Epitope-focused vaccine design

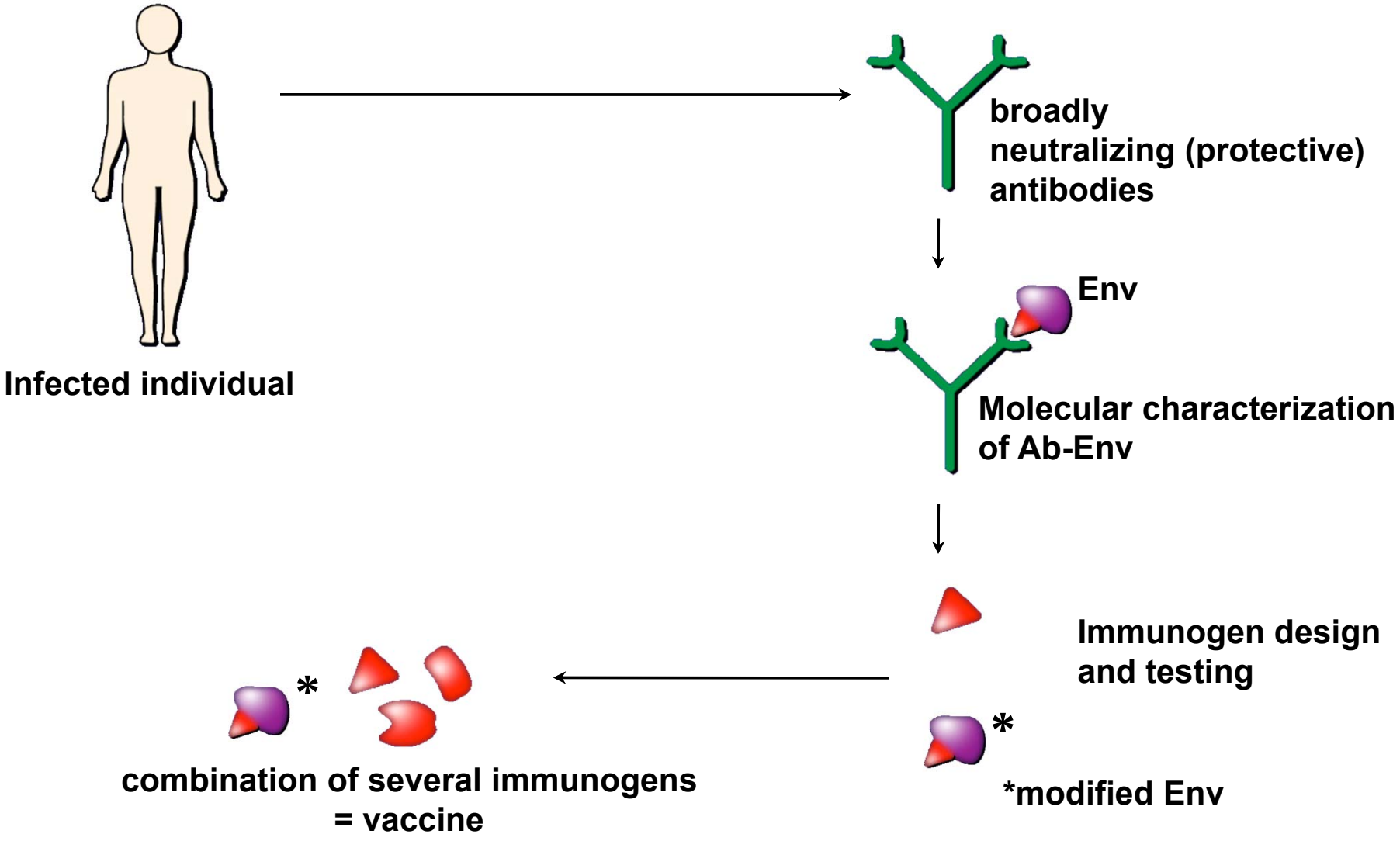
Bill Schief

Professor, The Scripps Research Institute
Director, Vaccine Design, International AIDS Vaccine Initiative
Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery, TSRI
Associate Member, Ragon Institute of MGH, Harvard and MIT

2016 Global Vaccine and Immunization Research Forum (GVIRF)

Johannesburg
March 15, 2015

Vaccine reverse engineering



(adapted from Burton, Nat. Rev. Immunol., 2:706, 2002)

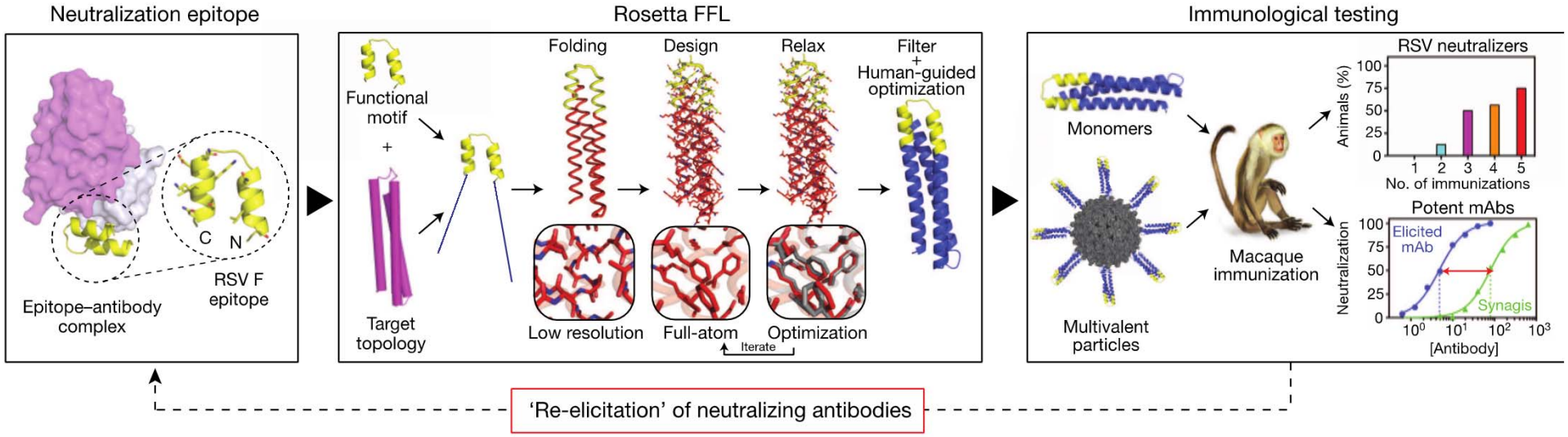
Three stories

- Proof of principle for epitope-focused vaccine design: Epitope-scaffolds for motavizumab elicit potent neutralization of RSV in NHPs

- Toward an HIV vaccine based on the CD4-binding site: germline targeting to initiate induction of VRC01-class broadly neutralizing antibodies (bnAbs)

- Proof of principle for elicitation of HIV bnAbs starting from human germline B cells: vaccine induction of PGT121-class glycan-dependent bnAbs by germline targeting and reductionist boosting

Proof of concept for epitope-focused vaccine design: Epitope-scaffolds induce potent neutralization of RSV in NHPs



A. **Potent polyclonal serum neutralizing responses.**

B. **Rhesus mAbs isolated from an immunized macaque are more potent than Synagis**

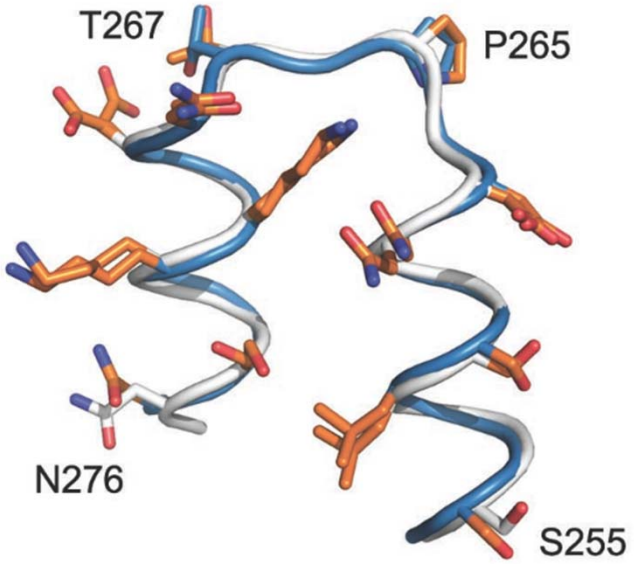
C. **Rhesus mAbs recapitulate Mota structural specificity.**

Correia et al, Nature 2014

"Re-elicitation" of a neutralizing specificity: Vaccine-elicited mAb targets the same epitope structure as the humanized mAb that guided vaccine design

Guide structure (Motavizumab+epitope)

Structure of vaccine-elicted mAB (17HD9+epitope)

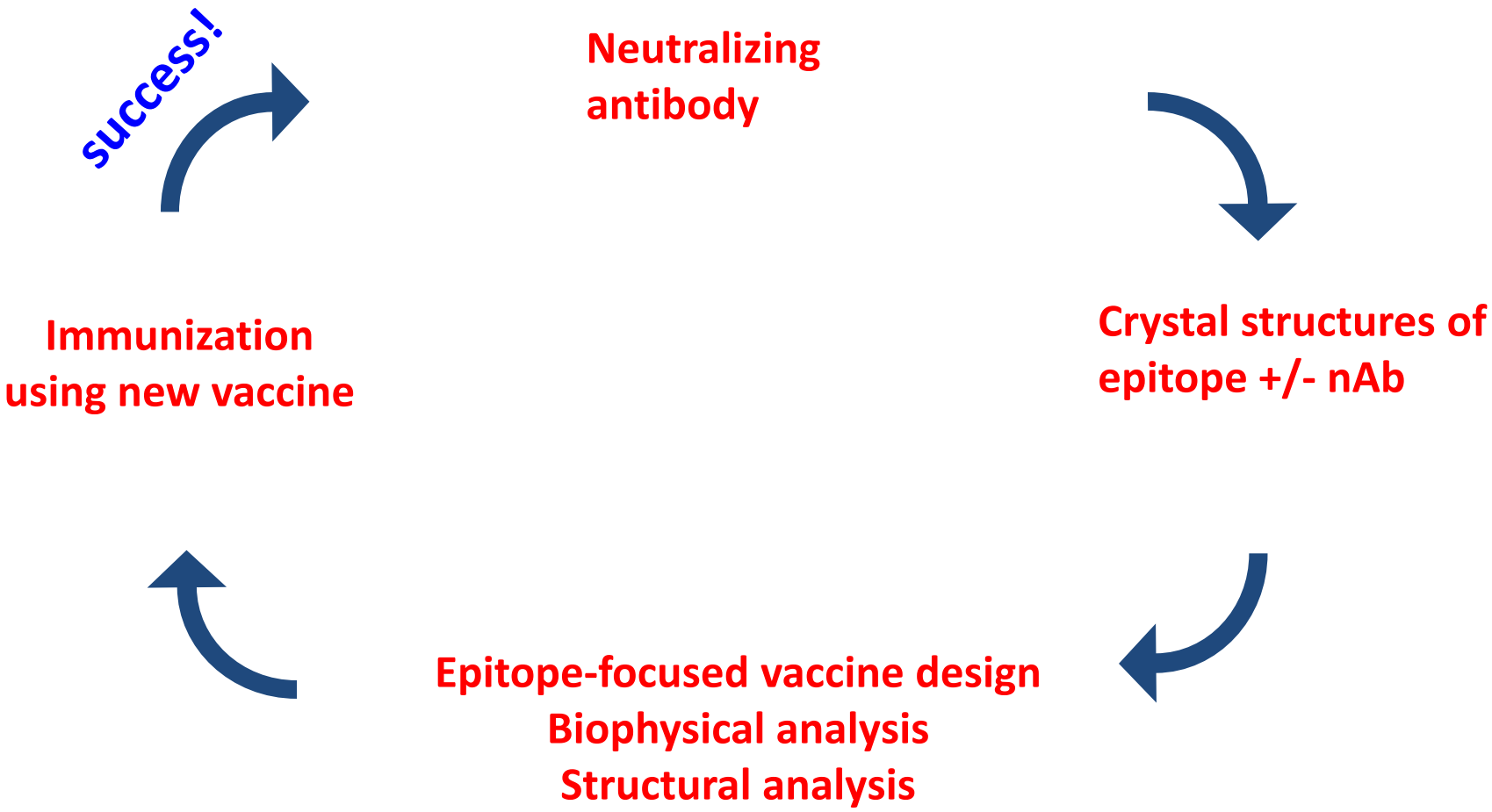


✔epitope structures superimpose (RMSD = 0.5 Å)

✔85% of buried side-chains are shared

Correia et al, Nature 2014

“Closing the loop” of Reverse Vaccine Engineering



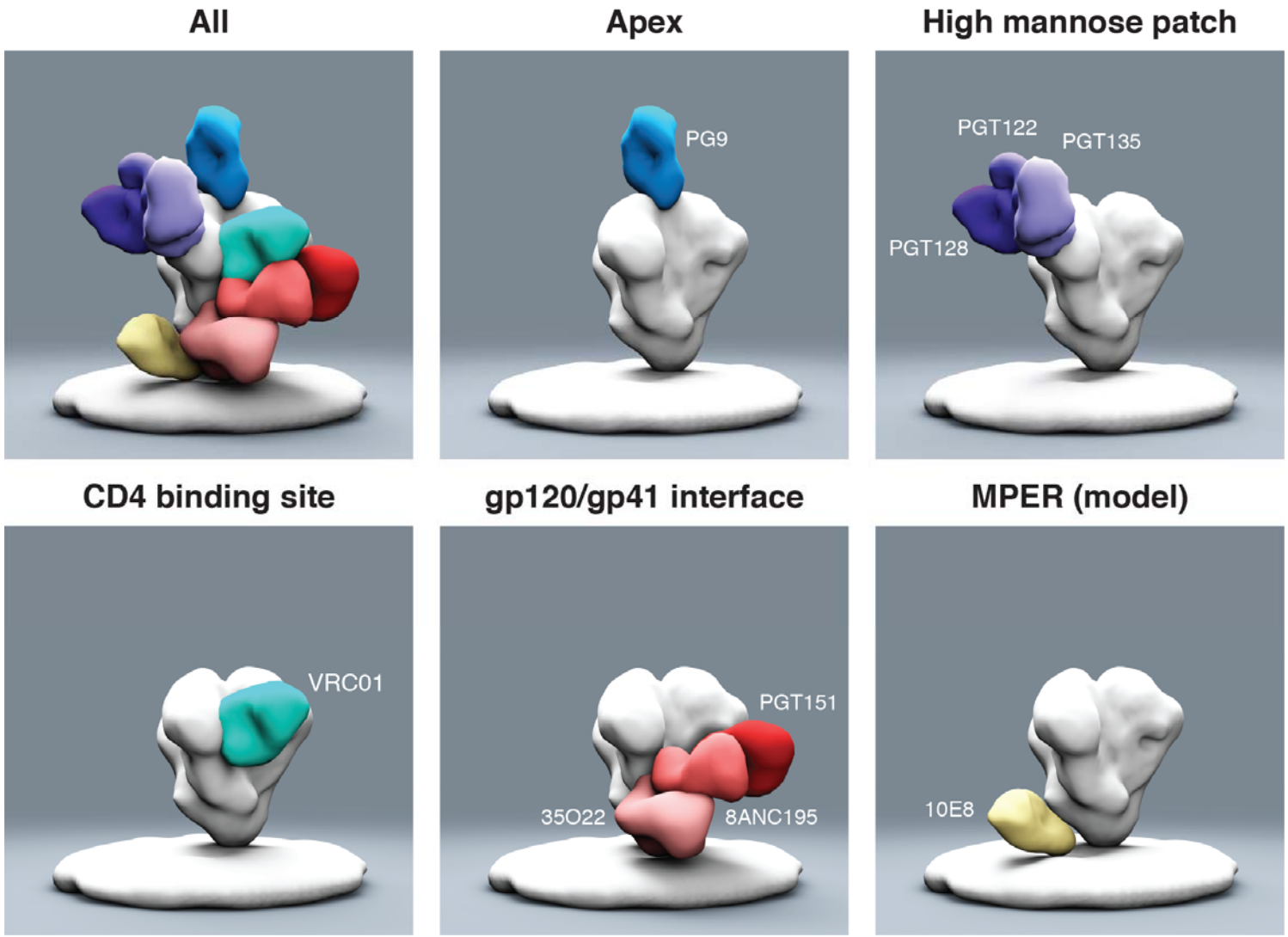
Three stories

- Proof of principle for epitope-focused vaccine design: Epitope-scaffolds for motavizumab elicit potent neutralization of RSV in NHPs

- Toward an HIV vaccine based on the CD4-binding site: germline targeting to initiate induction of VRC01-class broadly neutralizing antibodies (bnAbs)

- Proof of principle for elicitation of HIV bnAbs starting from human germline B cells: vaccine induction of PGT121-class glycan-dependent bnAbs by germline targeting and reductionist boosting

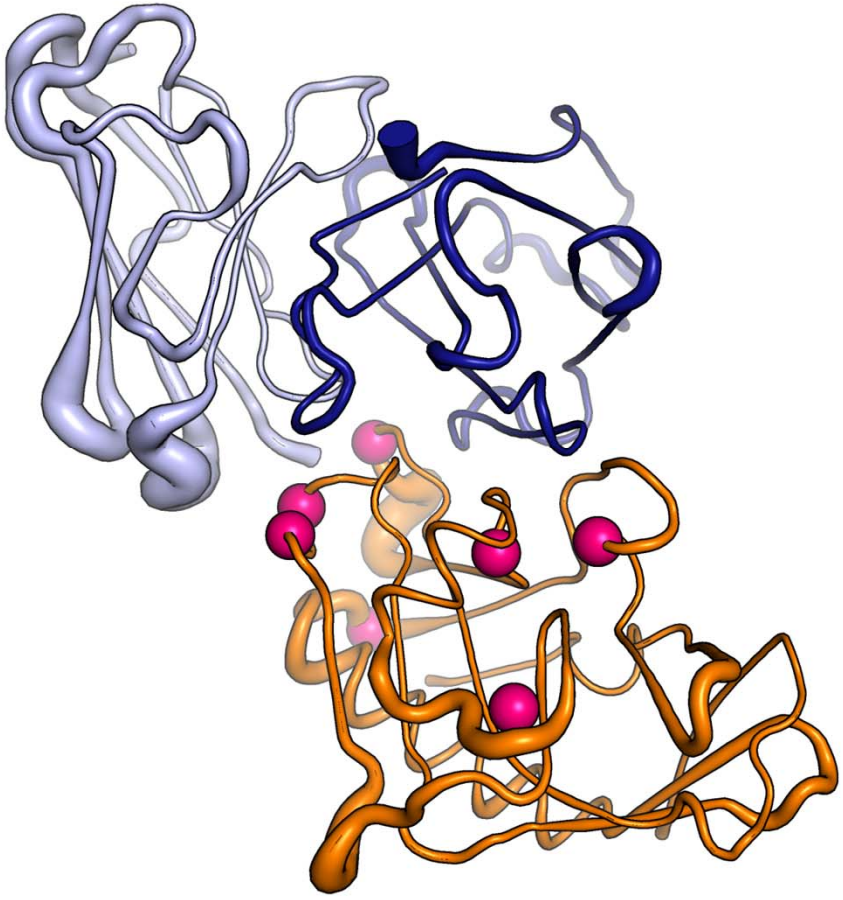
Prototype HIV bnAbs: binding regions



A. Ward & C. Corbaci

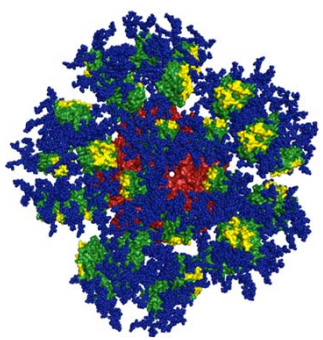
Development of VRC01-class Germline-Targeting Immunogen

eOD-GT6 bound to GL-VRC01

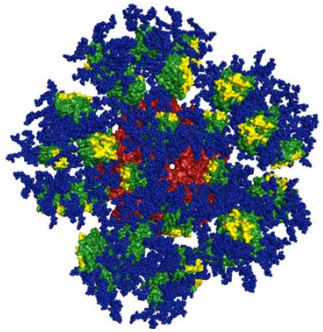


Jardine, Julien, Menis et. al., Science, 2013

Self Assembling Nanoparticles

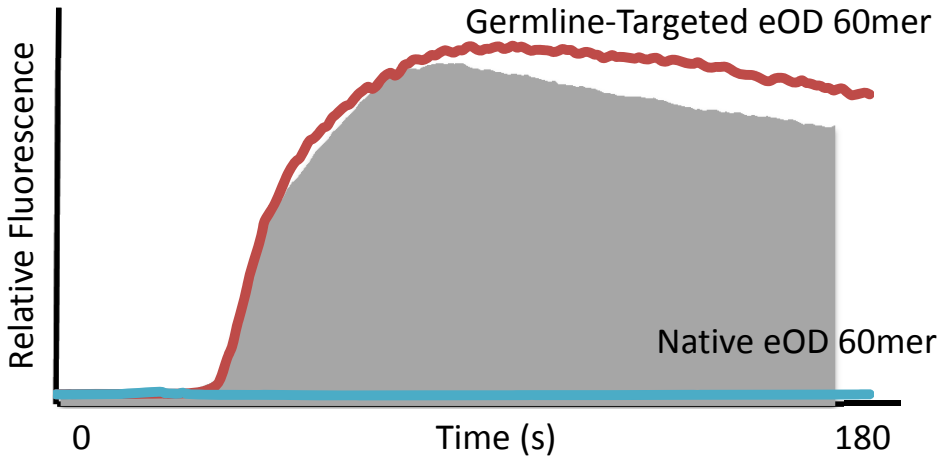


Germline-Targeted eOD 60mer

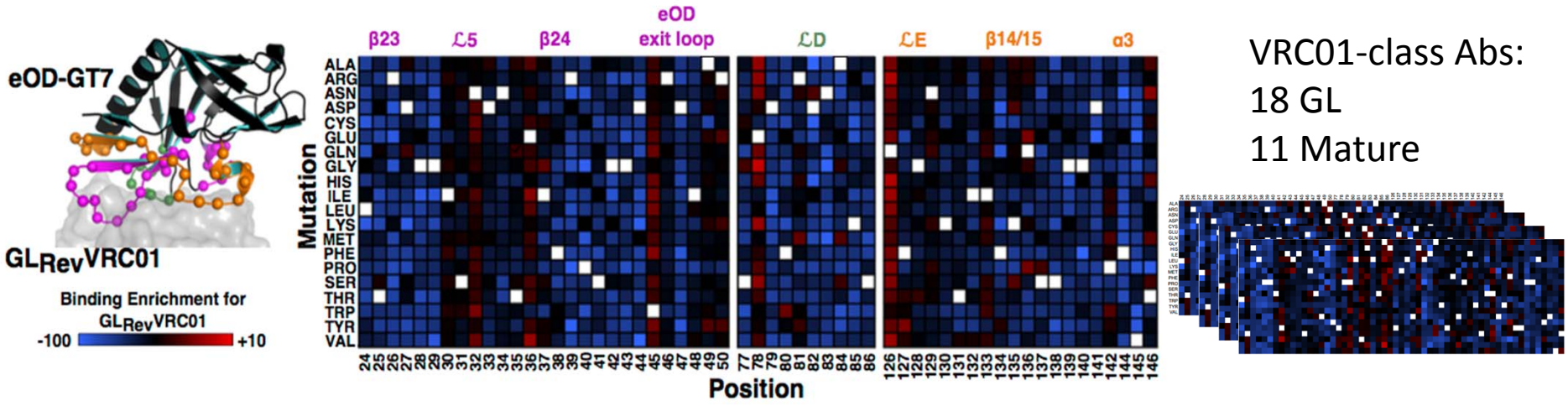


eOD 60mer (Native CD4bs)

In Vitro Germline VRC01 B Cell Activation

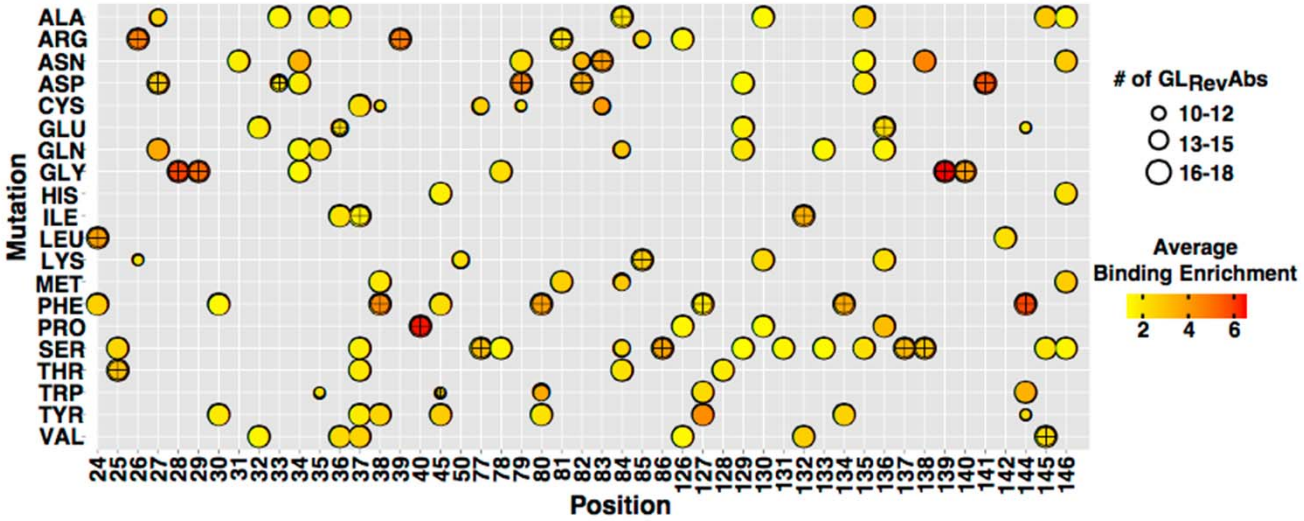


Improvement of germline-targeting immunogen by deep mutational scanning and multitarget optimization



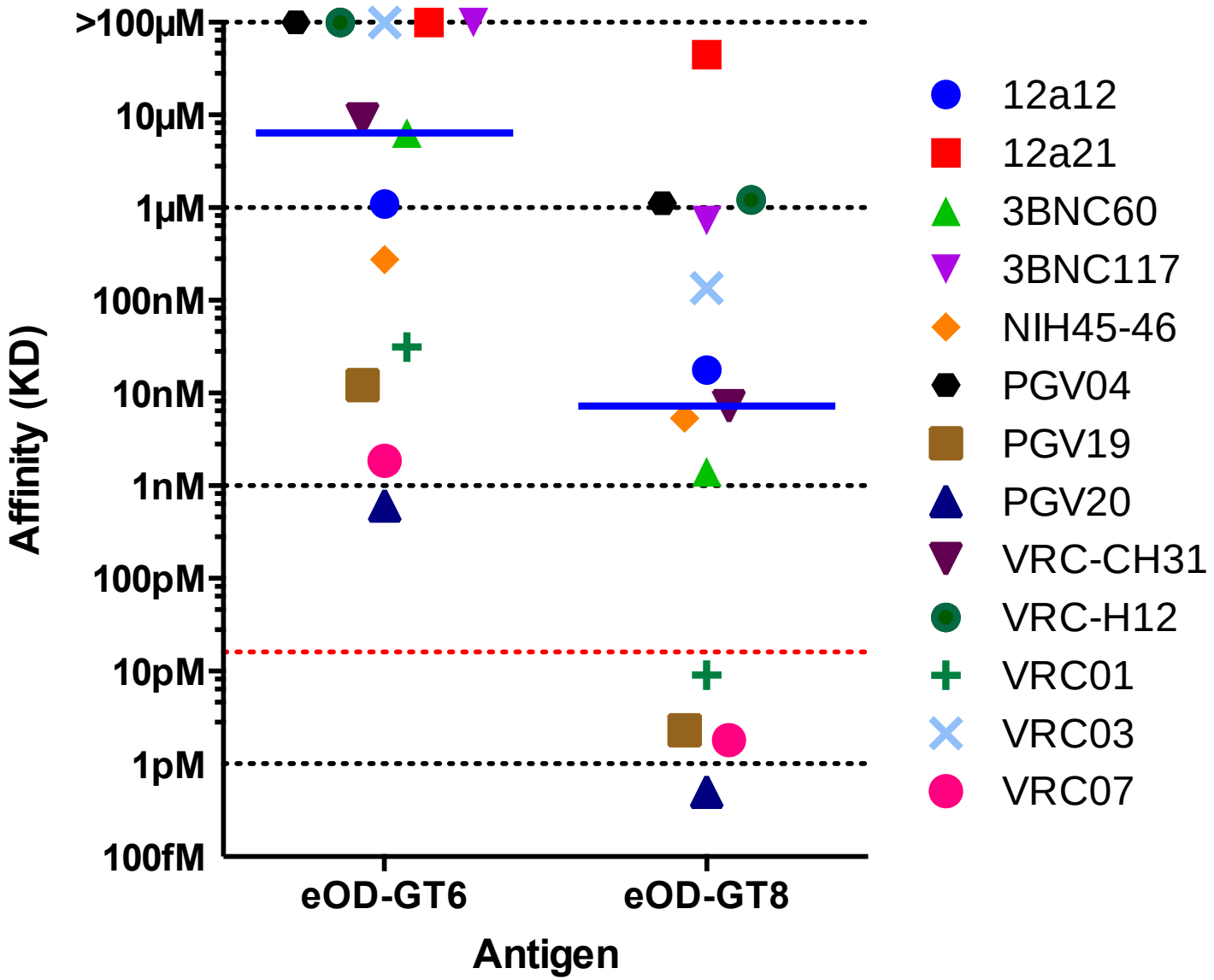
VRC01-class Abs:
18 GL
11 Mature

Breadth analysis of mutational scanning data →



Jardine, Kulp, Havenar-Daughton, Sarkar, Briney, Sok et al. Science 2016 (in press)

eOD-GT8 has improved binding to VRC01-class germline antibodies compared to eOD-GT6



Jardine, Kulp, Havenar-Daughton, Sarkar, Briney, Sok et al. Science 2016 (in press)

True vs germline-reverted VRC01-class precursors

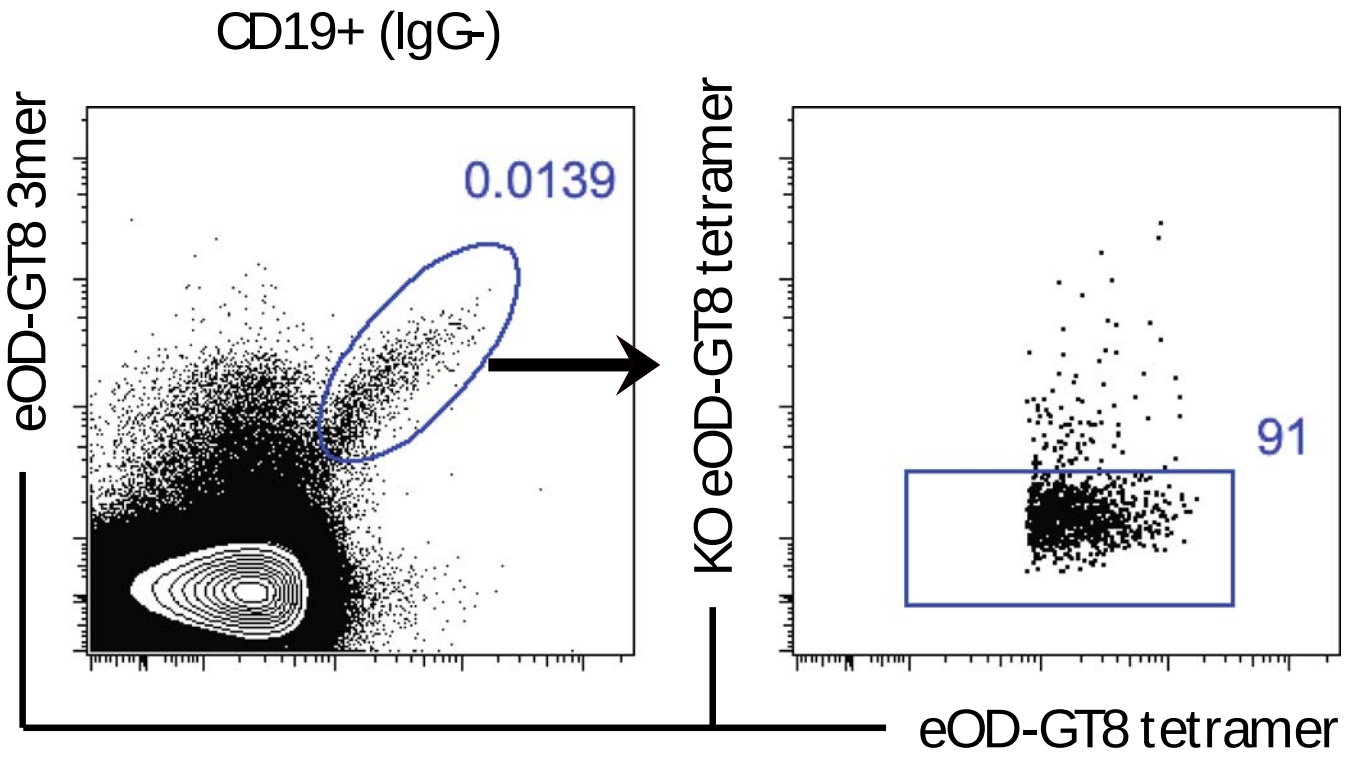
Design and validation of germline-targeting immunogens has been based on “germline-reverted” precursors that use CDRH3 and CDRL3 loops from mature bnAbs.

This raises several important questions:

- what do “true” VRC01-class human precursors look like?
- How frequently do they occur in HIV-naïve humans?
- Do “true” VRC01-class precursors bind to eOD-GT8?
  - With sufficient affinity to allow B cell activation?

Jardine, Kulp, Havenar-Daughton, Sarkar, Briney, Sok et al. Science 2016 (in press)

Sorting GT8 specific naïve human B cells



Jardine, Kulp, Havenar-Daughton, Sarkar, Briney, Sok et al. Science 2016 (in press)

eOD-GT8 isolates VRC01-class precursors from 1 in 2.4 million human naïve B cells

Donor	B cells Screened (millions)	VRC01-class naive B cells
1	1.6	1
2	2.1	1
3	0.9	0
4	5.4	2
5	0.6	0
6	0.5	0
7	1.8	0
8	14.4	4
9	7.8	6
10	4.5	2
11	7.0	1
12	5.9	1
13	1.1	2
14	6.7	5
15	1.3	1
Total	61.6	26

Frequency: 1 in 2.4 million

VH1-2 (*02/*03/*04)
+
5aa CDRL3

Jardine, Kulp, Havenar-Daughton, Sarkar, Briney, Sok et al. Science 2016 (in press)

VRC01-class precursors that bind eOD-GT8 are common in humans

- 10^{10}-10^{11} B cells in adult human
- ~50 million B cells per human lymph node
- 65-75% are naïve B cells
- 96% of humans are hetero/homozygous for VRC01-class VH1-2 alleles (*02, *03, *04)

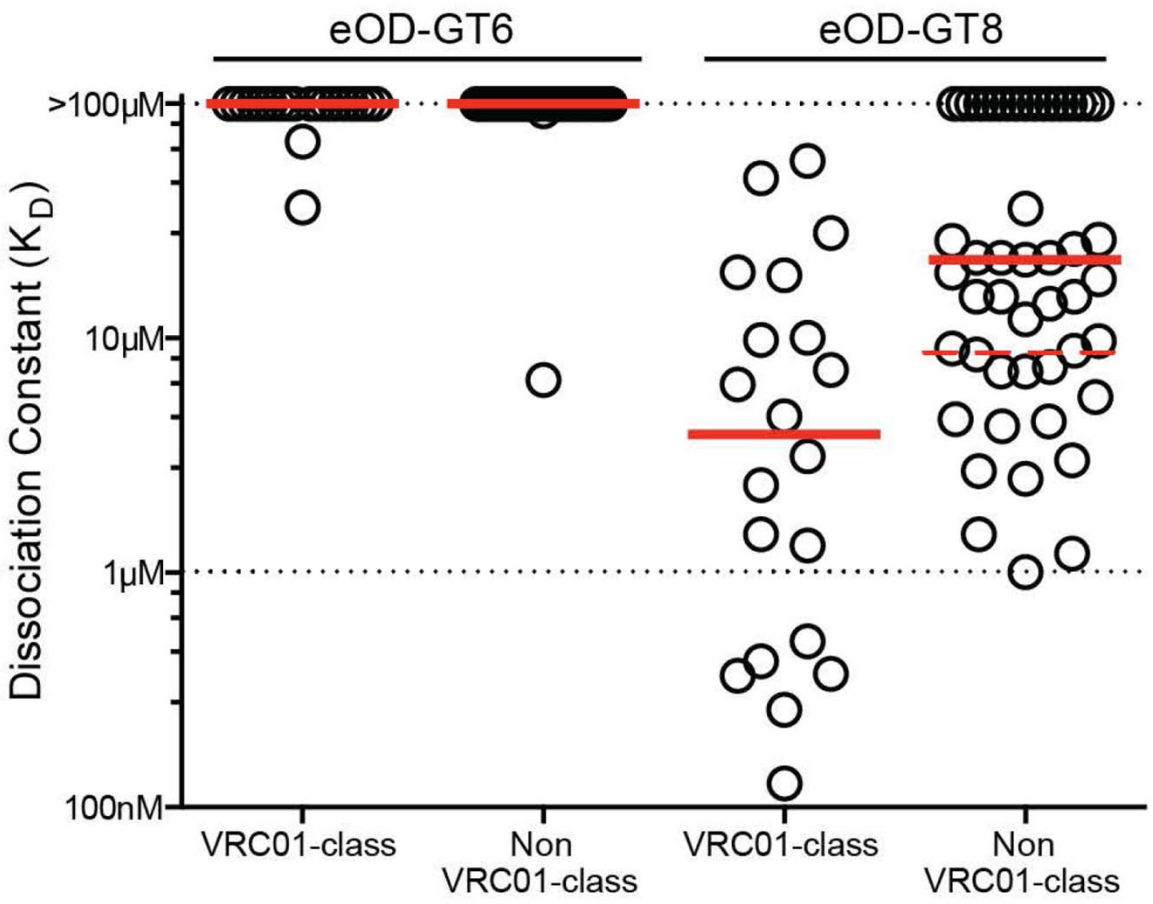
A frequency of 1 VR01-class precursor in 2.4 million naïve B cells means that:

- nearly all humans have 2700 to 31,000 VRC01-class precursors that bind eOD-GT8
- each human lymph node has ~15 VRC01-class precursors that bind eOD-GT8

Jardine, Kulp, Havenar-Daughton, Sarkar, Briney, Sok et al. Science 2016 (in press)

eOD-GT8 binds with 0.1-30 μM affinity to VRC01-class precursors

(and has higher affinity for VRC01-class compared to non-VRC01-class)



This is promising for in vivo activation and VRC01-class memory B cell generation during human vaccination:

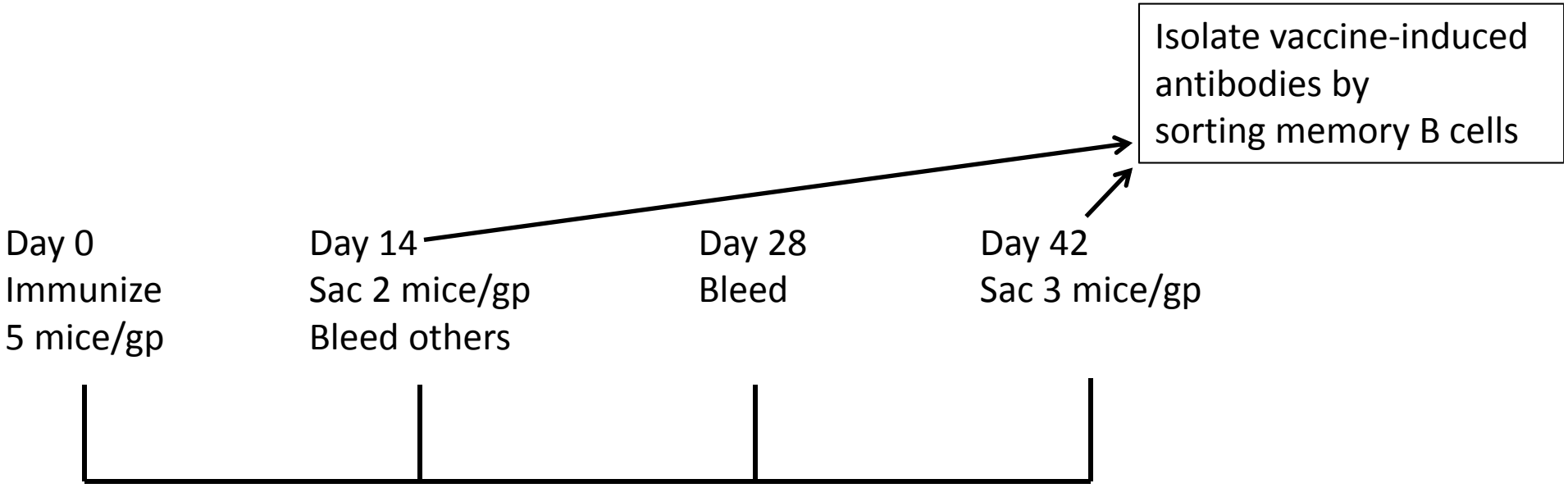
- Batista, Neuberger JEM 1998
- Dal Porto, Shlomchick JEM 2002
- Shih, Nussenzweig Nat Imm 2002
- Paus, Brink JEM 2006

Jardine, Kulp, Havenar-Daughton, Sarkar, Briney, Sok et al. Science 2016 (in press)

Test of germline-targeting immunogens in VRC01 gH mice

(David Nemazee)

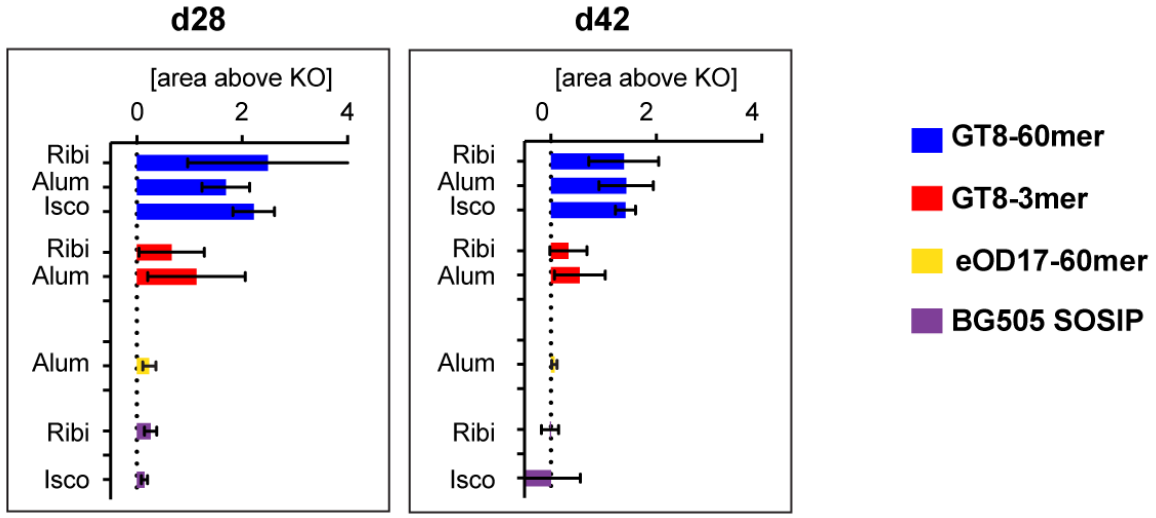
Can eOD-GT8 activate appropriate B cells and select productive mutations, to produce memory B cells that could be boosted by a more native-like immunogen?



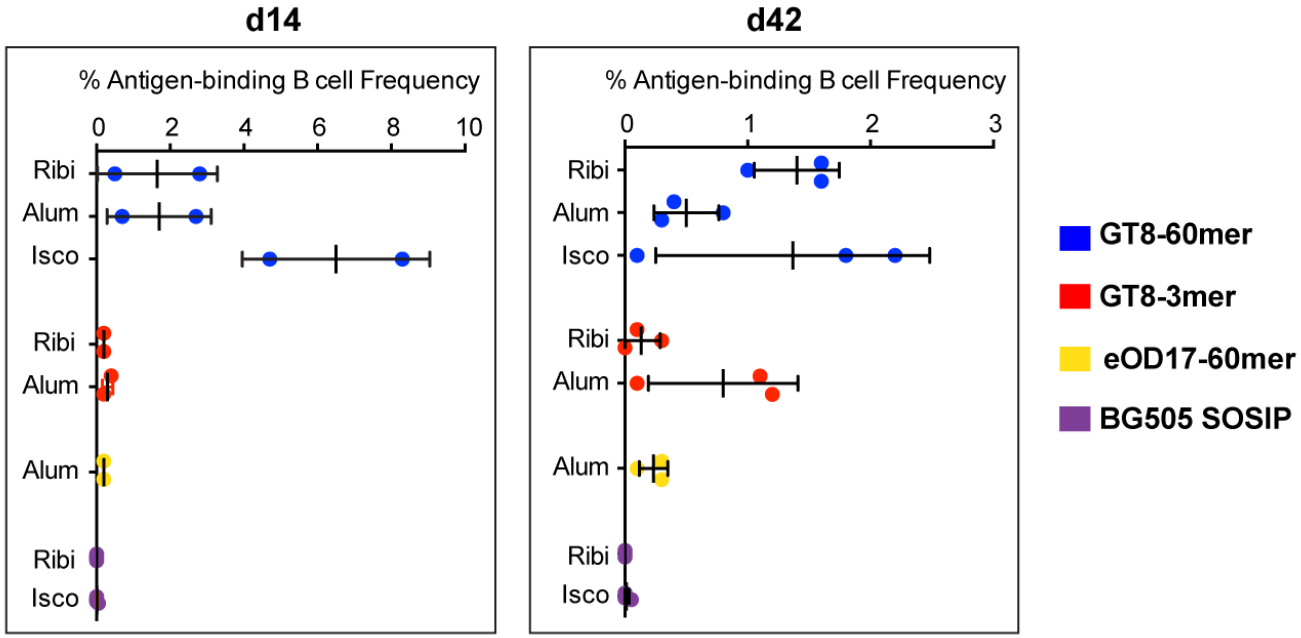
Jardine, Ota, Sok et al Science 2015

Serum and B cell responses in VRC01 gH mice showed robust reponses to the eOD-GT8 60mer

ELISA responses

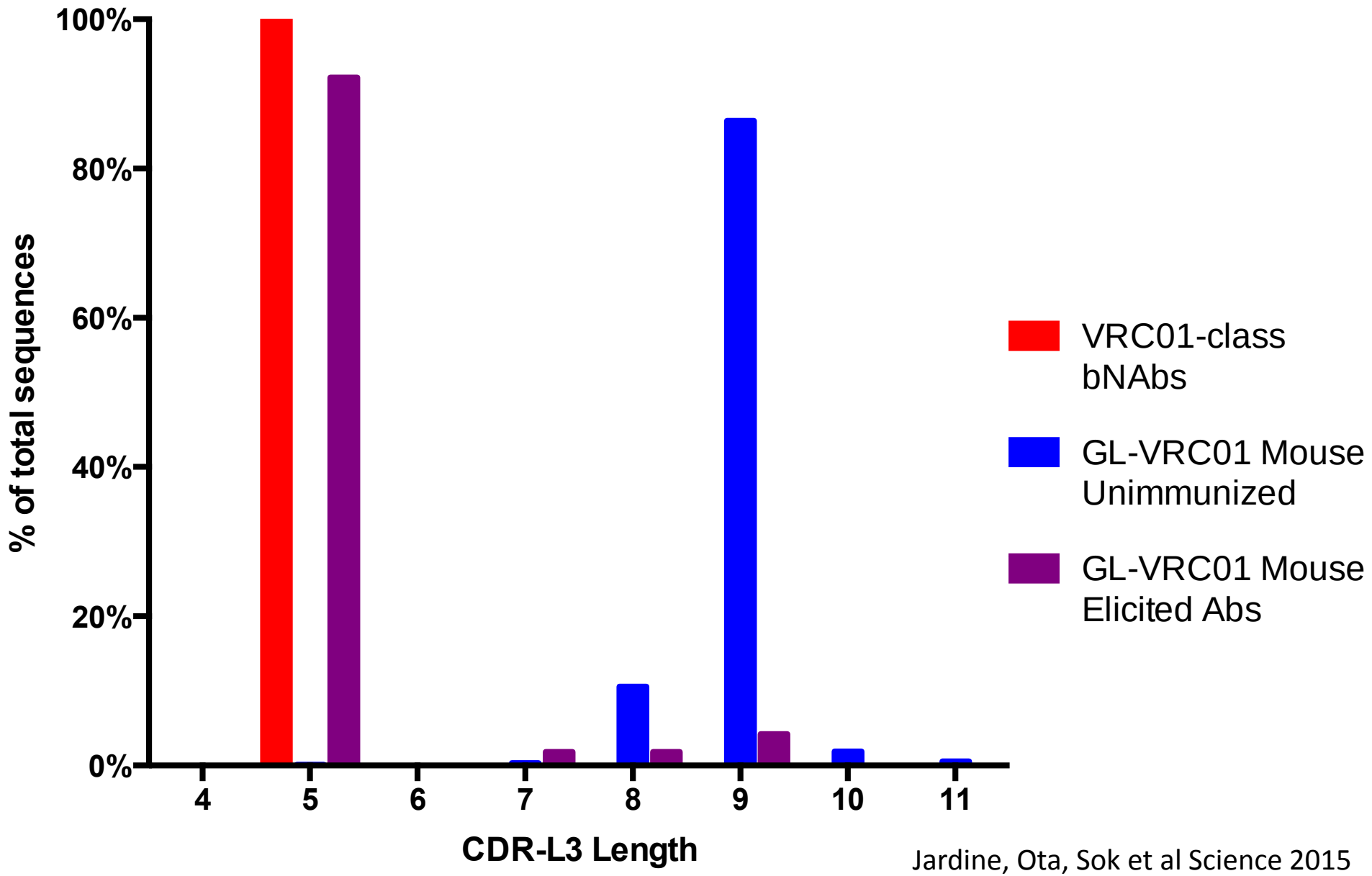


Epitope-specific B cell frequencies



Jardine, Ota, Sok et al
Science 2015

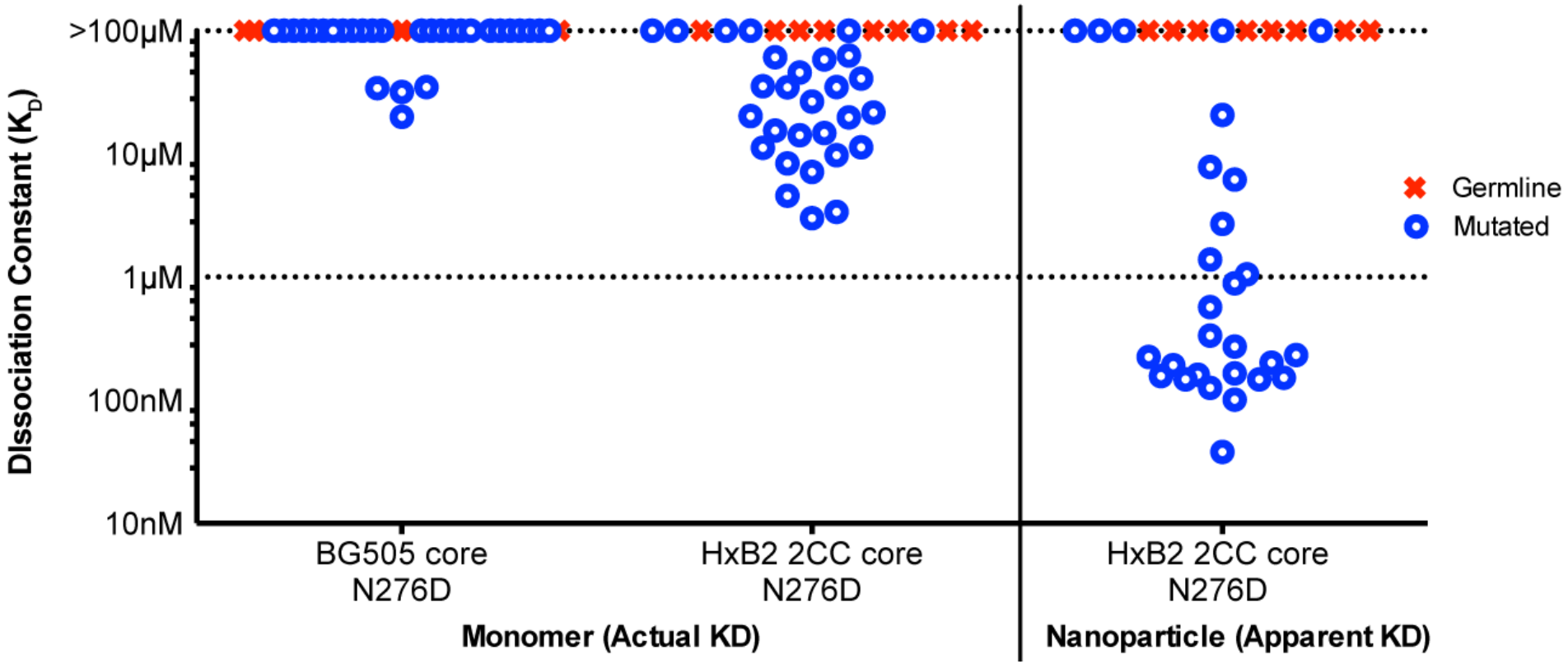
eOD-GT8 60mer reliably elicits Abs with 5AA CDR-L3



Jardine, Ota, Sok et al Science 2015

eOD-GT8 60mer induced Abs bind to near-native CD4bs in candidate boost immunogens

- GT8-induced monoclonal Abs were isolated by sorting of memory B cells from day 42
- Antibody affinities for boost candidates were measured by SPR



Jardine, Ota, Sok et al Science 2015

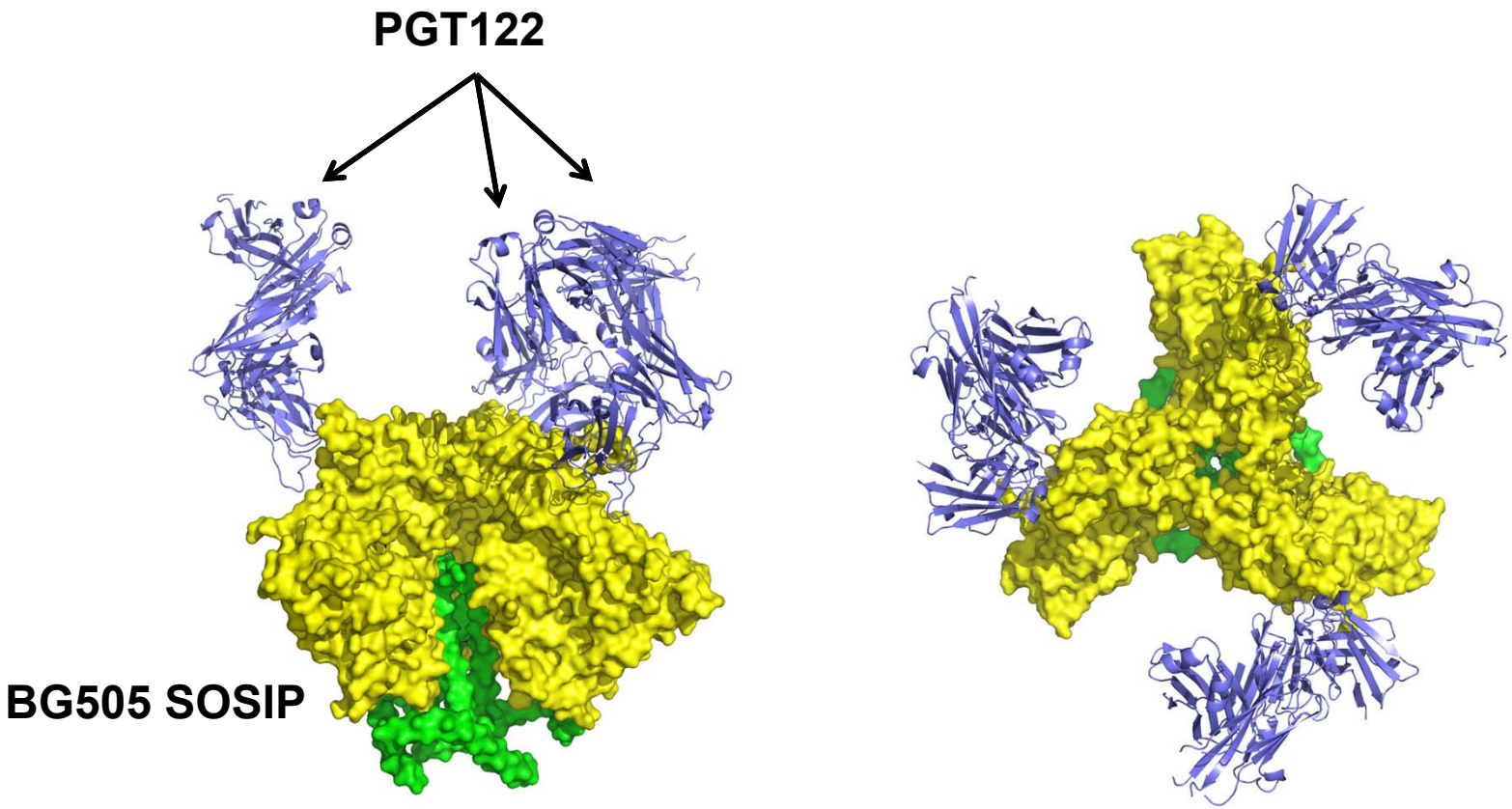
Three stories

- Proof of principle for epitope-focused vaccine design: Epitope-scaffolds for motavizumab elicit potent neutralization of RSV in NHPs

- Toward an HIV vaccine based on the CD4-binding site: germline targeting to initiate induction of VRC01-class broadly neutralizing antibodies (bnAbs)

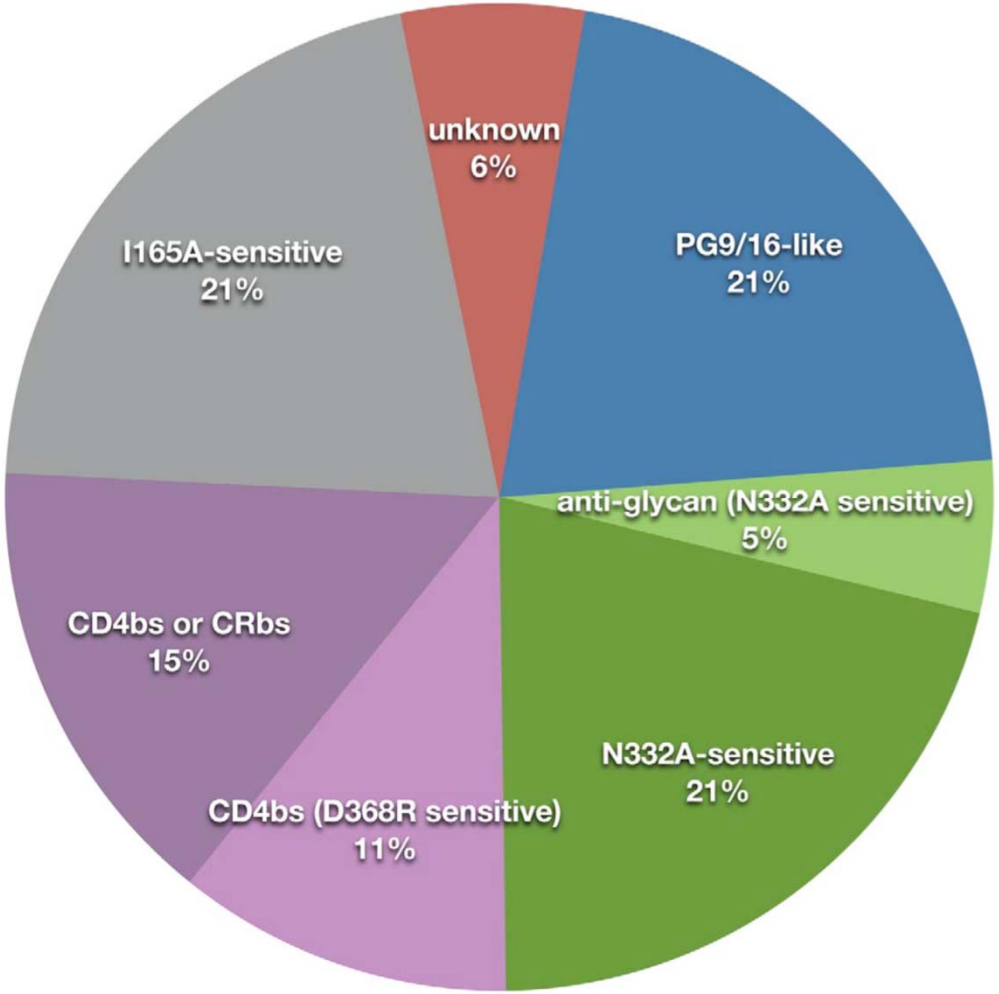
- Proof of principle for elicitation of HIV bnAbs starting from human germline B cells: vaccine induction of PGT121-class glycan-dependent bnAbs by germline targeting and reductionist boosting

PGT121-class interaction with native-like trimer defined



Julien et al Science 2013

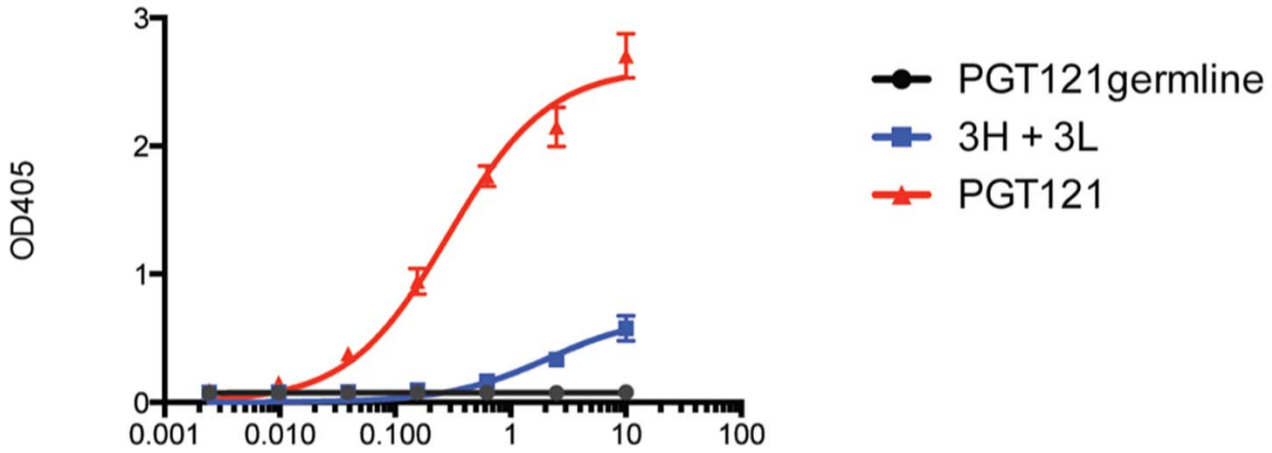
PGT121-class bnAbs among the most common from infection



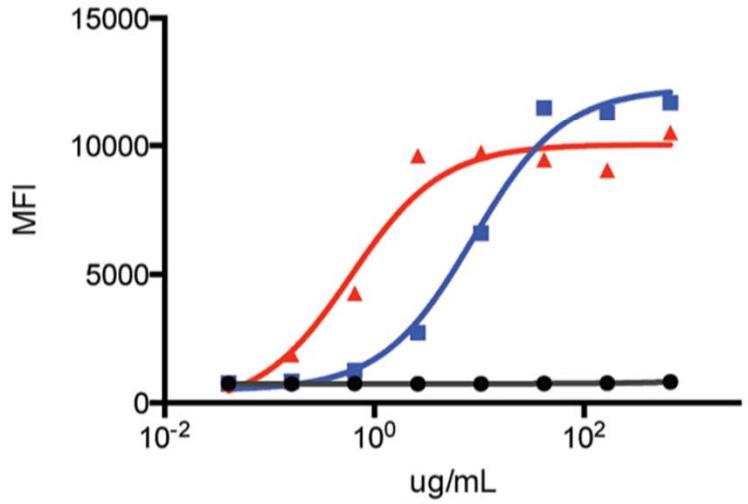
Walker et al Plos Path 2010

Barrier to elicitation: PGT121 germline-reverted Abs lack detectable affinity for gp120 or cell-surface Env

gp120



Cell-surface Env



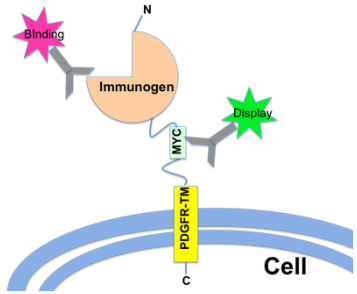
Sok et al Plos Path 2013

Mammalian display/ directed evolution overview

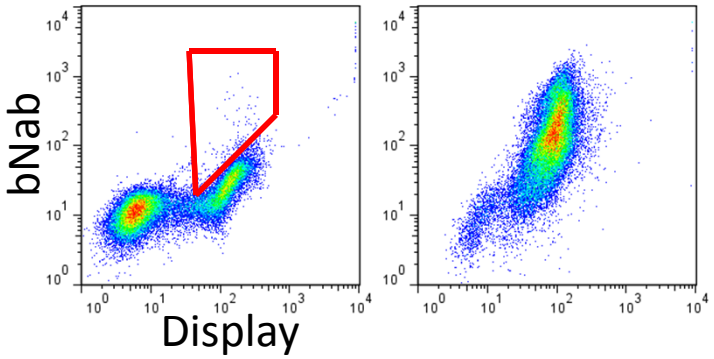
1. Produce lentivirus containing antigen library

2. Transduce 293T cells Low moi (<0.1)

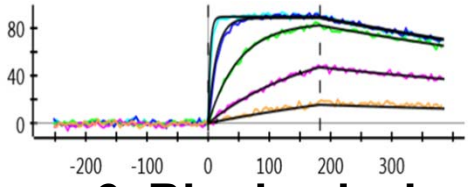
3. Induce expression (Doxycycline)



4. Sort cells



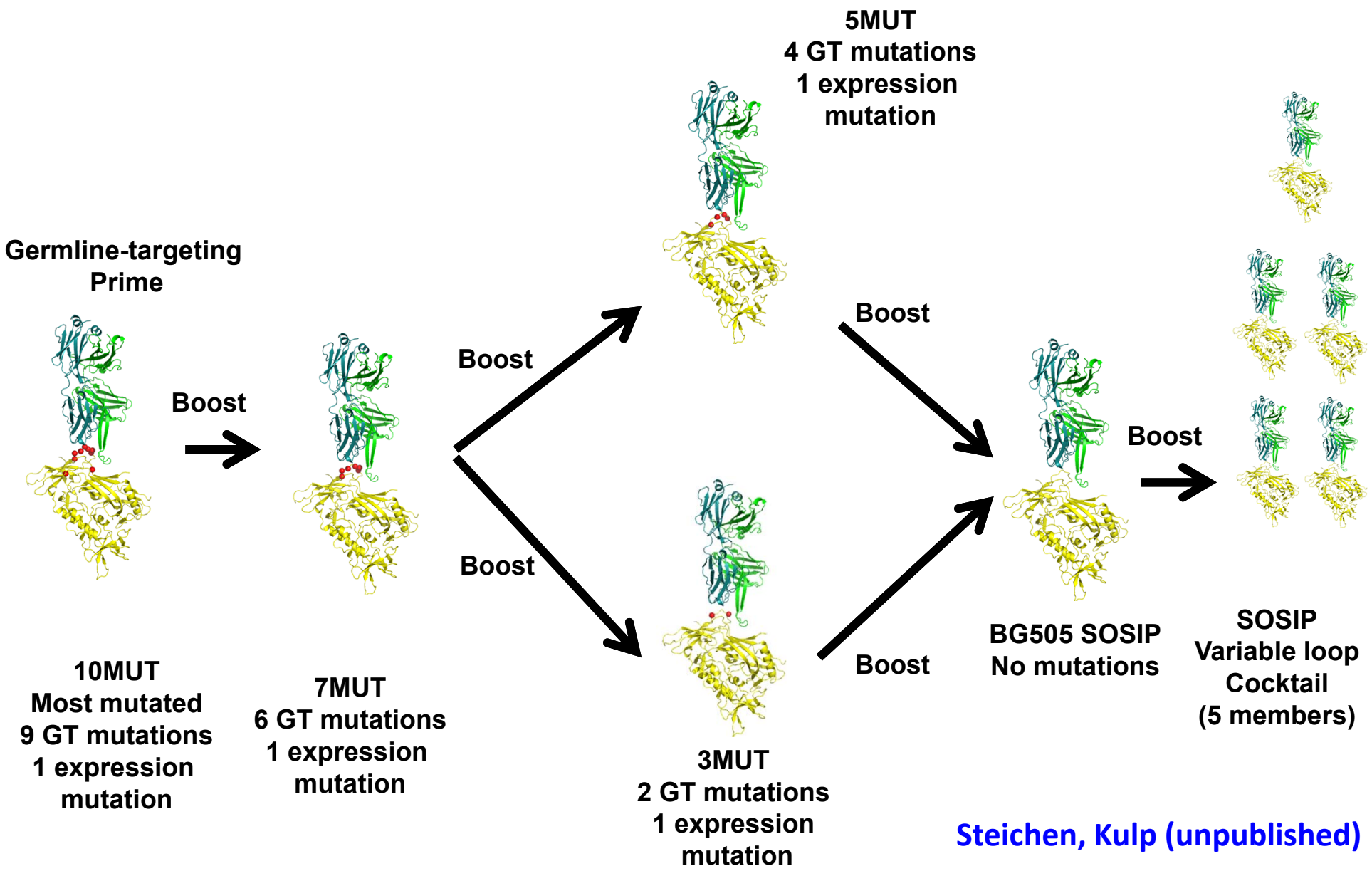
5. Purify genomic DNA, PCR and sequence



6. Biophysical Characterization

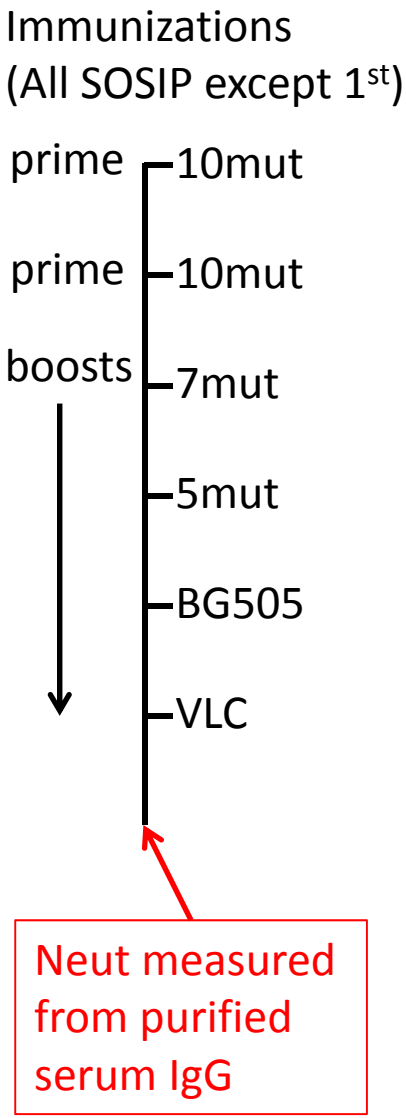
Jon Steichen (unpublished)

Reductionist germline-targeting/boosting strategies to induce PGT121-like bnAbs



Steichen, Kulp (unpublished)

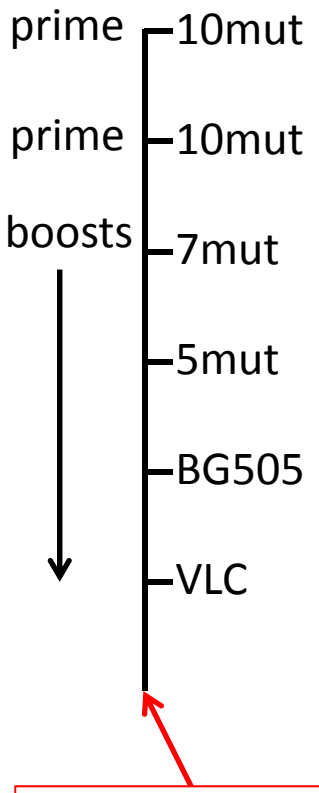
Elicitation of tier 2 cross-neutralizing antibodies by reductionist vaccine design in PGT121 gHgL mouse (with Nussenzweig, Burton)



Escolano, Steichen, et al. (unpublished)

Elicitation of tier 2 cross-neutralizing antibodies by reductionist vaccine design in PGT121 gHgL mouse (with Nussenzweig, Burton)

Immunizations
(All SOSIP except 1st)



Neut measured from purified serum IgG

		mHgL			gHgL			
Virus	Clade	OG10	OG11	OG12	MJ5	MJ6	MJ7	PGT121
6535.3	B	> 5000	> 5000	> 5000	< 100	1019	< 100	0.005
QH0692.42	B	< 100	< 100	< 100	< 100	< 100	< 100	0.187
SC422661.8	B	< 100	< 100	< 100	< 100	< 100	< 100	0.077
PVO.4	B	< 100	< 100	< 100	< 100	< 100	< 100	0.153
TRO.11	B	> 5000	> 5000	> 5000	< 100	< 100	< 100	0.017
AC10.0.29	B	< 100	< 100	< 100	< 100	< 100	< 100	0.037
RHPA4259.7	B	< 100	< 100	< 100	< 100	< 100	< 100	0.026
REJO4541.67	B	< 100	< 100	< 100	< 100	< 100	< 100	>1
TRJO4551.58	B	< 100	< 100	< 100	ND	ND	ND	ND
WITO4160.33	B	< 100	< 100	< 100	< 100	< 100	< 100	>1
CAAN5342.A2	B	100	> 5000	> 5000	< 100	1800	< 100	0.031
WEAU_d15_410_5017	B (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.067
1006_11_C3_1601	B (T/F)	535	2036	1130	< 100	< 100	< 100	0.013
1054_07_TC4_1499	B (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.103
1056_10_TA11_1826	B (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.031
1012_11_TC21_3257	B (T/F)	181	1820	< 25	< 100	< 100	< 100	0.008
6240_08_TA5_4622	B (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.062
6244_13_B5_4576	B (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.139
62357_14_D3_4589	B (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
SC05_8C11_2344	B (T/F)	< 100	308	133	< 100	< 100	< 100	0.060
Du156.12	C	> 5000	> 5000	> 5000	< 100	2877	< 100	0.007
Du172.17	C	< 100	556	< 100	< 100	< 100	< 100	0.031
Du422.1	C	< 100	< 100	< 100	< 100	< 100	< 100	0.054
ZM197M.PB7	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
ZM214M.PL15	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
ZM233M.PB6	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
ZM249M.PL1	C	< 100	< 100	< 100	ND	ND	ND	ND
ZM53M.PB12	C	< 100	< 100	< 100	< 100	< 100	< 100	0.009
ZM109F.PB4	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
ZM135M.PL10a	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
CAP45.2.00.G3	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
CAP210.2.00.E8	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
HIV-001428-2.42	C	< 100	< 100	< 100	< 100	< 100	< 100	0.041
HIV-0013095-2.11	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
HIV-16055-2.3	C	< 100	< 100	< 100	< 100	< 100	< 100	>1
HIV-16845-2.22	C	ND	ND	ND	ND	ND	ND	ND
Ce0393_C3	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
Ce1176_A3	C (T/F)	100	> 5000	> 5000	< 100	> 5000	< 100	0.010
Ce2010_F5	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
Ce1172_H1	C (T/F)	100	> 5000	1323	ND	ND	ND	ND
Ce2060_G9	C (T/F)	< 100	< 100	< 100	ND	ND	ND	ND
Ce703010054_2A2	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
BF1266.431a	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
246F_C1G	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.116
249M_B10	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
ZM247v1(Rev-)	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.024
7030102001E5(Rev-)	C (T/F)	ND	ND	ND	< 100	< 100	< 100	0.019
1394C9G1(Rev-)	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.152
Ce704809221_1B3	C (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	0.012

		mHgL			gHgL			
Virus	Clade	OG10	OG11	OG12	MJ5	MJ6	MJ7	PGT121
CNE19	BC	< 100	< 100	< 100	< 100	< 100	< 100	0.017
CNE20	BC	< 100	528	< 100	< 100	2073	< 100	0.012
CNE21	BC	< 100	573	122	< 100	< 100	< 100	0.006
CNE17	BC	< 100	< 100	< 100	< 100	< 100	< 100	>1
CNE30	BC	< 100	272	338	< 100	< 100	< 100	>1
CNE52	BC	< 100	< 100	< 100	< 100	< 100	< 100	>1
CNE53	BC	> 5000	> 5000	> 5000	ND	ND	ND	ND
CNE58	BC	< 100	< 100	< 100	< 100	< 100	< 100	>1
MS208.A1	A	< 100	< 100	< 100	< 100	< 100	< 100	0.012
Q23.17	A	> 5000	> 5000	> 5000	< 100	> 5000	< 100	0.019
Q461.e2	A	< 100	< 100	< 100	< 100	< 100	< 100	>1
Q769.d22	A	< 100	< 100	< 100	< 100	< 100	< 100	>1
0330.v4.c3	A	< 100	1720	223	< 100	< 100	< 100	>1
0260.v5.c36	A	< 100	< 100	< 100	< 100	< 100	< 100	0.057
191955_A11	A (T/F)	ND	ND	ND	ND	ND	ND	ND
191084_B7-19	A (T/F)	< 100	168	< 100	< 100	< 100	< 100	0.016
T257-31	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	0.057
928-28	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	0.057
263-8	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	0.123
T250-4	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	0.004
T251-18	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	>1
T278-50	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	>1
T255-34	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	>1
235-47	CRF02_AG	< 100	< 100	< 100	< 100	< 100	< 100	>1
620345.c01	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
C1080.c03	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
R2184.c04	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
R1166.c01	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
R3265.c06	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
C3347.c11	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
C4118.c09	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
CNE8	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
CNE5	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
BJOX009000.02.4	CRF01_AE	< 100	< 100	< 100	< 100	< 100	< 100	>1
BJOX015000.11.5	CRF01_AE (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
BJOX010000.06.2	CRF01_AE (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
BJOX025000.01.1	CRF01_AE (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
BJOX028000.10.3	CRF01_AE (T/F)	< 100	< 100	< 100	< 100	< 100	< 100	>1
X1193_c1	G	< 100	< 100	< 100	< 100	< 100	< 100	0.010
X1254_c3	G	< 100	< 100	< 100	< 100	< 100	< 100	0.045
X2088_c9	G	< 100	< 100	< 100	< 100	< 100	< 100	0.003
X2131_C1_B5	G	< 100	> 5000	< 100	< 100	< 100	< 100	0.005
P1981_C5_3	G	> 5000	> 5000	> 5000	< 100	> 5000	< 100	0.005
X1632_S2_B10	G	< 100	< 100	< 100	< 100	< 100	< 100	>1
A07412M1.vrc12	D	< 100	< 100	< 100	< 100	< 100	< 100	0.010
231965.c01	D	< 100	< 100	< 100	< 100	< 100	< 100	>1
3817.v2.c59	CD	< 100	< 100	< 100	< 100	< 100	< 100	>1
6480.v4.c25	CD	100	> 5000	> 5000	< 100	1120	< 100	0.010
6952.v1.c20	CD	< 100	< 100	< 100	< 100	< 100	< 100	0.016
6811.v7.c18	CD	> 5000	> 5000	> 5000	< 100	3417	< 100	0.013
89-F1_2_25	CD	< 100	< 100	< 100	< 100	< 100	< 100	>1
3301.v1.c24	AC	1745	> 5000	2747	< 100	< 100	< 100	0.021
6041.v3.c23	AC	< 100	< 100	< 100	< 100	< 100	< 100	>1
6540.v4.c1	AC	< 100	< 100	< 100	< 100	< 100	< 100	>1
6545.v4.c1	AC	< 100	< 100	< 100	< 100	< 100	< 100	>1
0815.v3.c3	ACD	< 100	< 100	< 100	< 100	< 100	< 100	0.048
3103.v3.c10	ACD	336	> 5000	> 5000	< 100	< 100	< 100	0.017

Escolano, Steichen, et al. (unpublished)

Specificity of tier 2 cross-neutralization from gHgL mouse tracks closely With PGT121 “ancestor” 3H3L

Virus	clade	MJ6	3H3L	9H3L	PGT121
6535.3	B	1019	0.043	0.03	0.002
TRO.11	B	<25	1.445	0.071	0.005
CAAN5342.A2	B	1800	0.914	0.236	0.007
RHPA4259.7	B	<25	>50	0.073	0.015
JR-CSF	B	~10	>50	0.277	0.02
AC10.0.29	B	<25	>50	2.643	0.024
PVO.4	B	<25	>50	>50	0.098
SC422661.8	B	<25	>50	>50	0.038
QH0692.42	B	<25	>50	>50	0.302
WITO4160.33	B	<25	>50	>50	0.334
REJO4541.67	B	<25	>50	>50	4.774
SC05_8C11_2344	B(T/F)	<25	0.386	0.475	0.019
WEAU_d15_410_50	B(T/F)	<25	1.329	0.3	0.026
6240_08_TA5_4622	B(T/F)	<25	4.137	0.145	0.033
1012_11_TC21_3257	B(T/F)	<25	>50	0.506	0.003
1006_11_C3_1601	B(T/F)	<25	>50	14.62	0.002
1056_10_TA11_182	B(T/F)	<25	>50	2.237	0.004
1054_07_TC4_1499	B(T/F)	<25	>50	34.74	0.064
6244_13_B5_4576	B(T/F)	<25	>50	>50	0.061
62357_14_D3_4589	B(T/F)	<25	>50	>50	2.597
IAVI C22	C	4429	0.012	0.008	0.002
DU156.12	C	2877	0.026	0.053	0.004
HIV-001428-2.42	C	<25	>50	19.74	0.014
ZM53M.PB12	C	<25	>50	>50	0.001
Du172.17	C	<25	>50	>50	0.033
Du422.1	C	<25	>50	>50	0.039
HIV-16055-2.3	C	<25	>50	>50	0.153
ZM214M.PL15	C	<25	>50	>50	0.46
ZM135M.PL10a	C	<25	>50	>50	0.716
CAP45.2.00.G3	C	<25	>50	>50	1.634
ZM109F.PB4	C	<25	>50	>50	8.639
Ce1176_A3	C(T/F)	>5000	0.026	0.078	0.013
7030102001E5(Rev-)	C(T/F)	<25	5.56	1.619	0.009
1394C9G1(Rev-)	C(T/F)	<25	17.108	1.081	0.264
Ce704809221_1B3	C(T/F)	<25	>50	11.58	0.025
246F C1G	C(T/F)	<25	>50	>50	0.041
ZM247v1(Rev-)	C(T/F)	<25	>50	>50	0.028
CNE20	BC	2073	0.006	0.005	0.003
CNE21	BC	<25	2.226	0.256	0.007
CNE52	BC	<25	>50	3.188	2.045
CNE19	BC	<25	>50	>50	0.008
CNE17	BC	<25	>50	>50	7.6
92RW020	A	1138	0.01	0.012	0.002
Q23.17	A	>5000	0.007	0.021	0.001
191084 B7-19	A	<25	38.078	3.994	0.011
0260.v5.c36	A	<25	>50	15.05	0.53
0330.v4.c3	A	<25	>50	>50	0.05
T250-4	CRF02_AG	<25	0.202	0.25	0.001
235-47	CRF02_AG	<25	>50	>50	0.137
T251-18	CRF02_AG	<25	>50	>50	29.016
P1981_C5_3	G	>5000	0.011	0.015	0.001
X2131_C1_B5	G	<25	8.487	0.224	0.004
X2088_c9	G	<25	31.256	7.019	0.003
X1193_c1	G	<25	29.989	11.29	0.016
X1254_c3	G	<25	1.271	1.832	0.014
A07412M1.vrc12	D	<25	1.532	0.173	0.009
6811.v7.c18	CD	3417	0.003	0.001	0.001
6480.v4.c25	CD	1120	0.033	0.015	0.001
6952.v1.c20	CD	<25	>50	>50	0.056
3817.v2.c59	CD	<25	>50	>50	18.888
3301.v1.c24	C	<25	0.793	0.432	0.008
3103.v3.c10	ACD	<25	0.062	0.03	0.009
0815.v3.c3	ACD	<25	0.622	1.549	0.025

IC50 ug/mL
<0.01
0.01 - 0.1
0.1 - 1.00
>1.00

Escolano, Steichen, et al. (unpublished)

Neutralization breadth of best MJ6 mAbs is similar to 3H3L

	MJ6-1	MJ6-2	MJ6-3	3H3L	PGT121
6535	0.009	0.014	0.026	0.043	0.002
92RW020	0.004	0.012	0.022	0.01	0.002
IAVI C22	0.003	0.008	0.011	0.012	0.002
Q23	0.005	0.016	0.024	0.007	0.001
DU156	0.011	0.024	0.059	0.026	0.004
P1981	0.004	0.007	0.016	0.011	0.001
X2088	0.037	0.609	0.316	31.3	0.003
191084B7	0.712	0.862	>50	38.1	0.011
JR-CSF	0.334	0.739	>50	>50	0.02
BG505 T332N	0.55	0.598	>50	0.064	0.026
T250	>50	>50	>50	0.202	0.001
HIV-001428	>50	>50	>50	>50	0.014
PV0.4	>50	>50	>50	>50	0.098
ZM53	>50	>50	>50	>50	0.001
CNE19	>50	>50	>50	>50	0.008
R1166	>50	>50	>50	>50	>50
MLV	>50	>50	>50	>50	>50

IC50 ug/mL

<0.01
0.01 - 0.1
0.1 - 1.00
>1.00

SHM AA%

Ab	H	L
MJ6-1:	9%	16.5%
MJ6-2:	6.8%	17.4%
MJ6-3:	6%	13.8%
3H3L:	11.4%	19.3%
PGT121:	27.3%	31.2%

Escolano, Steichen, et al. (unpublished)

Conclusions/Outlook

◆A key challenge for HIV vaccine design is immuno-focusing to bnAb epitopes

◆Similar challenges for other antigenically highly variable pathogens such as influenza and hepatitis C viruses, and related challenges for dengue virus

◆RSV scaffold immunogens:
Re-capitulation of Mota neutralization specificity provides proof of principle that epitope-focused vaccine design can achieve immuno-focusing with high precision

◆Vaccines to induce bnAbs against HIV:
Hypothesize that (a) germline-targeting is needed to consistently activate bnAb precursors in vaccine recipients and (b) structure-guided boosting strategies are needed to guide SHM to produce bnAbs.

VRC01 example: Germline-targeting eOD-GT8 60mer has promise to initiate induction of VRC01-class bnAbs. To be tested in humans (IAVI/BMGF). Reductionist boosting strategies to induce VRC01-class bnAbs being tested in various transgenic mice.

PGT121 example: Demonstrated proof of principle for vaccine-induction of HIV bnAbs starting from human germline B cells, by PGT121 germline-targeting and reductionist boosting (using engineered SOSIP trimers) in PGT121 gHgL mice. **A major milestone for HIV vaccine development.** Precursor frequency in humans remains a question.

Acknowledgments– RSV scaffolds

Schief lab

Bruno Correia (now EPFL faculty)
Joe Jardine
Sergey Menis
Possu Huang
Gretchen Baneyx
Oleksandr Kalyuzhniy
Skye MacPherson
Yumi Adachi
Andreia Serra
Eric Stevens
Meaghan Jones
Alex Schroeter

David Baker – UW

Rachel Klevit – UW
Vinayak Vittal

Phil Johnson – CHOP
Mary Connell
Becky Loomis

James Crowe – Vanderbilt
John Bates
Bryan Briney

Roland Strong – FHCRC
Chris Carrico
Pete Rupert
Colin Correnti

Rich Wyatt – IAVI/TSRI
Yuxing Li

Barney Graham – VRC
Man Chen

Funding:
IAVI
NIH

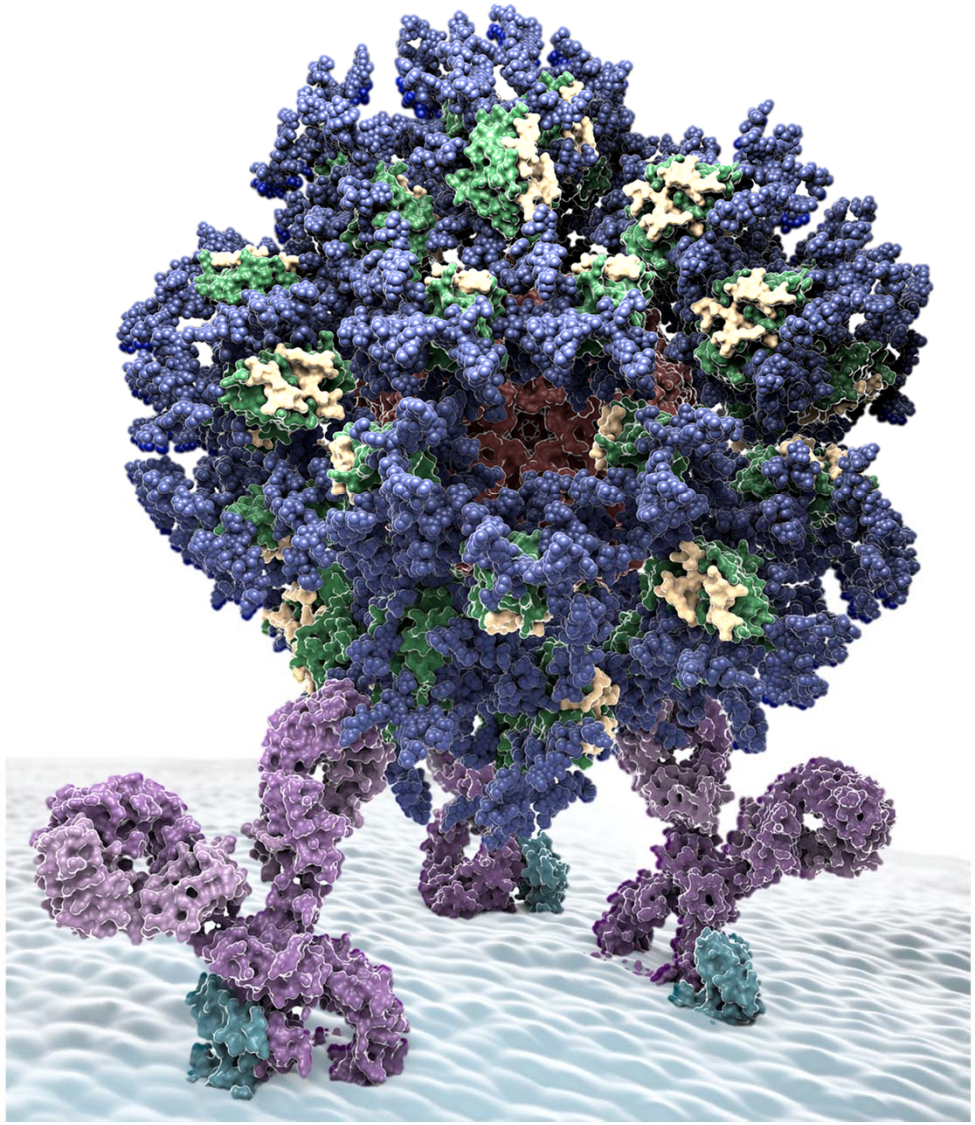
Acknowledgements—VRC01

Schief lab (UW/TSRI/IAVI)
Joe Jardine
Dan Kulp
Sergey Menis
Possu Huang
Oleksandr Kalyuzhniy
Meaghan Jones
Yumi Adachi
Mike Kubitz
Skye MacPherson
Gretchen Baneyx
Eric Stevens
Alex Schroeter

TSRI/IAVI
David Nemazee
Taka Ota
Patrick Skog
Terri Thinnes

Dennis Burton
Devin Sok
Bryan Briney
Matthias Pauthner

Ian Wilson
Jean-Philippe Julien
Anita Sarkar



FHCRC
Leo Stamatatos
Andy McGuire
Allan deCamp

LIAI
Shane Crotty
Colin Havenar-Daughton
Isaiah Deresa

Rockefeller
Michel Nussenzweig
Pia Dosenovic
Amelia Escolano
Lotta von Boehmer

SickKids
Jean-Philippe Julien
June Ereño

Funding
NIH
IAVI/BMGF
CHAVI-ID (Scripps)

Acknowledgements–PGT121

Schief Lab
Jon Steichen
Yumiko Adachi
Jared Adolf-Bryfogle
Shantanu Bhattacharyya
Erik Georgeson
Jenny Hu
Joe Jardine
Oleksandr Kalyuzhniy
Mike Kubitz
Dan Kulp
Sergey Menis
Angel Nikolov
Justin Ozeki
Torben Schiffner
Skye Spencer
Ryan Tingle
Jordan Willis

Burton lab
Laura McCoy
Bryan Briney
Devin Sok

Nemazee lab
Taka Ota
Deepika Bhullar

Nussenzweig lab
Amelia Escolano

Wilson lab
Fernando Garces

Crotty lab
Colin Havenar-Daughton

CHAVI ID

iavi
International AIDS Vaccine Initiative