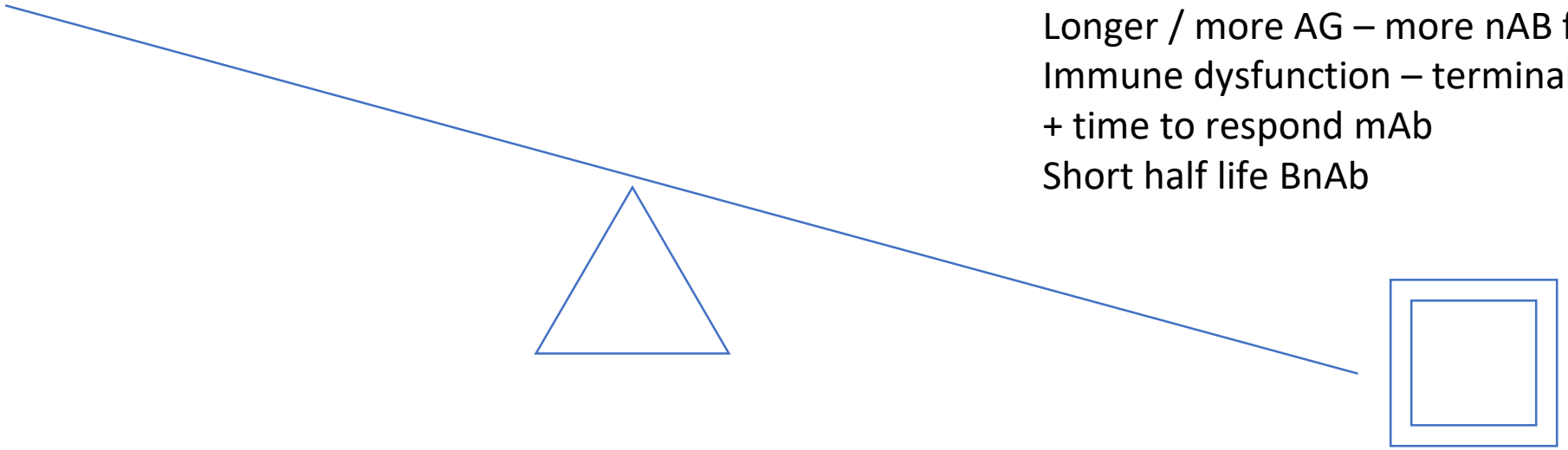


Rosas-Umbert, Sogaard; CROI 2022

Gag-specific CD8s increase

Few conserved cell epitopes surface HIV
Dynamic oscillations / conformational binding
Gylcan shield
Diverse quasispecies
Complex reservoir

HIV

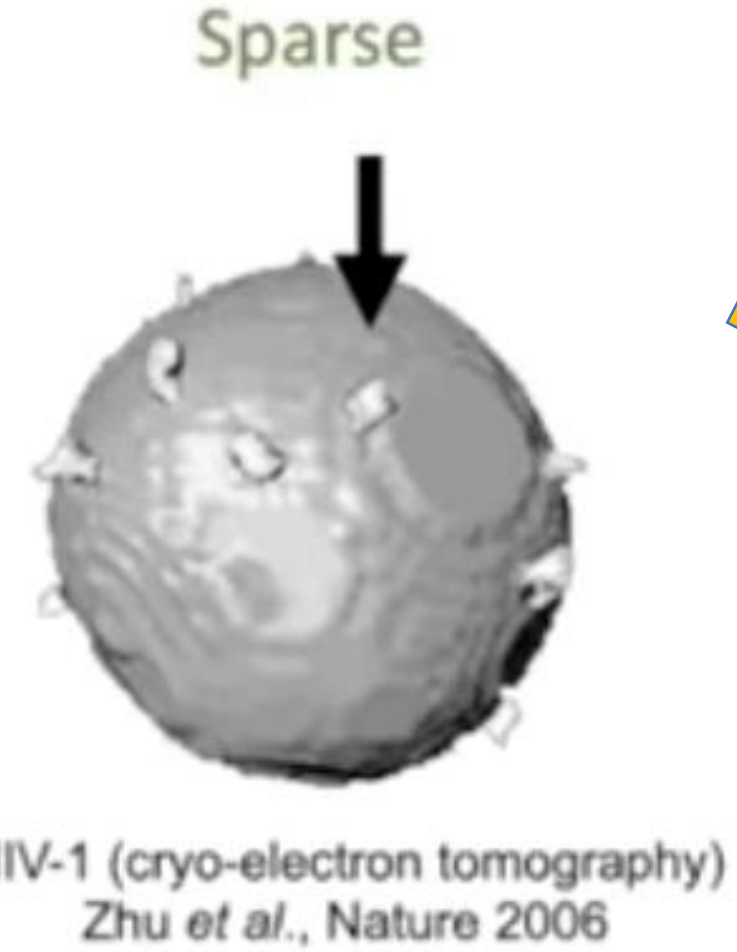


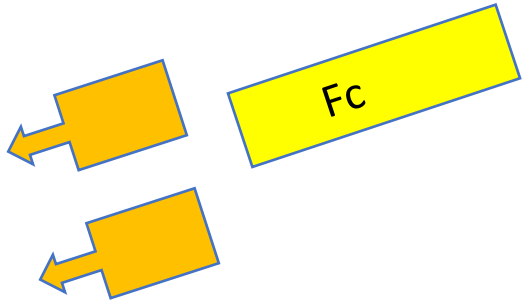
Longer / more AG – more nAB formed
Immune dysfunction – terminal otogeny
+ time to respond mAb
Short half life BnAb

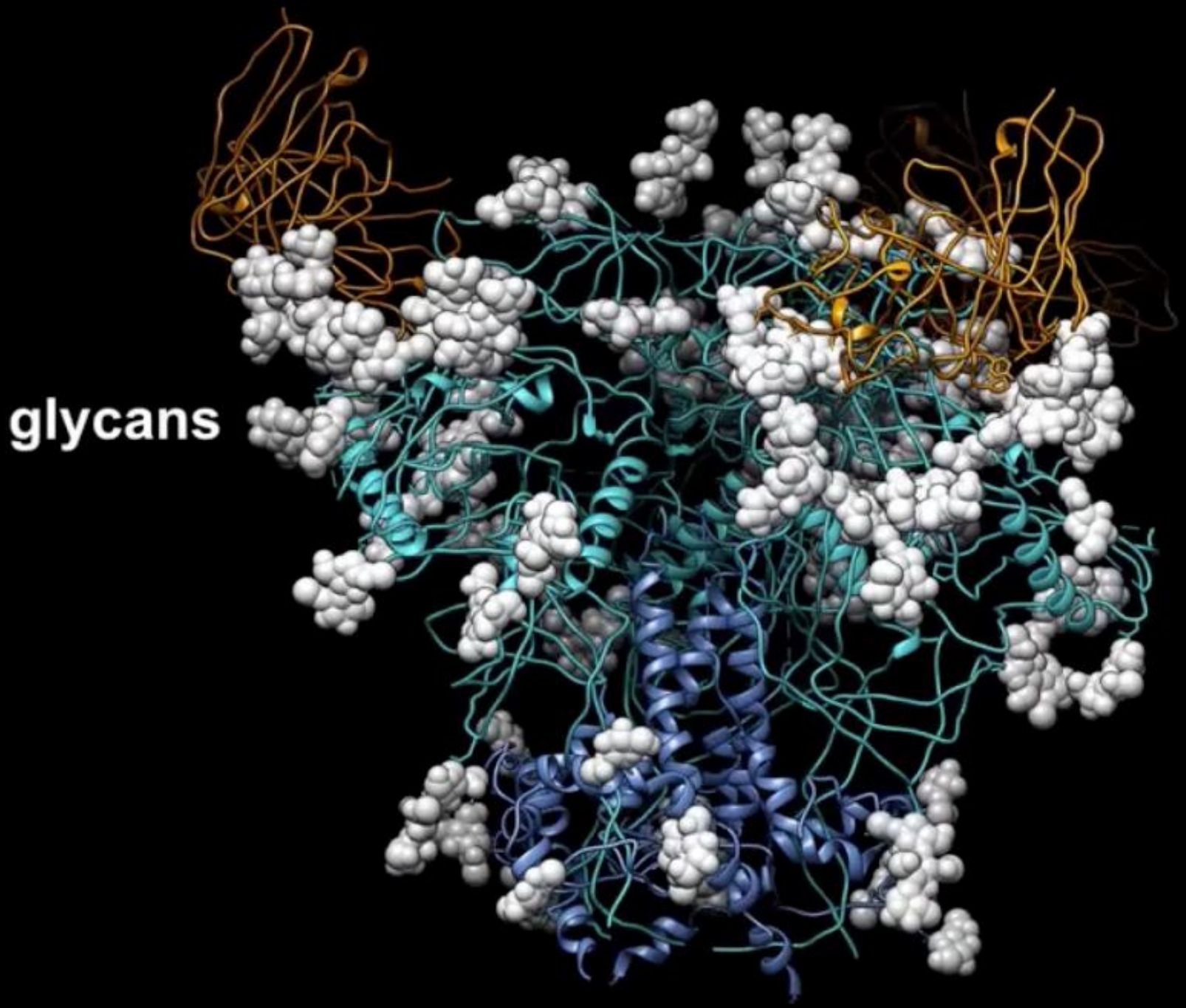
Patient

Few surface epitopes

Non-neutralizing one attachment






glycans

activated

+ transcription

no full length HIV

- *Short abortive* HIV

- ***? rare HIV epitopes***

No sig RV

Latency: ? Lack production

large deletions

++ and NOT activated

+++transcription HIV RNA

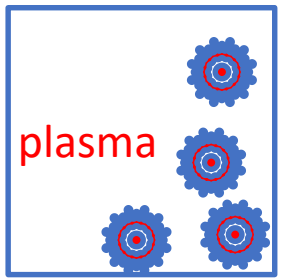
MINOR defective HIV

defective HIV

+ HIV protein produced

+ HIV epitopes

+ RV ? infectious

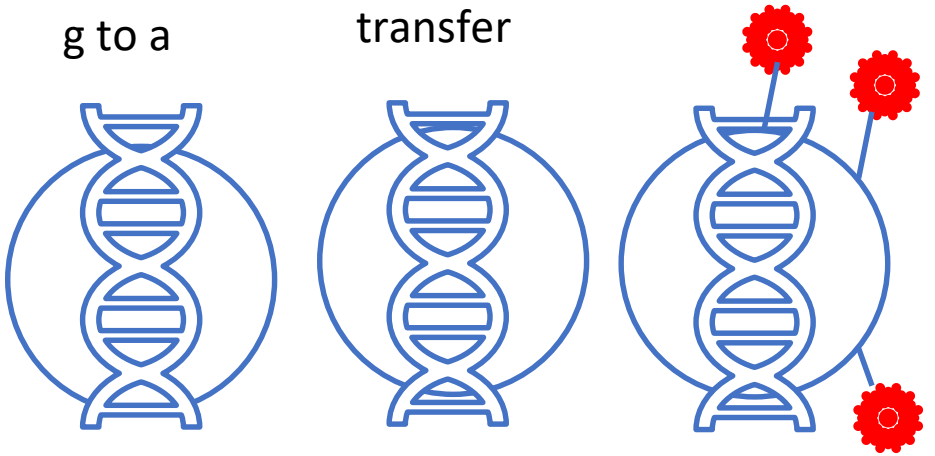


minor deletions

APOBEC

g to a

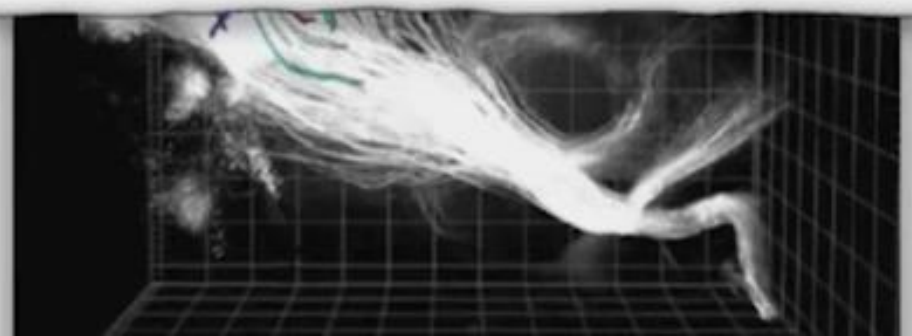
5 ‘ strand transfer



Antibodies with Improved Potency/Breadth

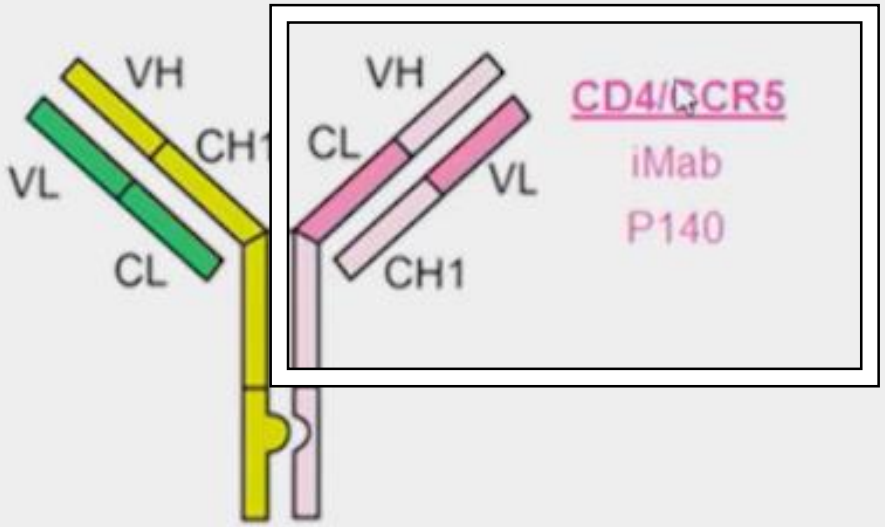
Engineered Bispecific Antibodies with Exquisite HIV-1-Neutralizing Activity.

Huang Y, Yu J, Lanzi A, Yao X, Andrews CD, Tsai L, Gajjar MR, Sun M, Seaman MS, Padte NN, Ho DD.



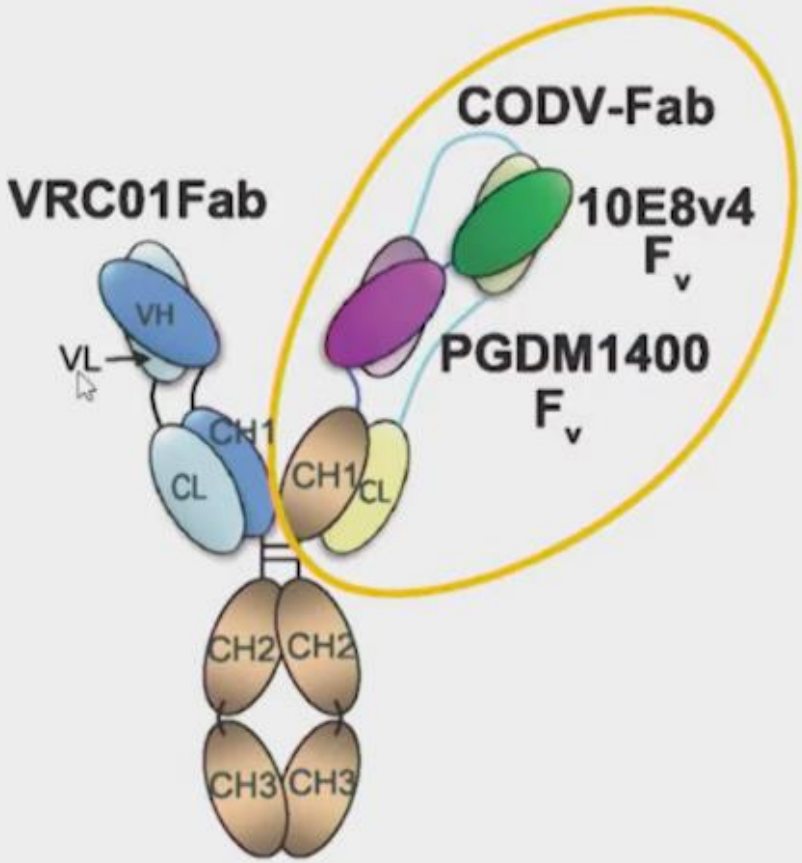
Cross-MAb Technology

Env
10E8
3BNC117
PGT128
PGT145
PGT151

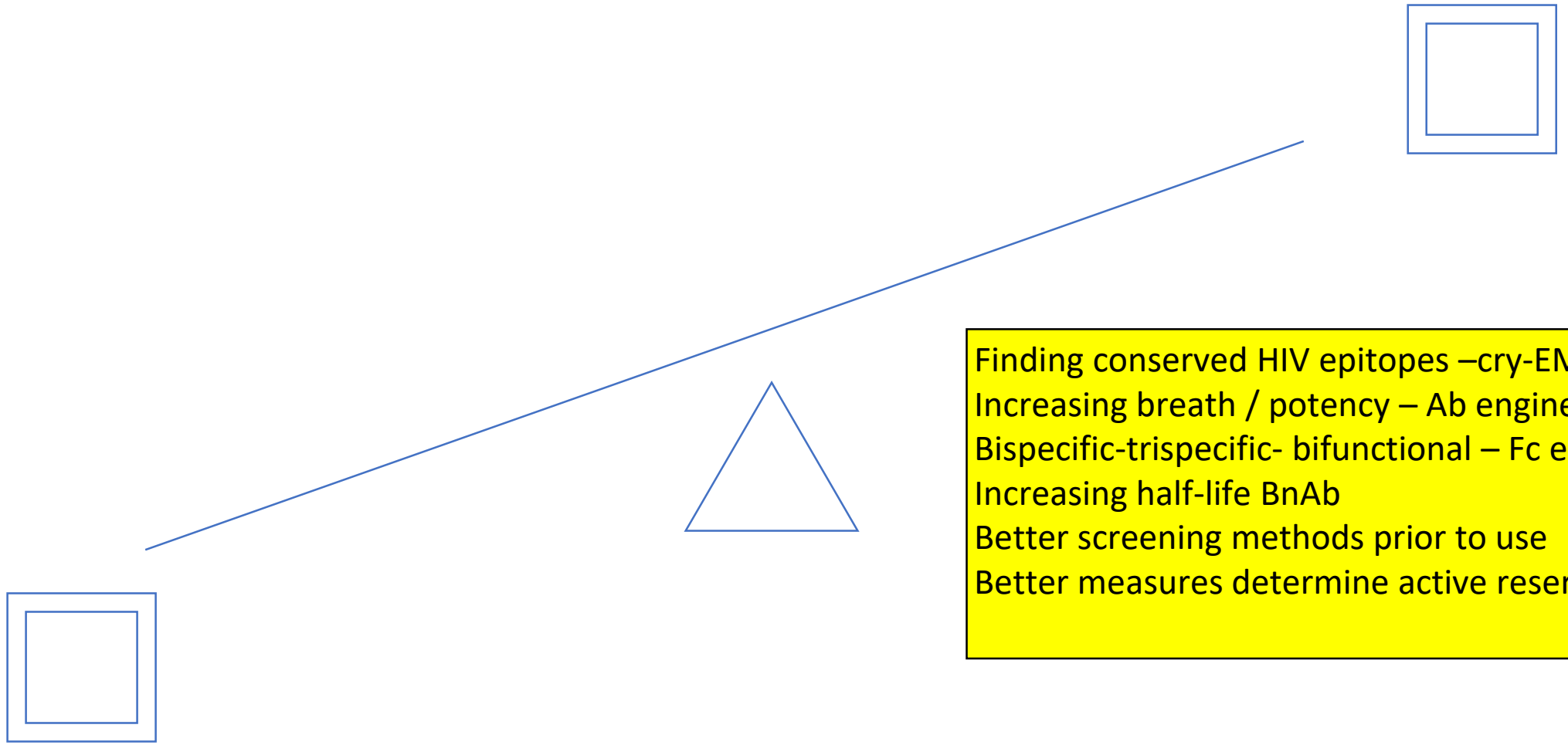


CD4/CCR5
iMab
P140

Three Antibody Specificities on One Antibody Molecule



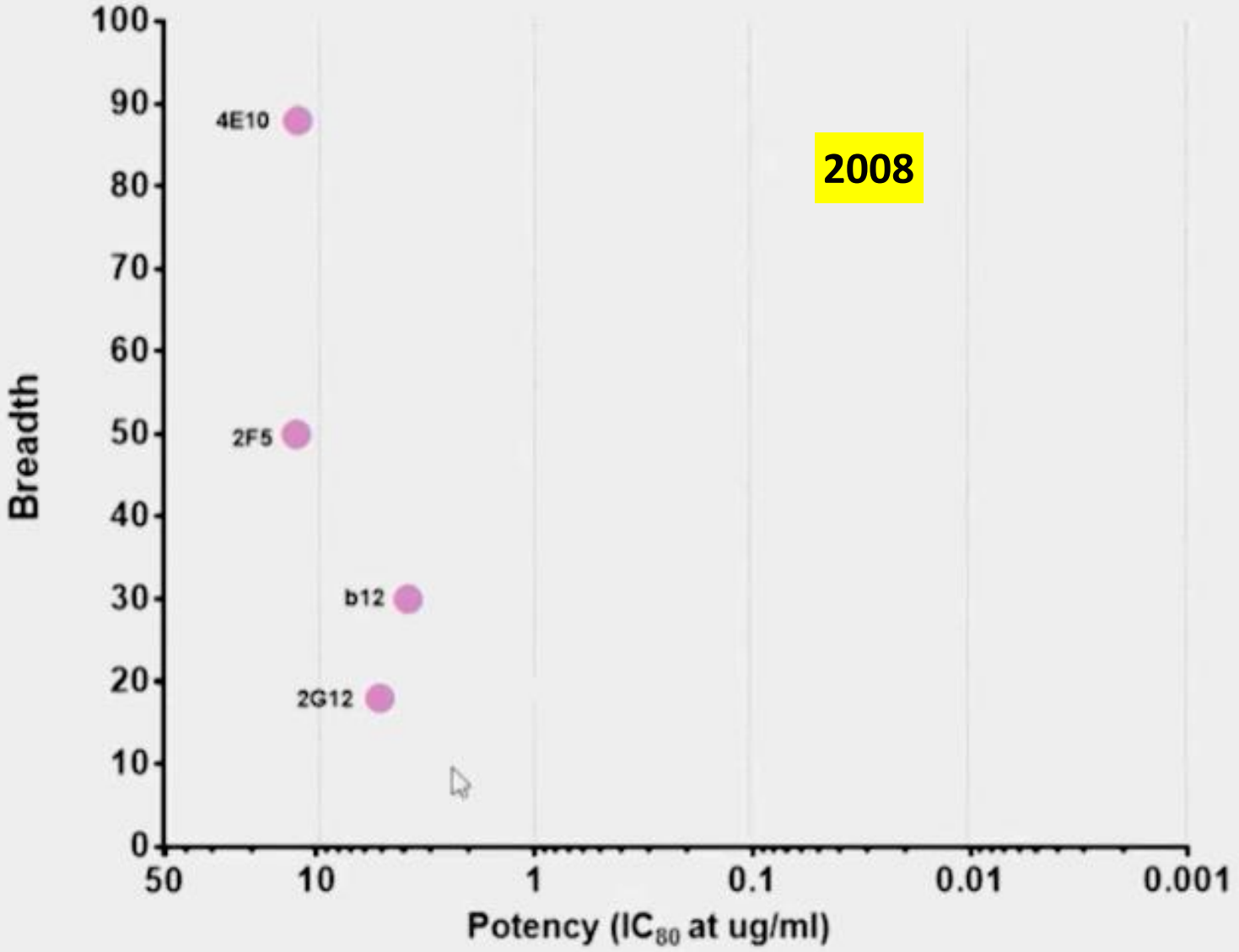
Patient



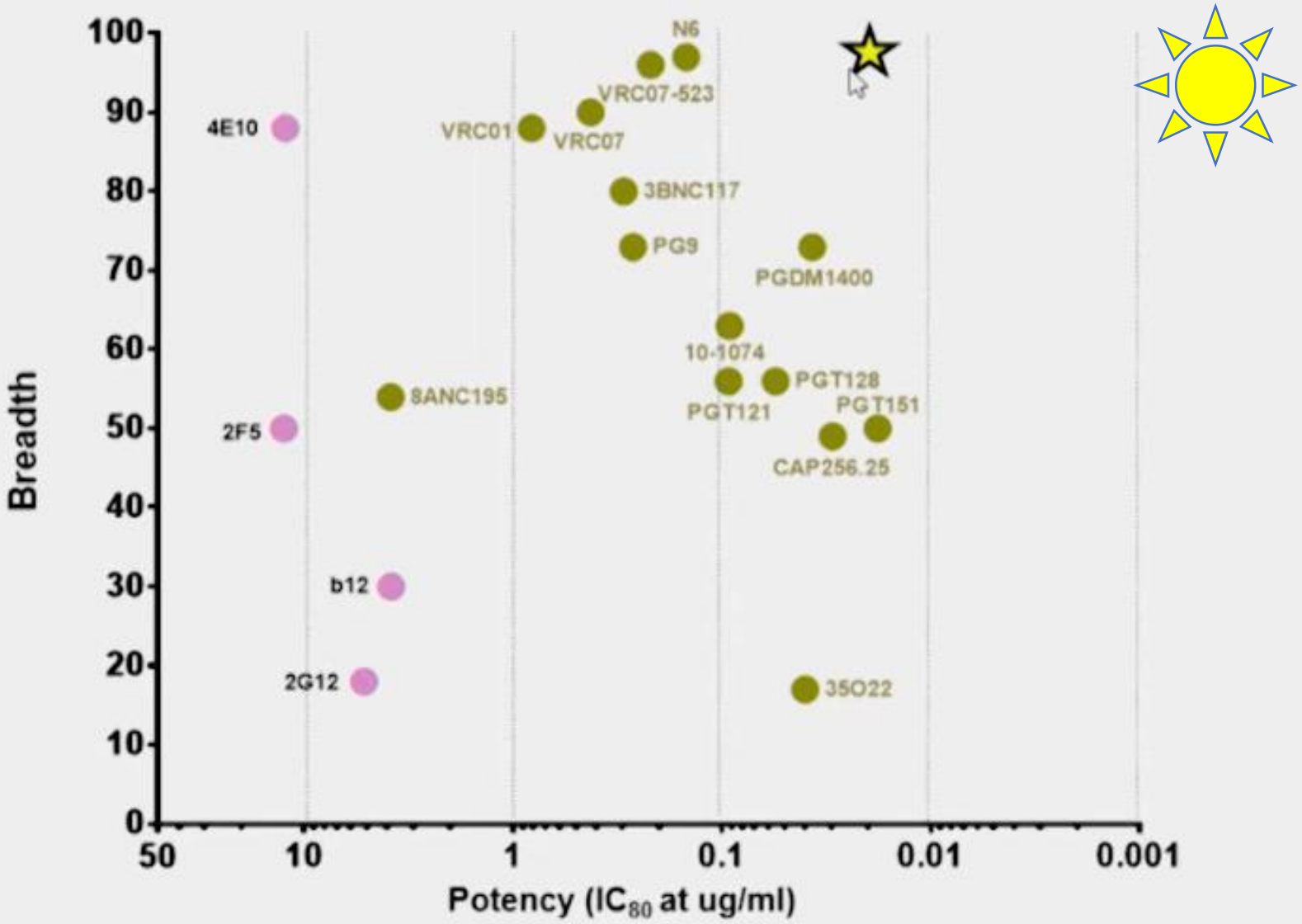
Finding conserved HIV epitopes –cry-EM
Increasing breath / potency – Ab engineering
Bispecific-trispecific- bifunctional – Fc effector function
Increasing half-life BnAb
Better screening methods prior to use
Better measures determine active reservoir

HIV

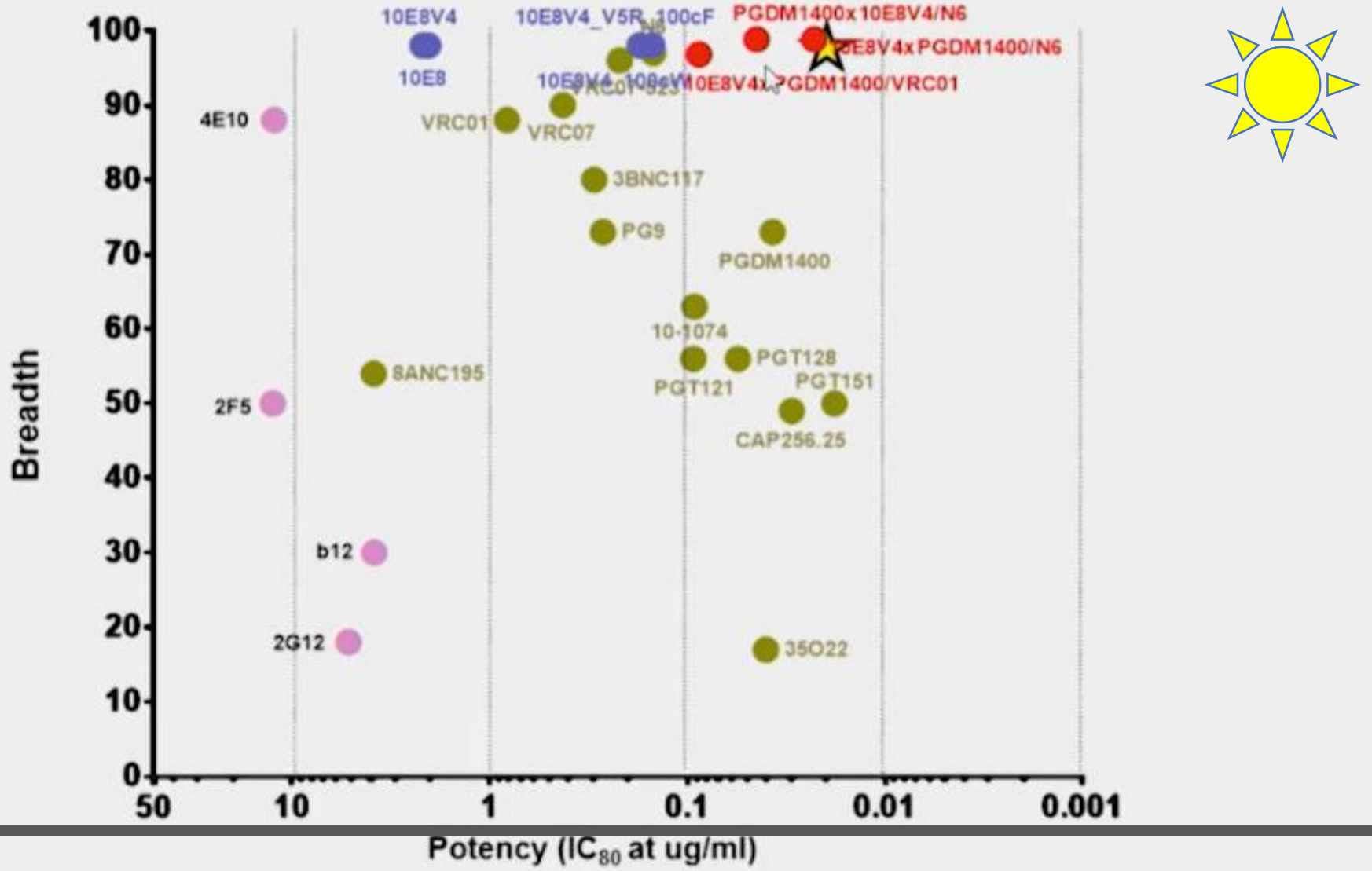
Potency and Breadth



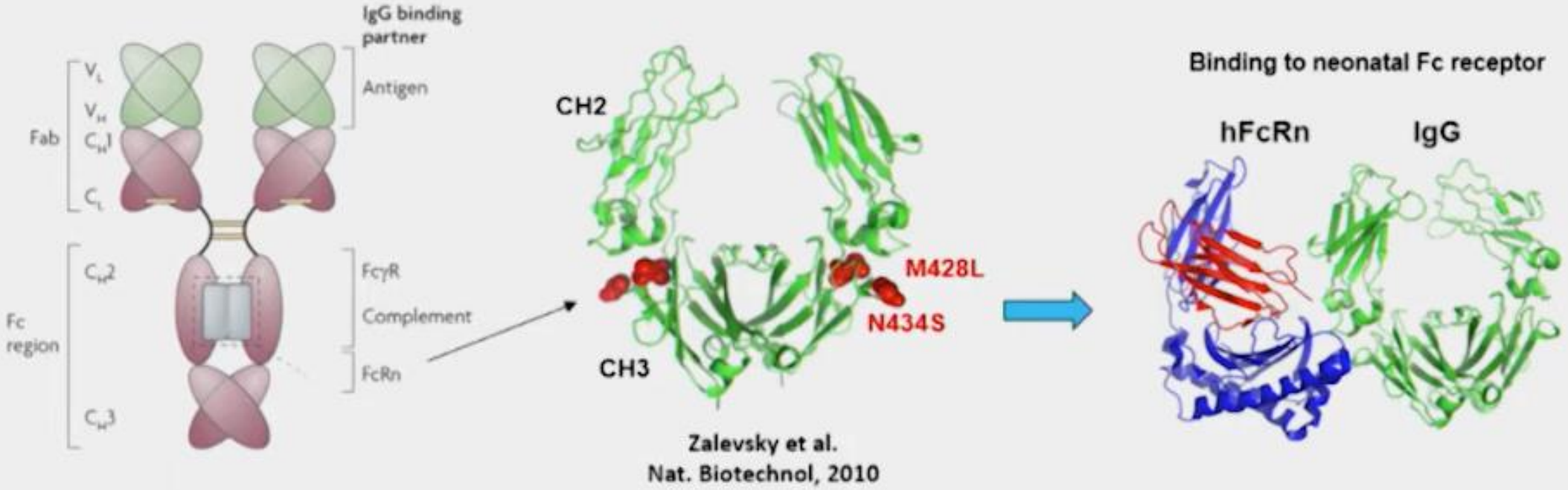
Potency and Breadth



Potency and Breadth



Extending mAb half-life in humans

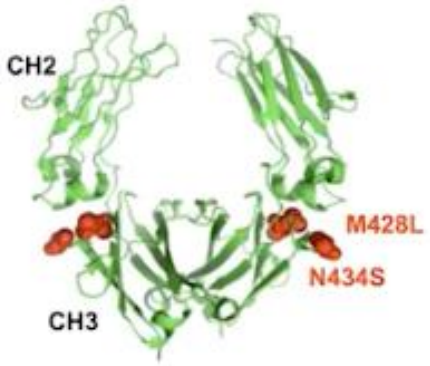


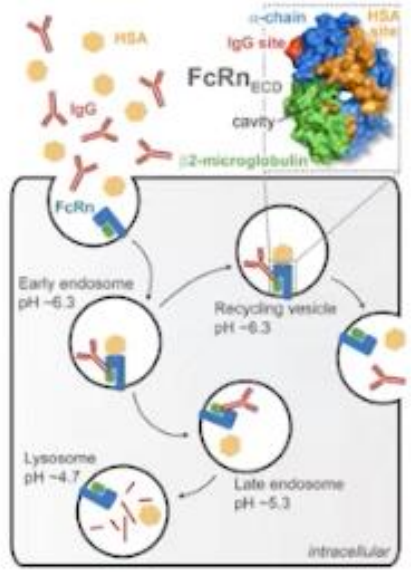
Zalevsky et al.
Nat. Biotechnol, 2010

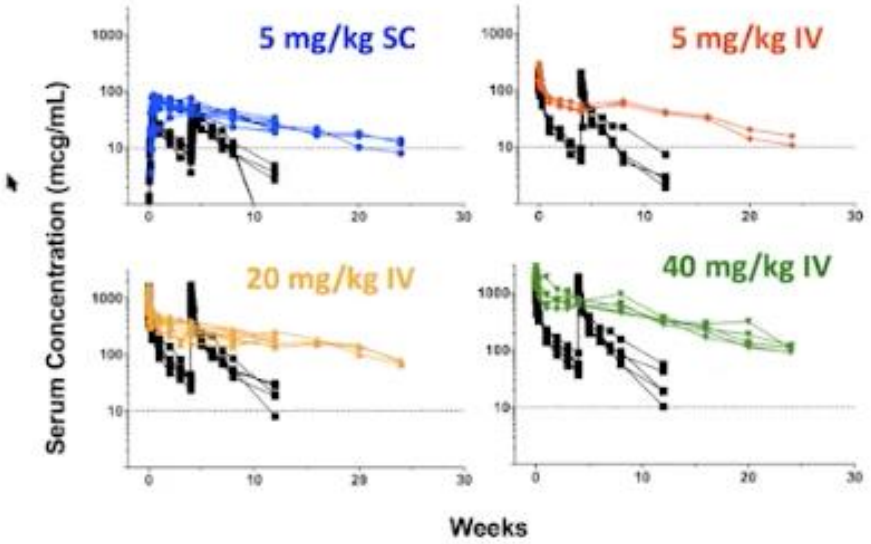
- Fc region binds with high affinity to FcRn at acidic pH (<6.5) in endosome
- Protects antibody from endosomal degradation
- IgG released back into circulation at physiological pH (7.4)
- <u>Results in prolonged circulating half life</u>

Improving serum half-life

LS Mutations







VRC01LS Group	$t_{1/2}$ (days)	12 wk trough (mcg/mL)
5 mg/kg SC	66	25
5 mg/kg IV	83	40
20 mg/kg IV	78	160
40 mg/kg IV	55	326
Historical VRC01 wildtype		

Gaudinski, Coates. PLoS Med. 2018

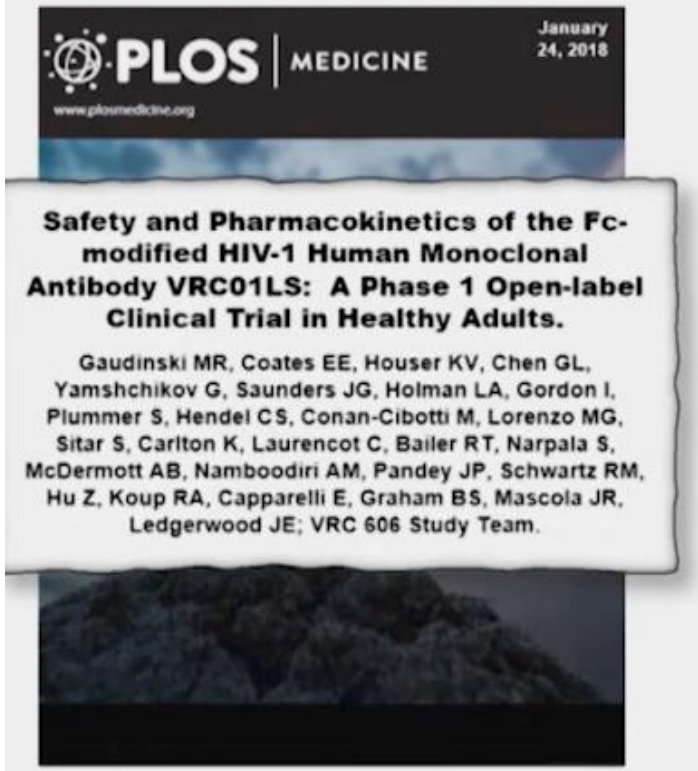
NATURE BIOTECHNOLOGY VOLUME 28 NUMBER 2 FEBRUARY 2010

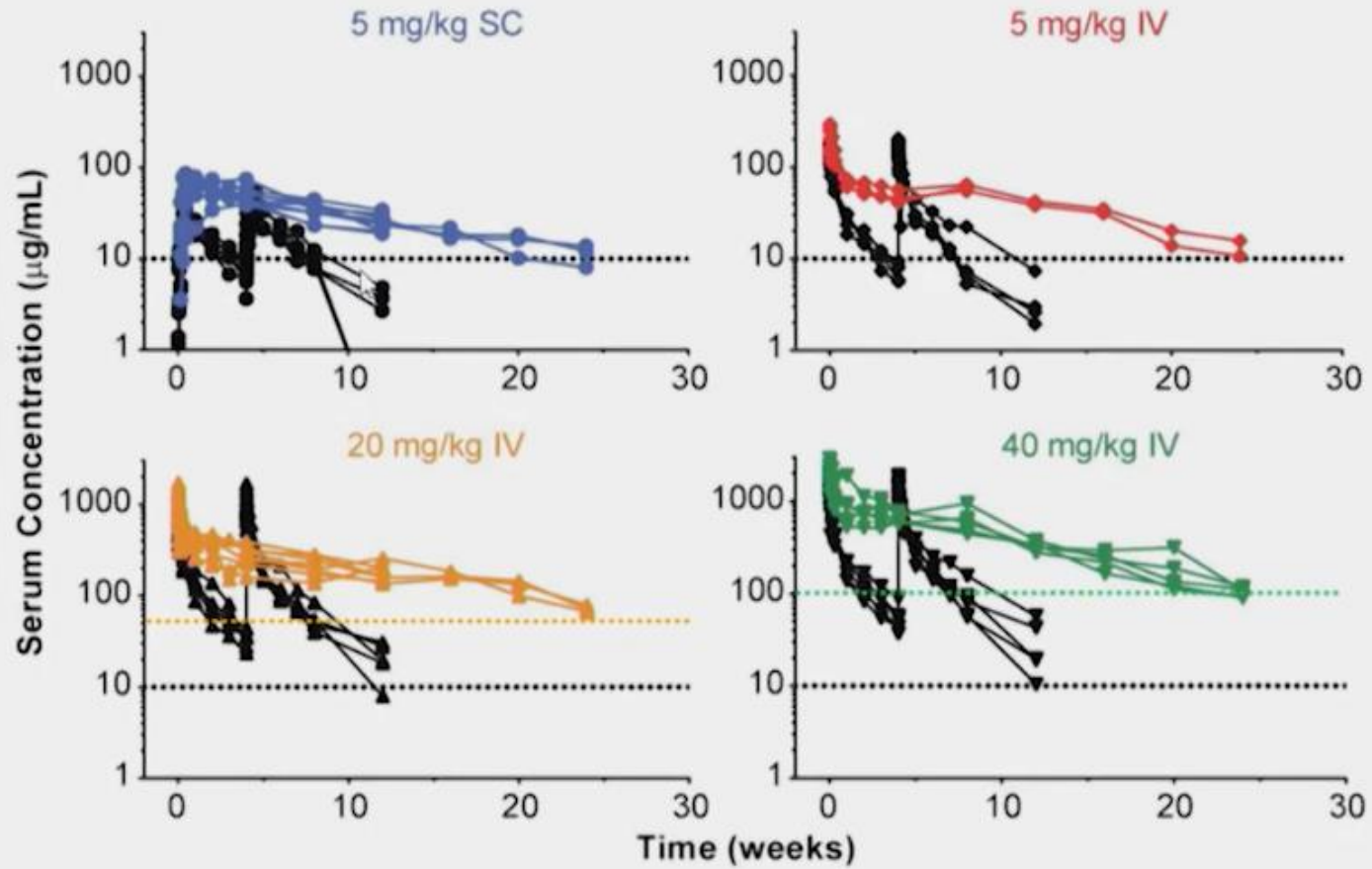
Enhanced antibody half-life improves *in vivo* activity

Jonathan Zalevsky[1,3], Aaron K Chamberlain[1], Holly M Horton[1], Sher Karki[1], Irene W L Leung[1], Thomas J Sproule[2], Greg A Lazar[1], Derry C Roopenian[2] & John R Desjarlais[1]

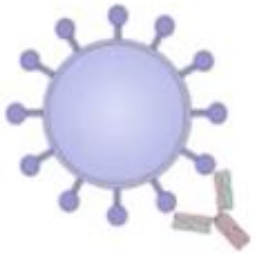
Name BnAb- **LS**

VRC01LS Extended Half-Life





Improving effector functions



Virus neutralization

ADCC

Antibody-mediated cell cytotoxicity

Activation of complement

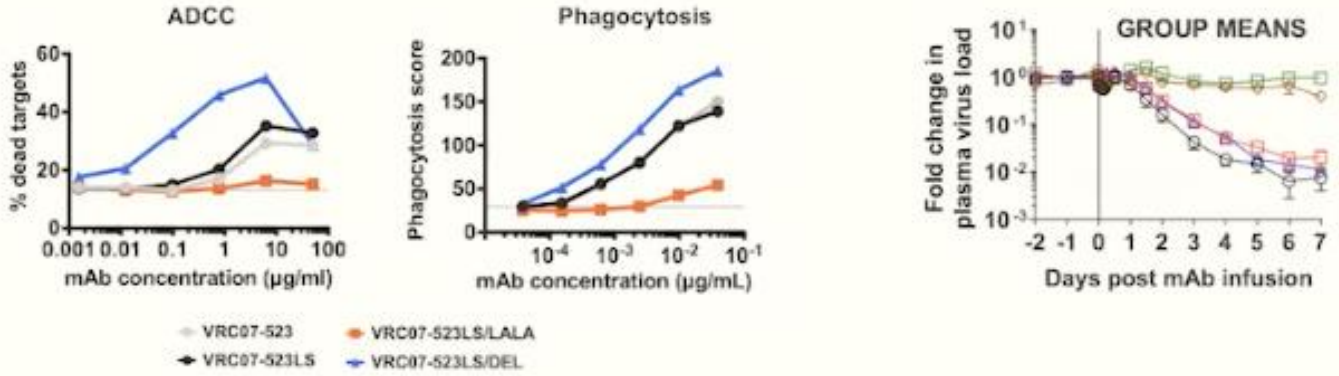
CDC

Phagocytosis

PNAS | August 4, 2020 | vol. 117 | no. 31

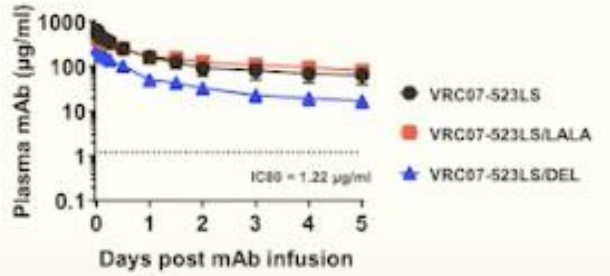
Fc-mediated effector function contributes to the in vivo antiviral effect of an HIV neutralizing antibody

Mangaiarkarasi Asokan[a,1], Joana Dias[b], Cuiping Liu[a], Anna Maximova[a], Keenan Ernste[a], Amarendra Pegu[a], Krisha McKee[a], Wei Shi[a], Xuejun Chen[a], Cassandra Almasri[a], Wanwisa Promsote[b], David R. Ambrozak[b], Lucio Gama[b], Jianfei Hu[c], Daniel C. Douek[c], John-Paul Todd[d], Jeffrey D. Lifson[e], Slim Fourati[f], Rafick P. Sekaly[f], Andrew R. Crowley[g], Margaret E. Ackerman[g], Sung Hee Ko[h], Divya Kilam[h], Eli A. Boritz[h], Laura E. Liao[i], Katharine Best[i], Alan S. Perelson[i], John R. Mascola[a], and Richard A. Koup[b,1]



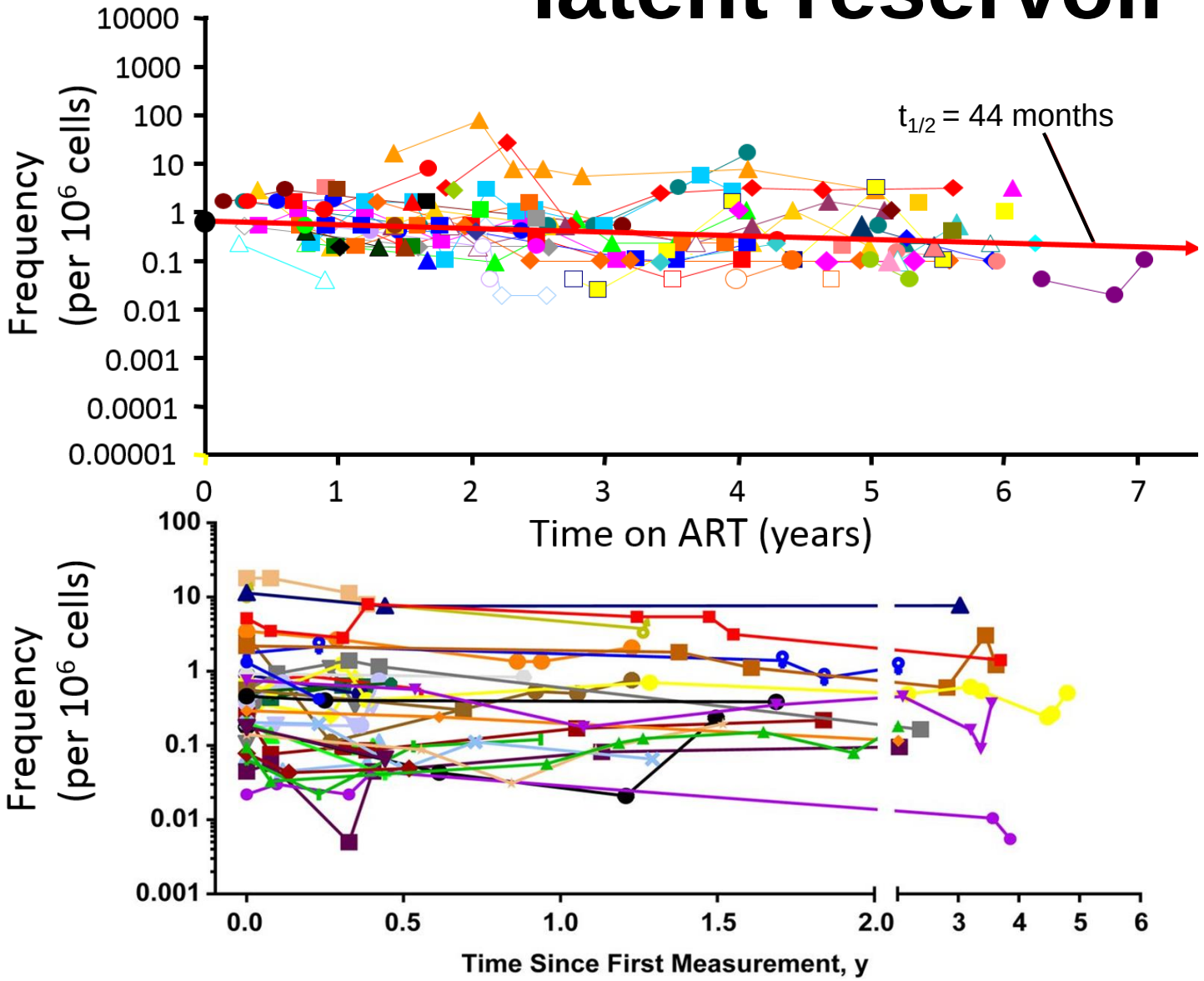
DEL ↑ ADCC

LALA ↓ ADCC



Method	Description	Logistics	Advantages	Disadvantages
PhenoSense Monogram assay	Measures the response of an individual's virus to antiretroviral therapy (ART)	Cost: Hight ime: several days to weeks Effort: specialized equipment and personnel training	Provides insights regarding an individual's susceptibility to various antiretroviral therapies	High cost and time
TZM-bl Neutralization assay	Measures the neutralization capacity of antibody against various strains of HIV-1	Cost: hight ime: several days Effort: specialized equipment and personnel training	Provides a functional measure of the neutralizing capacity of antibodies	High cost and time
Genotyping	Analyzes the genetic composition of HIV-1 to predict antibody sensitivity	Cost: lowt ime: several days Effort: computational database	Provides mutational sequencing information from the virus genetic composition	Limited by availability of sequencing datasets
Sequencing Q4 assay	Analyzes HIV-1 genetic composition at different	Cost: lowt ime: several days	Provides specific sequencing information as the virus	Multiple samples required at different

QVOA demonstrates slow decay of the latent reservoir



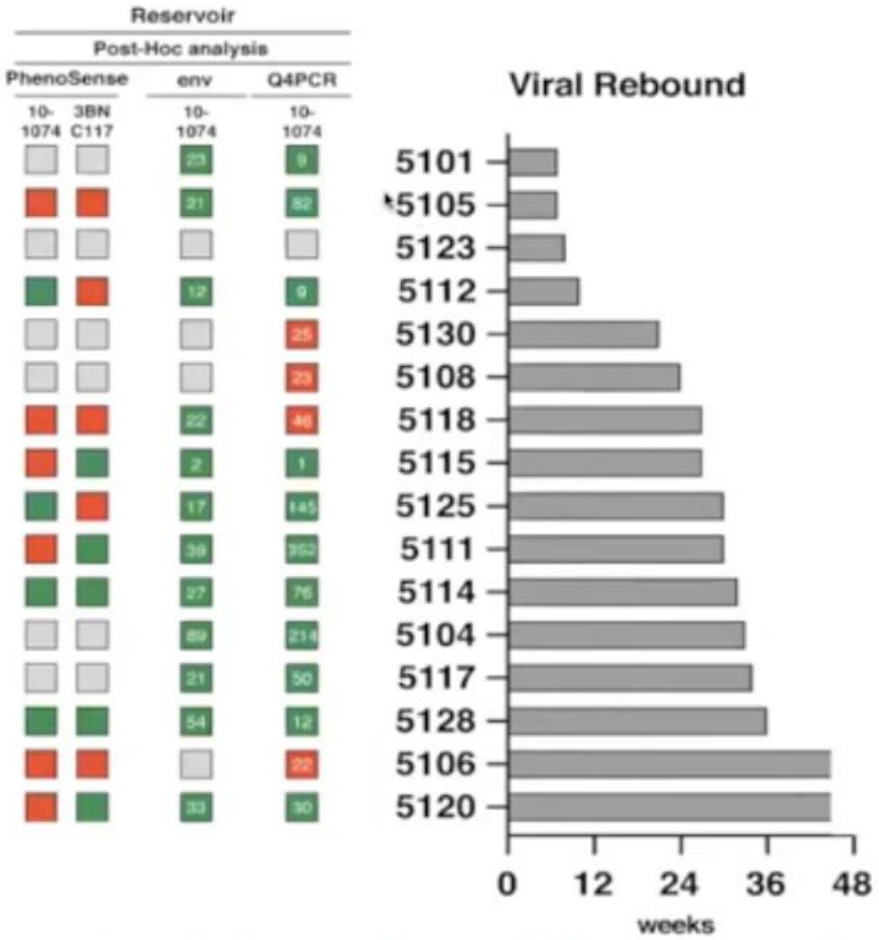
$t_{1/2}$ = 44 months

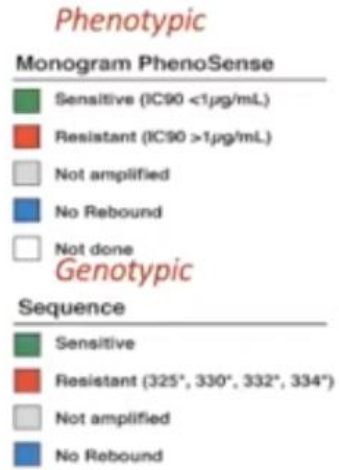
Finzi et al, Nature Med, 1999
Siliciano et al, Nature Med., 2003

$t_{1/2}$ = 43 months

Crook et al, JID 2015

Assessment of Baseline bNAb Sensitivity: Phenotypic and Genotypic Methods





Christian Gaebl
Thiago Olivei
Jackie Reeves(Monograr

- Both genotypic and phenotypic sensitivity **analyses of proviruses would not** have reliably **predicted clinical outcome and time to viral rebound.**

Key Sites of Neutralization-Sensitivity on HIV-1 gp160

What immune systems sees -- Env

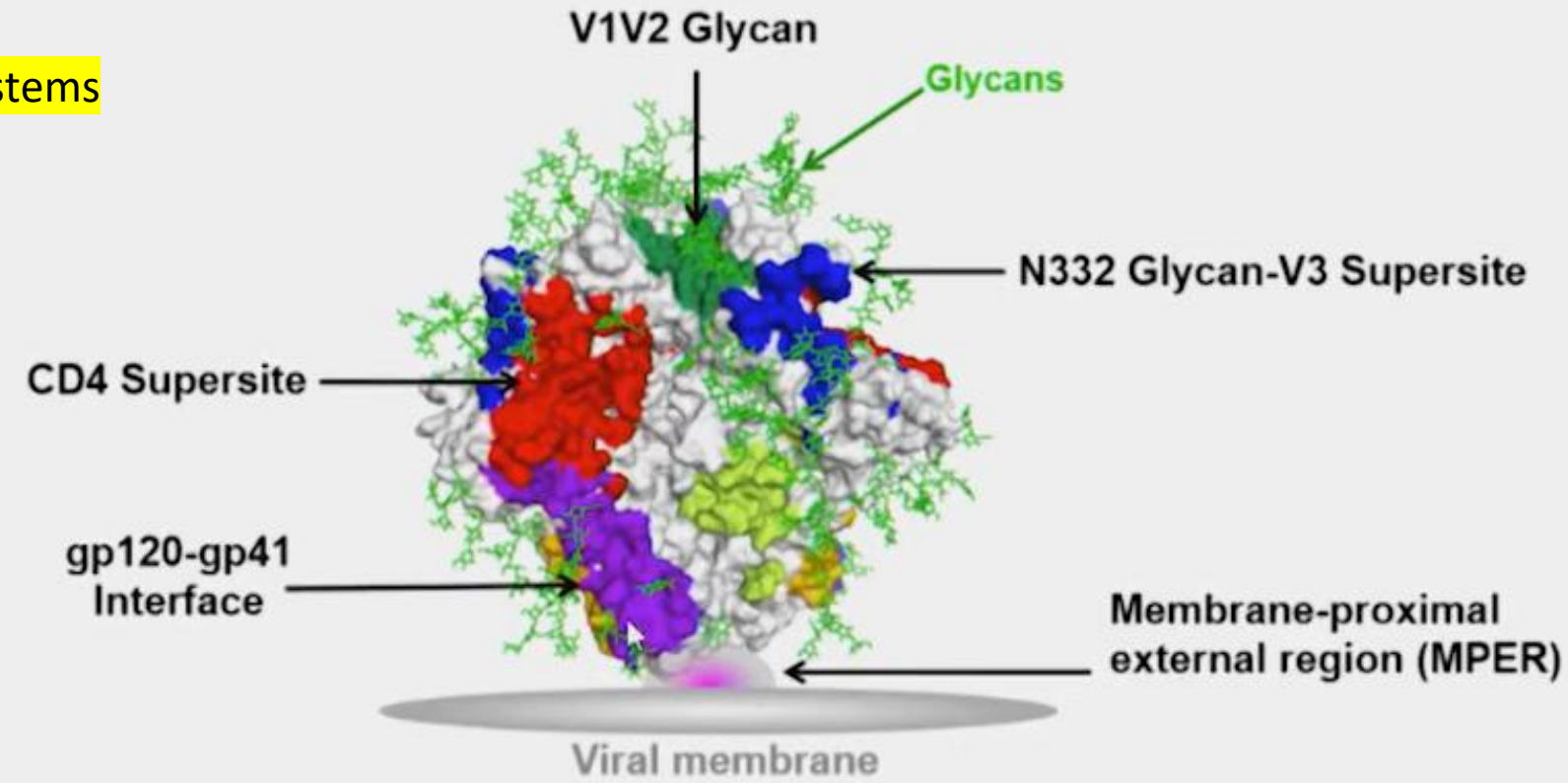
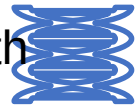


Image by Stewart-Jones, Doria-Rose, Stuckey

Resting latent

Full length HIV



→ Homeostatic proliferation

3 fold higher

Large deletions

→ Short abortive RNA sequences / low Tat
unable to produce HIV proteins

Minor deletions

Central memory effector

→ +Transcriptionally
Produce multiple spliced RNA

→ Produce p24 Ag

Pos VL plasma

Env/gag depleted
bNAb neg

Factors in production of BnAb in HIV infection

Consistent antigenic stimulation: increase neutralization breath

(length of infection , amount of viral load

[**BUT also happens in elite LTNP**]

too much – end termination otogeny

? Difference in evolution in viral diversity

? Differences in glycosylation , variable loop formation, etc

No difference in mode of transmission of infection , sex

More common in maternal –fetal transmission

One bNAb may not be enough

HIV-1 Antibody 3BNC117 Suppresses Viral Rebound in Humans During Treatment Interruption.

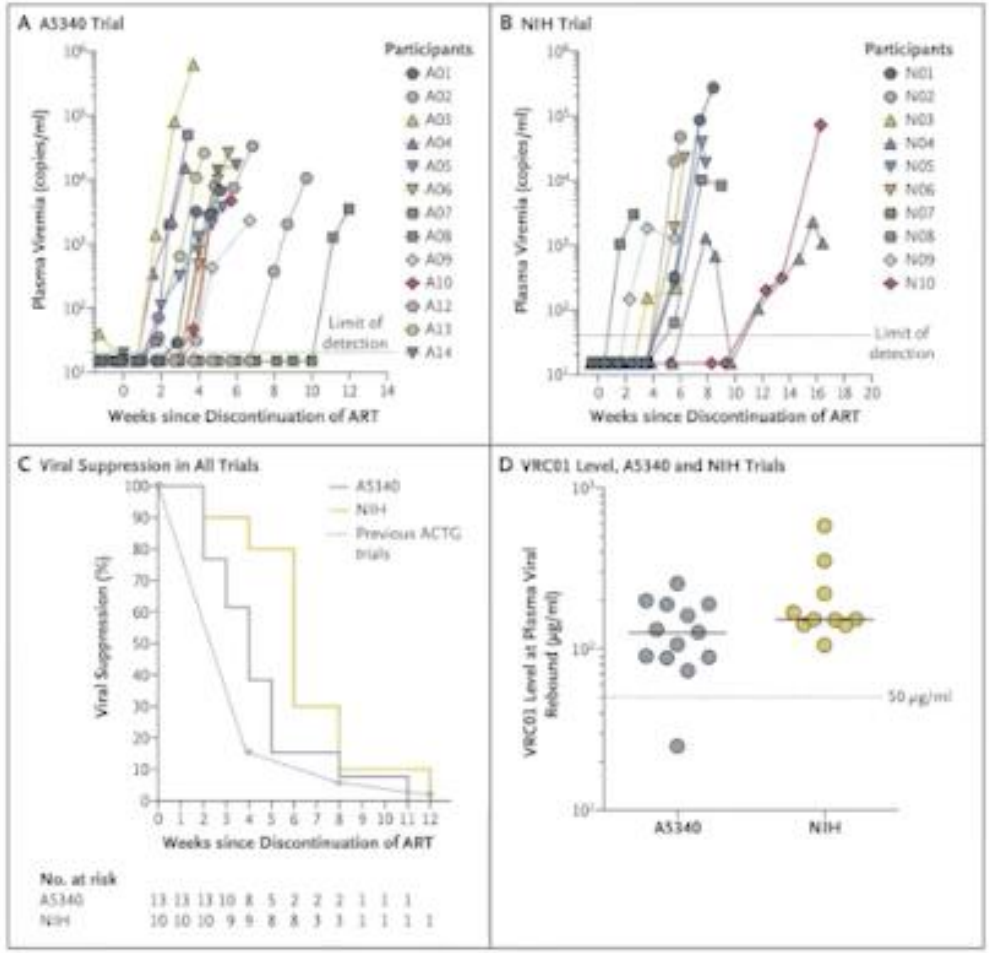
Scheid JF, Horwitz JA, Bar-On Y, Kreider EF, Lu CL, Lorenzi JC, Feldmann A, Braunschweig M, Nogueira L, Oliveira T, Shimeliovich I, Patel R, Burke L, Cohen YZ, Hadrigan S, Settler A, Witmer-Pack M, West AP Jr, Juelg B, Keler T, Hawthorne T, Zingman B, Gulick RM, Pfeifer N, Learn GH, Seaman MS, Bjorkman PJ, Klein F, Schlesinger SJ, Walker BD, Hahn BH, Nussenzweig MC.

Nature July, 2016

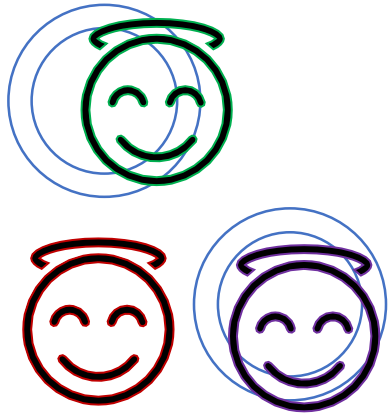
Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption.

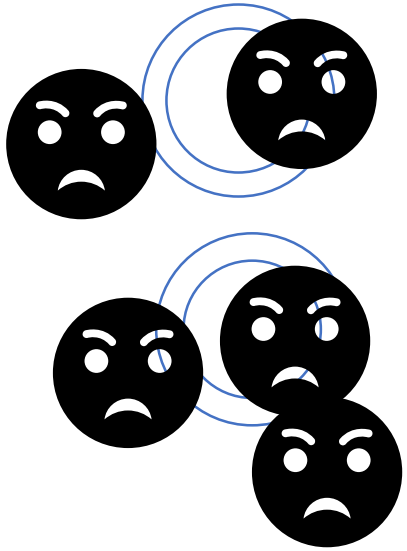
Bar KJ, Sneller MC, Harrison LJ, Justement JS, Overton ET, Petrone ME, Salantes DB, Seamon CA, Scheinfeld B, Kwan RW, Learn GH, Proschan MA, Kreider EF, Blazkova J, Bardsley M, Refsland EW, Messer M, Clarridge KE, Tustin NB, Madden PJ, Oden K, O'Dell SJ, Jarocki B, Shiakolas AR, Tressler RL, Doria-Rose NA, Bailer RT, Ledgerwood JE, Capparelli EV, Lynch RM, Graham BS, Moir S, Koup RA, Mascola JR, Hoxie JA, Fauci AS, Tebas P, Chun TW.

NEJM November 2016



Simple Complex reservoir fully suppressed





Longer viremia:

larger tissue burden
more diverse
70% 1-2 years pre-ART

Wax and waning clones

95-98 %

Basic vaccinology

- 1st nobel prize - diptheria horse serum

➢95 % vaccines are humoral mediated

➢1st protein based mid 80's – hep b vaccine

[prev. dead or live attenuated]

- Fc effecture functions for treatment and cure
- ? Are Abs recognized at initial infection or at spread
- transfer immune escaped variants
- what is needed prevention vs within patient
- NK activity is needed – killing requires recruitment of innate immune cells
- Neutralization alone is not enough

- 25 % protein serum is Ab [immunoglobulin]