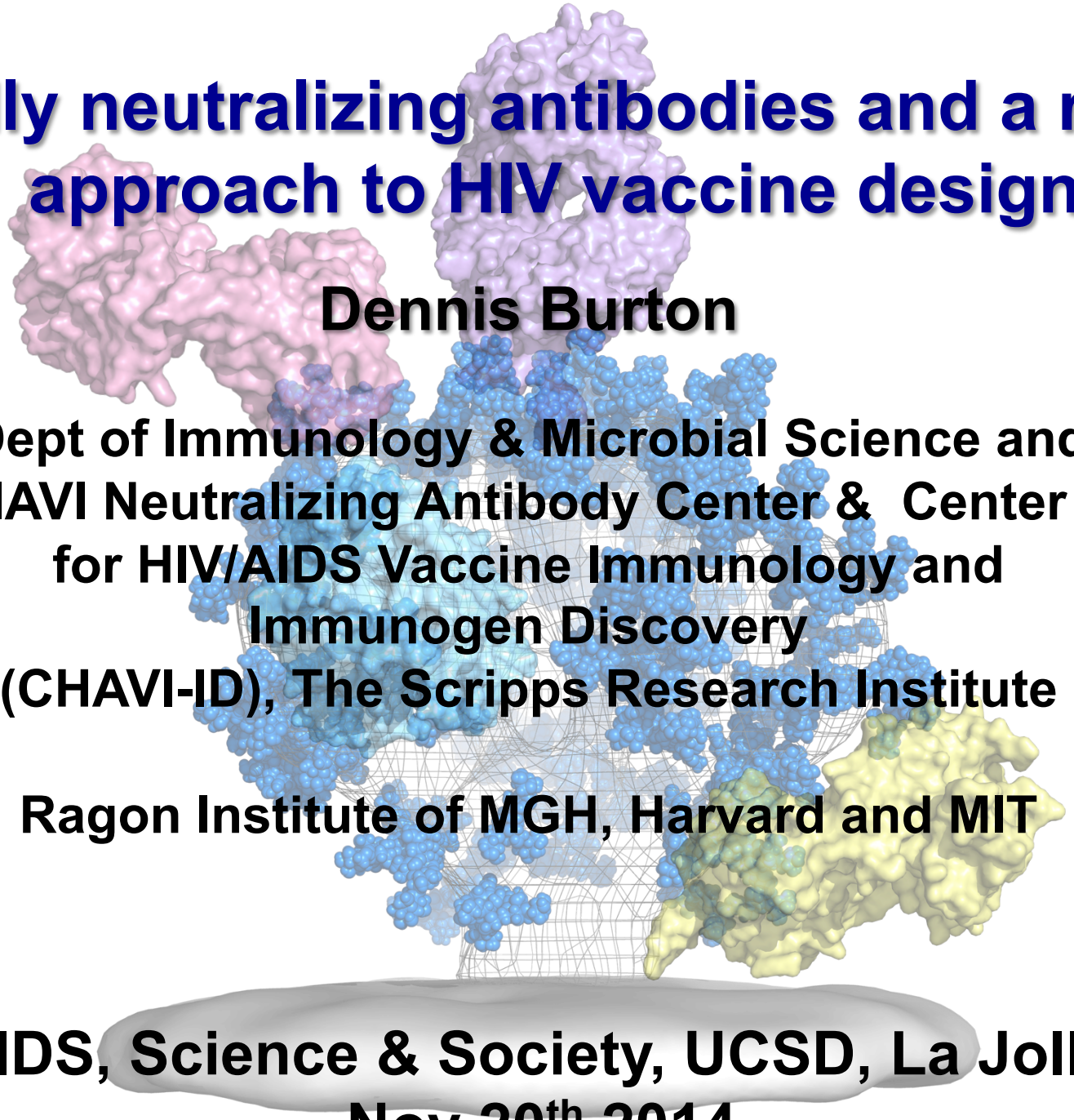
Broadly neutralizing antibodies and a rational approach to HIV vaccine design



Dennis Burton

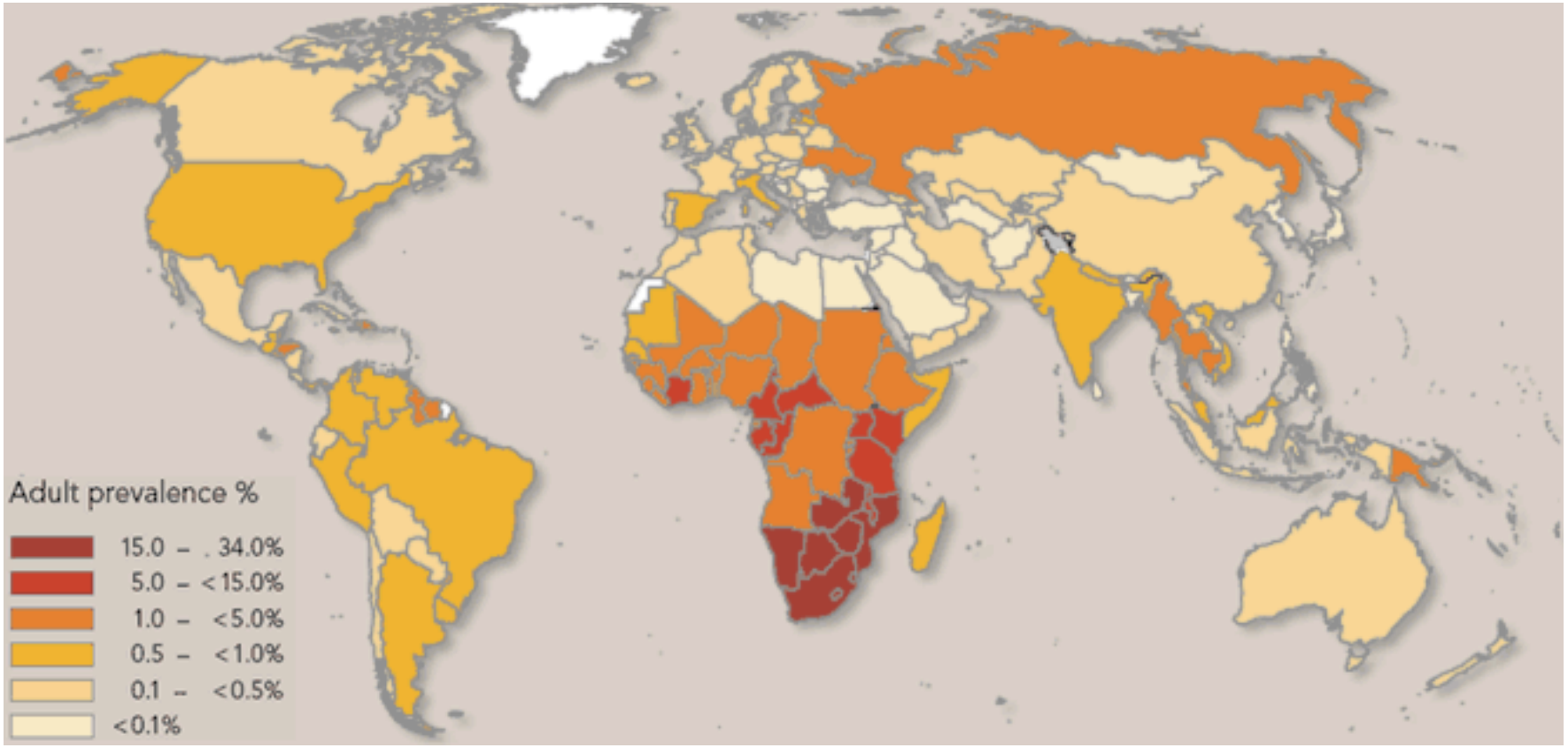
Dept of Immunology & Microbial Science and IAVI Neutralizing Antibody Center & Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID), The Scripps Research Institute

Ragon Institute of MGH, Harvard and MIT

AIDS, Science & Society, UCSD, La Jolla, Nov 20th 2014

A global view of HIV infection

33 million people living with HIV, 2009



UNAIDS: 2010 Report on the global AIDS epidemic. 2010

AIDS compromises human development …

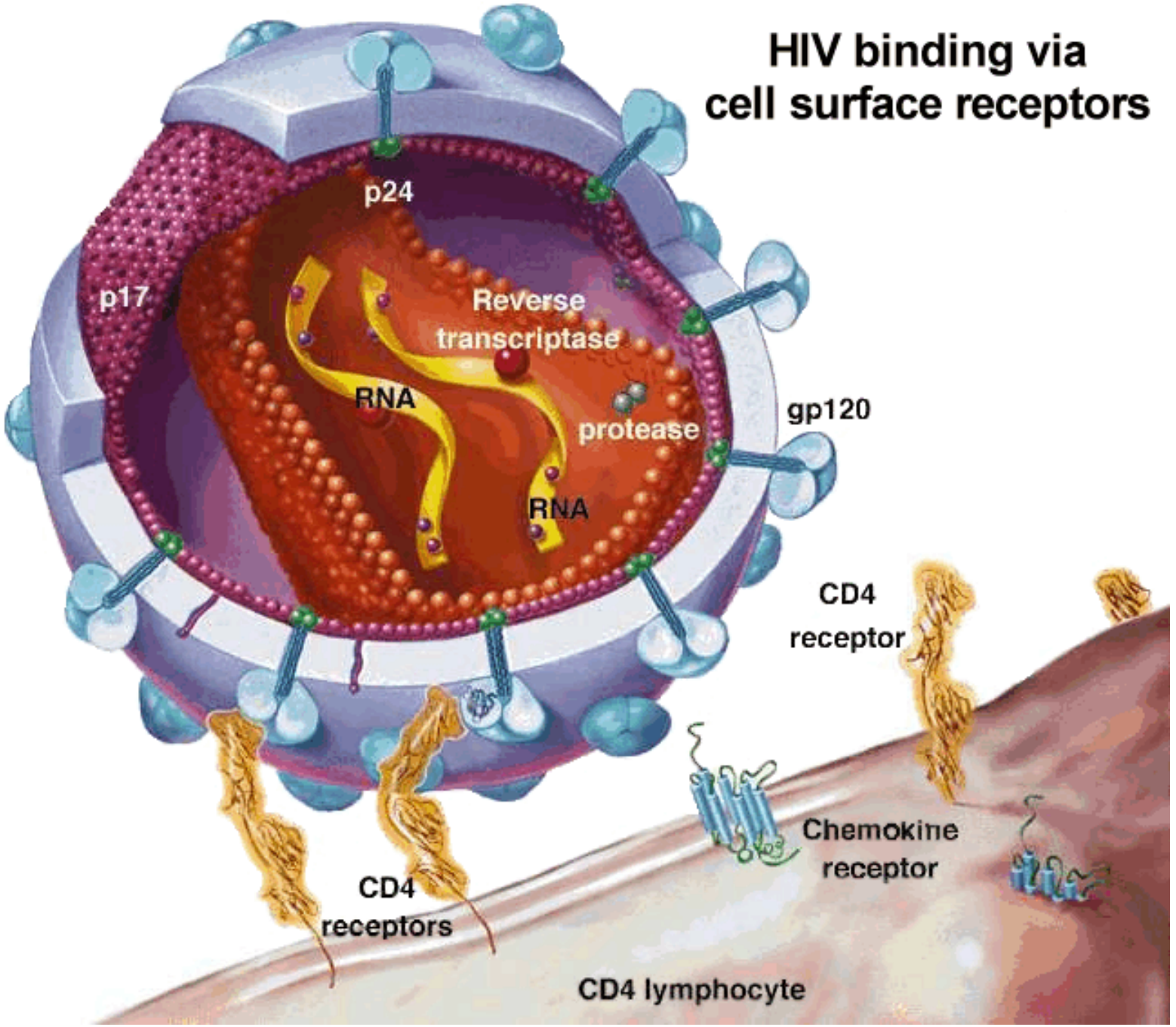
- Reversing the spread of AIDS is one of the eight U.N. Millennium Development Goals

- The AIDS pandemic undermines:
  - Poverty reduction
  - Improvements in child and maternal health
  - Improvements in nutrition
  - Gains in basic education
  - Control of other infectious diseases

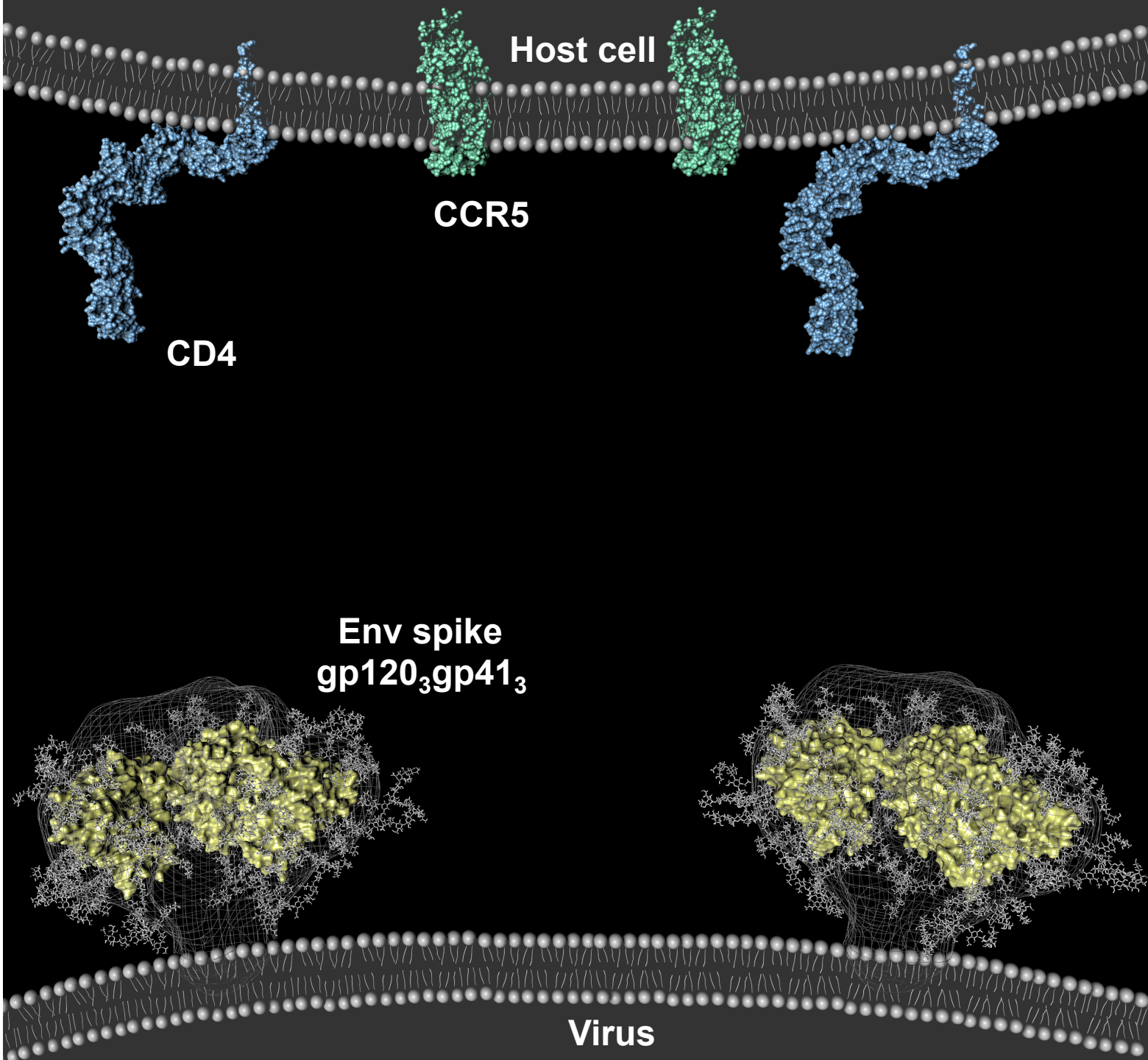
The power of vaccines

- **Approximately 300m individuals died of smallpox in the 20th Century.**
- **Following the eradication program based on vaccination, the last person died of smallpox on 9/11/1978.**

Oldstone, MBA "Viruses, Plagues & History", 1998, Oxford University Press.


HIV binding via
cell surface receptors
p24
p17
Reverse
transcriptase
RNA
protease
RNA
gp120
CD4
receptor
Chemokine
receptor
CD4
receptors
CD4 lymphocyte

The players in HIV entry.

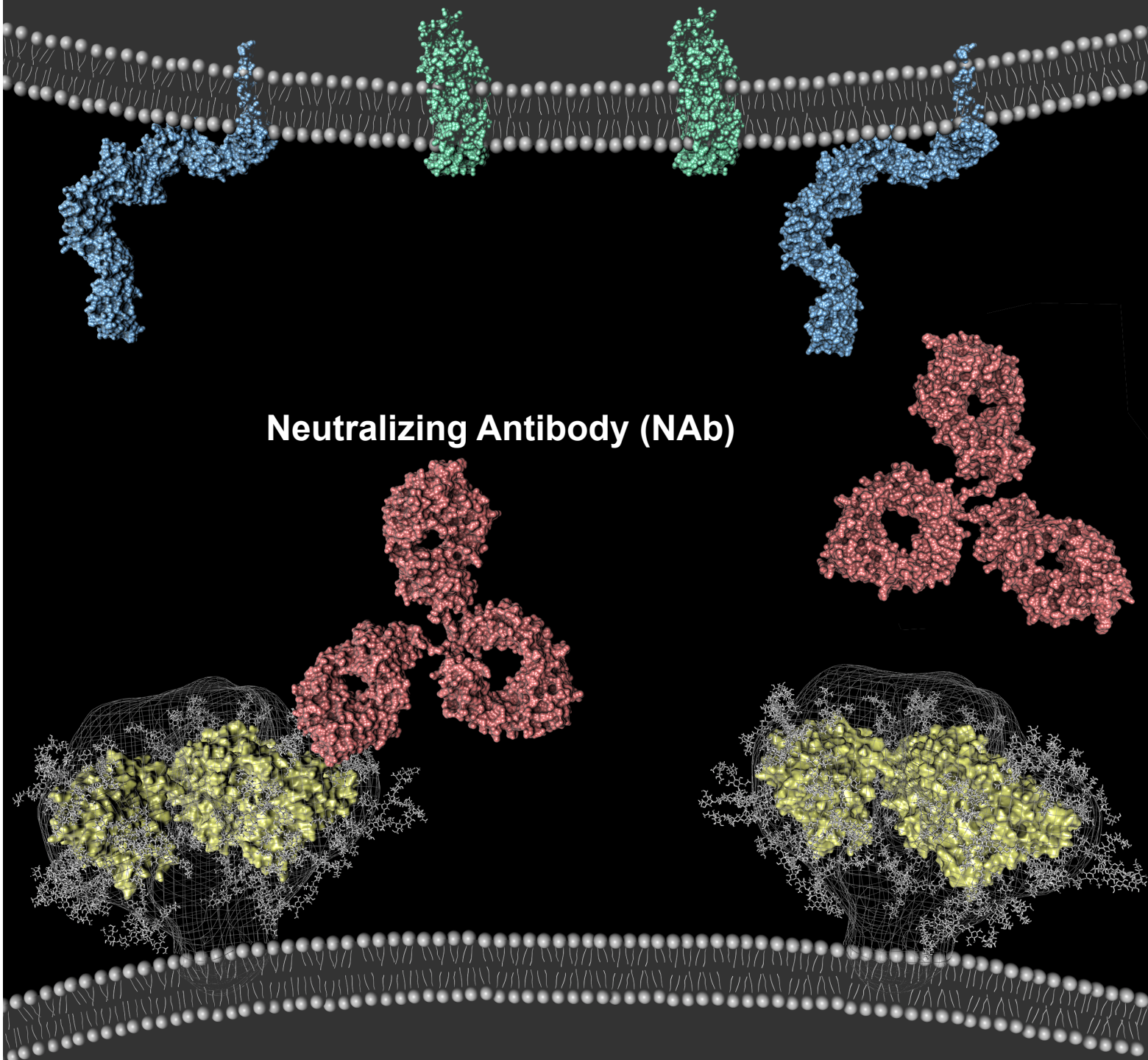


NAbs block viral entry.

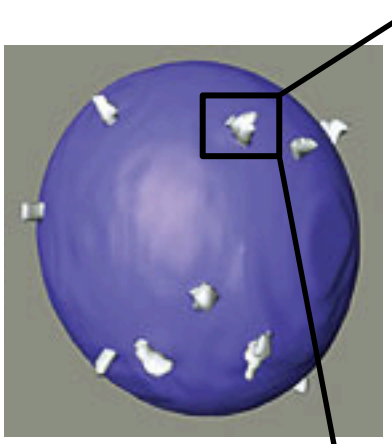
Binding to Env spike is necessary & sufficient for neutralizn.

Vaccine problem is to induce Abs that bind to Env spikes.

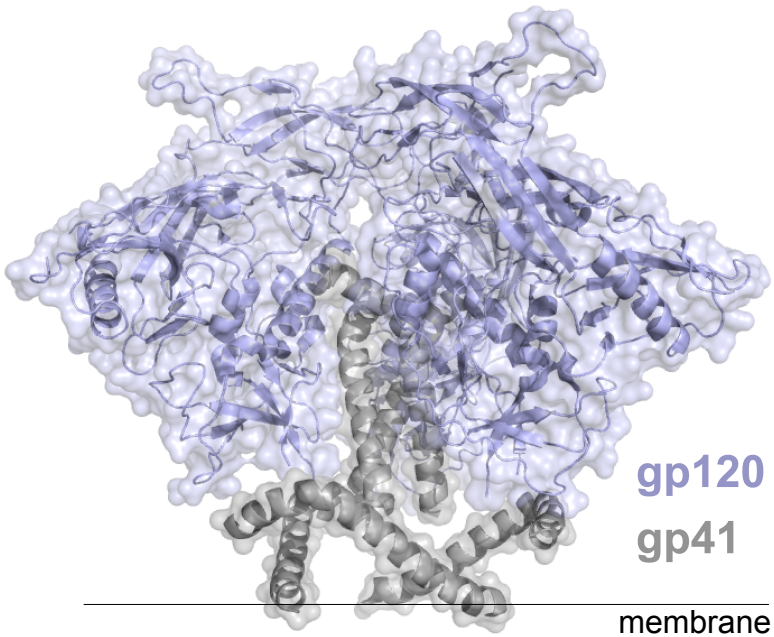
HIV variability dictates need for broadly NAbs



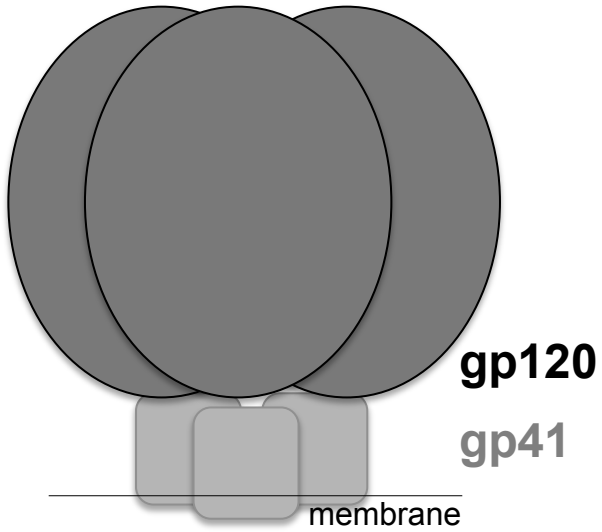
The HIV Env spike is a metastable trimer of heterodimers



HIV



Structural representation
(BG505 SOSIP.664)

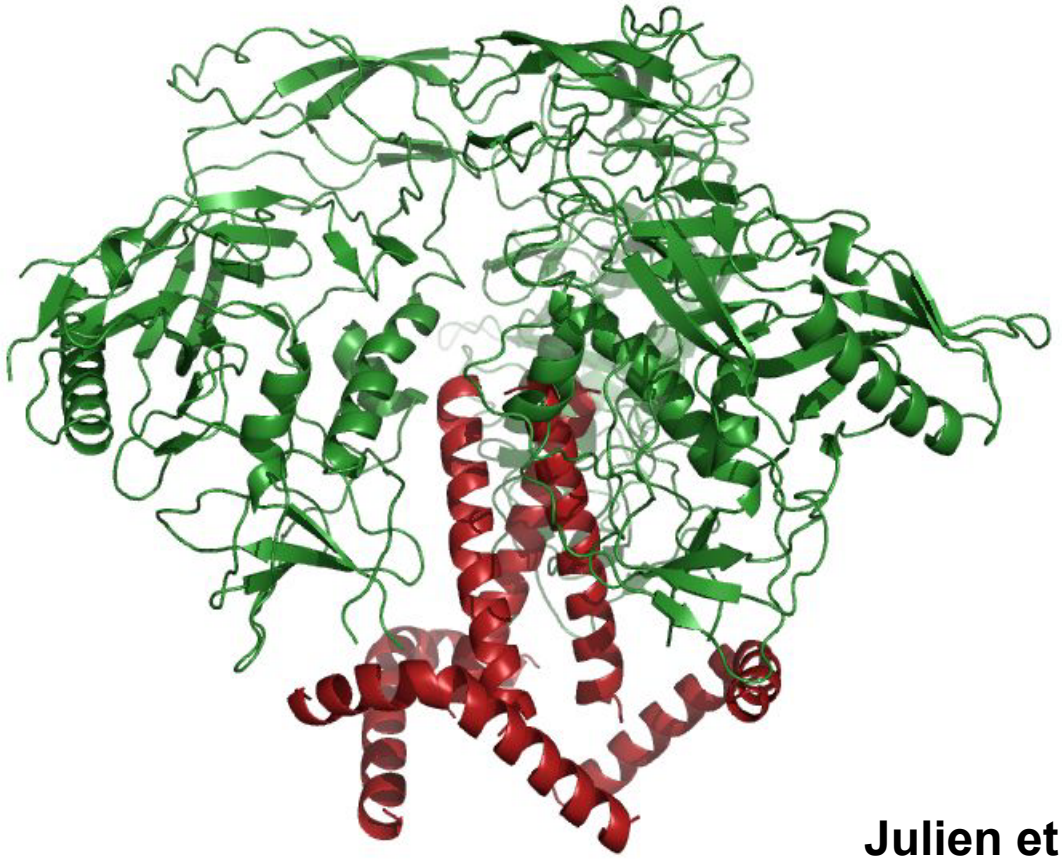


Cartoon illustration

Zhu et al, Nature, 2006
Julien et al, Science, 2013
Lyumkis et al, Science, 2013

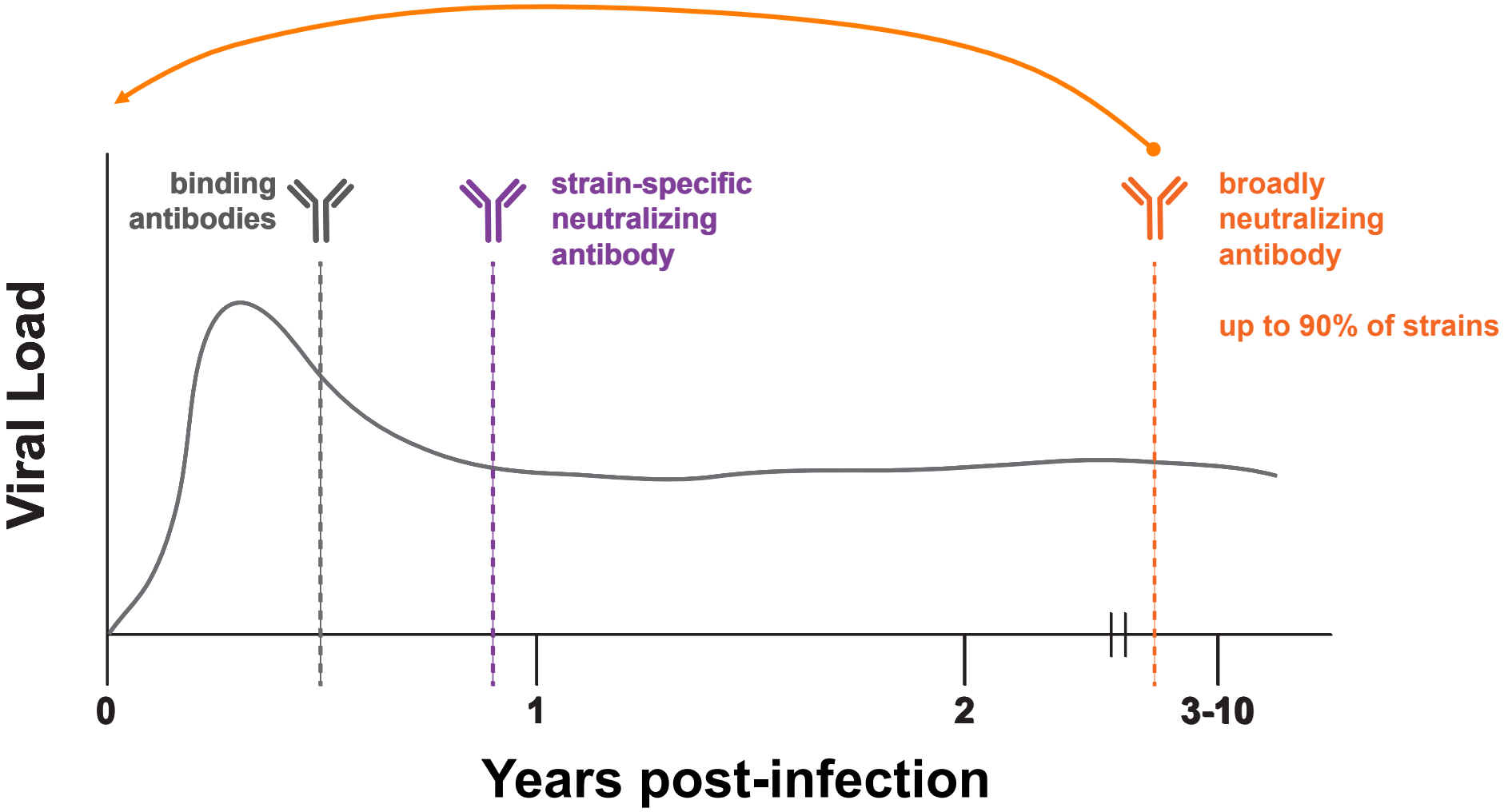
HIV Env Trimer

Jardine, Menis & Schief

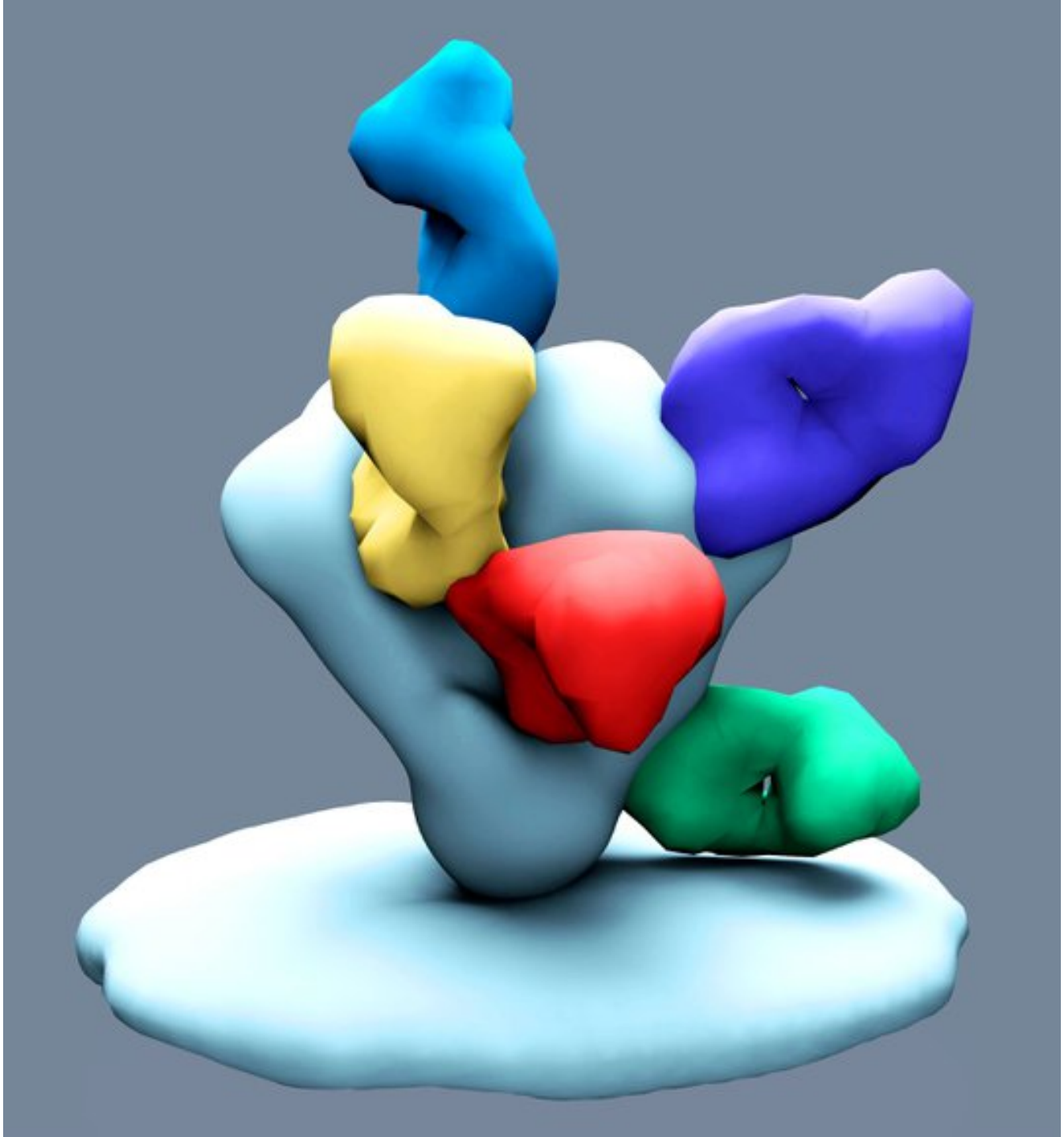


Julien et al, 2013, Science

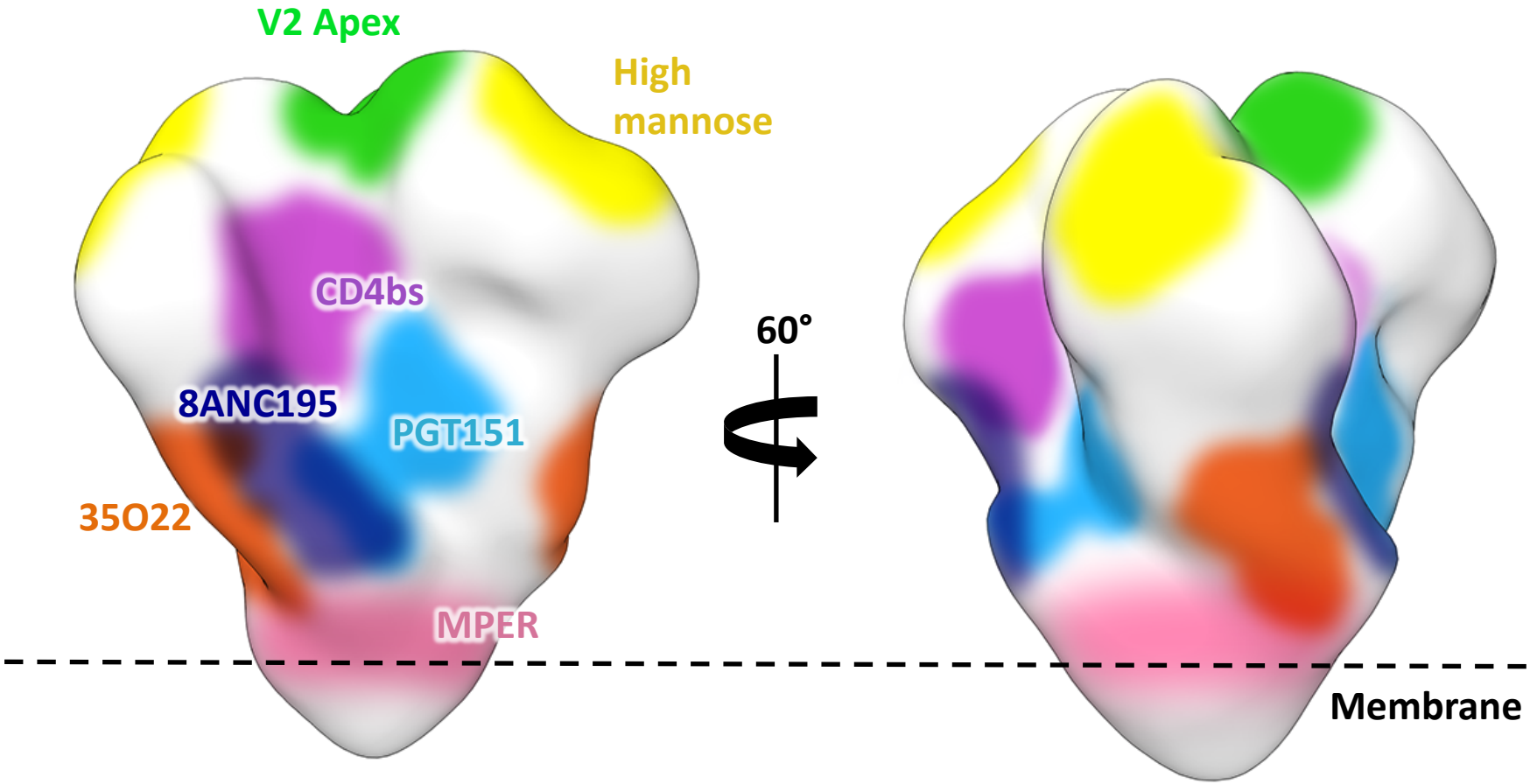
Despite the evasion tactics by HIV Env, up to 20% of chronically-infected individuals develop broadly neutralizing antibodies



Adapted from Mascola & Montefiori, Annu Rev Immunol, 2010

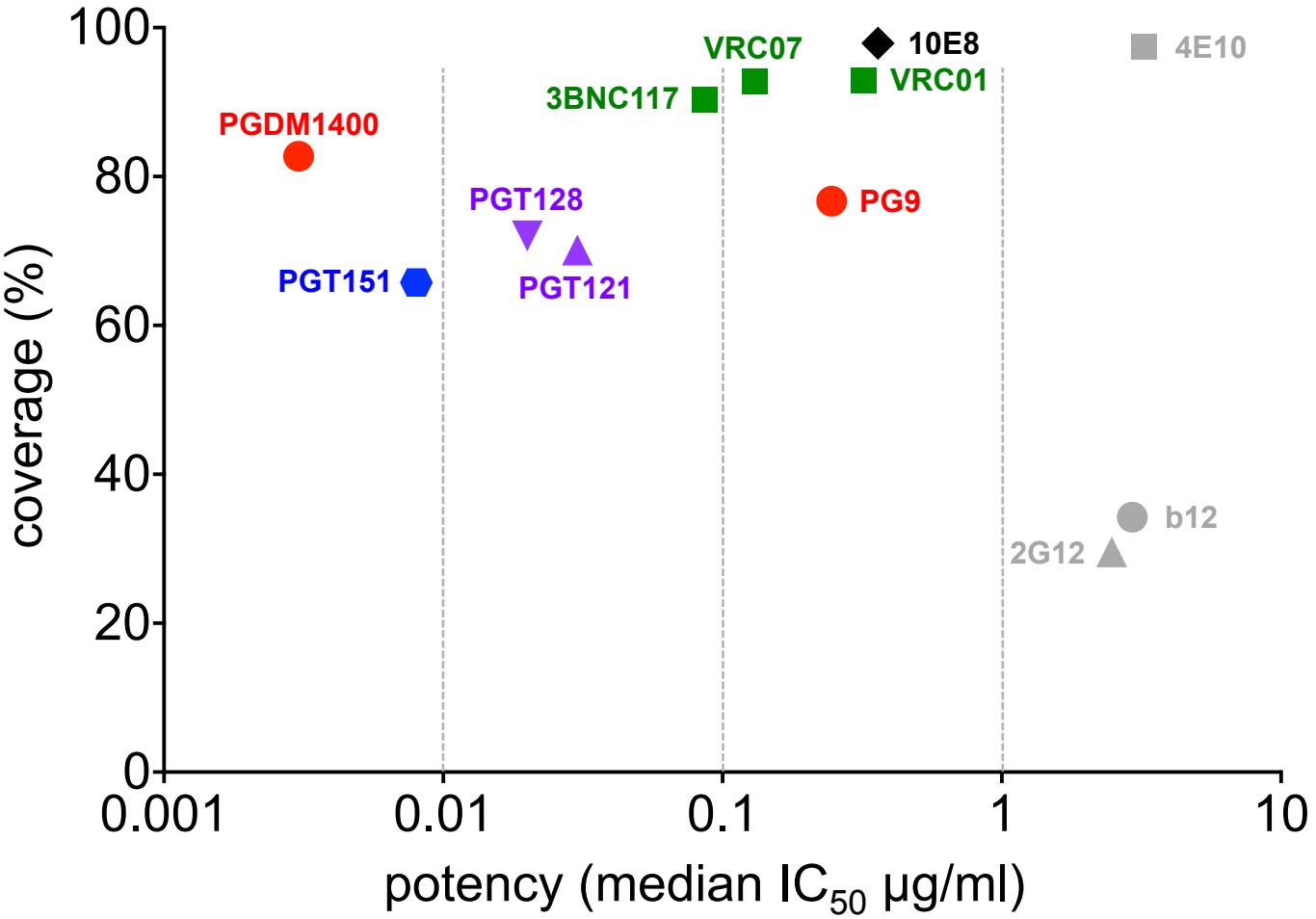


Broadly neutralizing MAbs define Env sites of vulnerability



J.H. Lee, A.B.Ward

Breadth and potency of prototype HIV bnAbs



Critical: better donors & HuMAb isolation methods

Example of broad serum neutralization by an IAVI Protocol G "elite neutralizer"

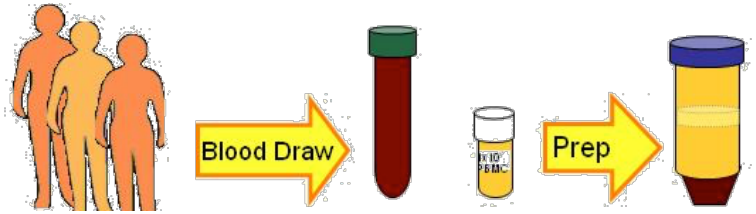
	Clade A	Clade B		Clade C		CRF01_AE
Virus	94UG103	92BR020	JRCSF	IAVI C22	93IN905	92TH021
Serum IC_{50}	900	900	2700	2700	2700	2700

IC_{50}= serum dilution giving 50% neutralization of virus isolate in Monogram pseudovirus assay

(Simek et al, J Virol, 2009)

Isolation of bnMAbs from Protocol G donors

IAVI/Theraclone/ Monogram/Scripps

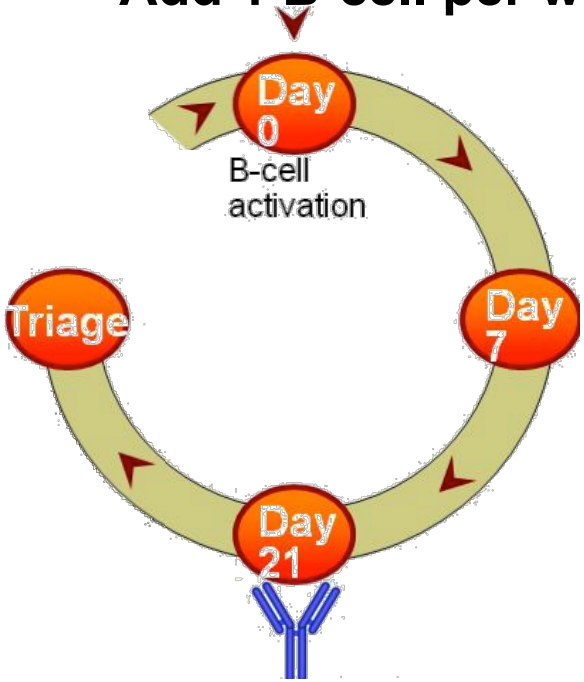


Protocol G donor

PBMCs

>30,000 B-cells

Add 1 B-cell per well

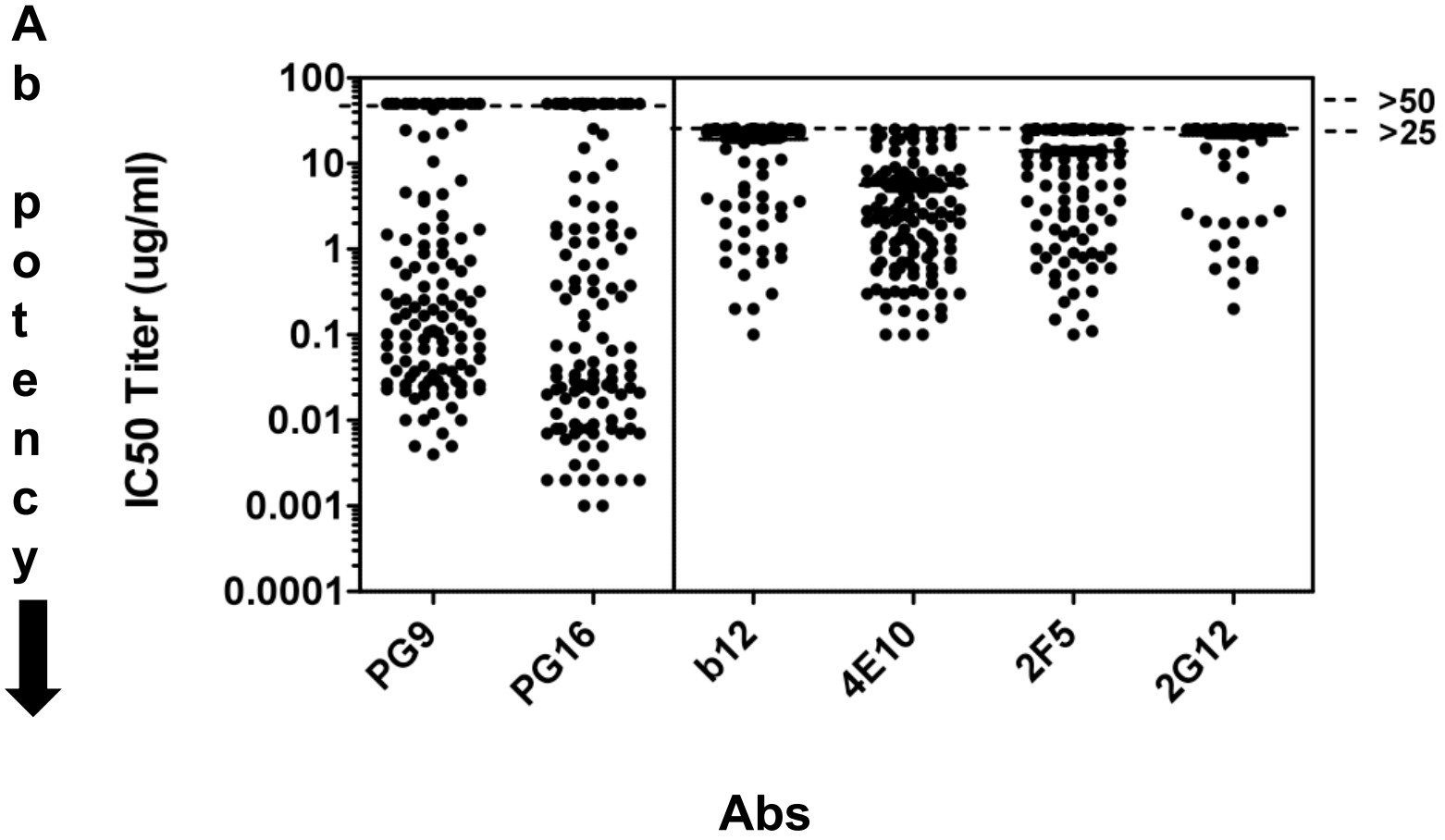


Potent bnMAbs

Test supernates in high-throughput micro-neutralization assay

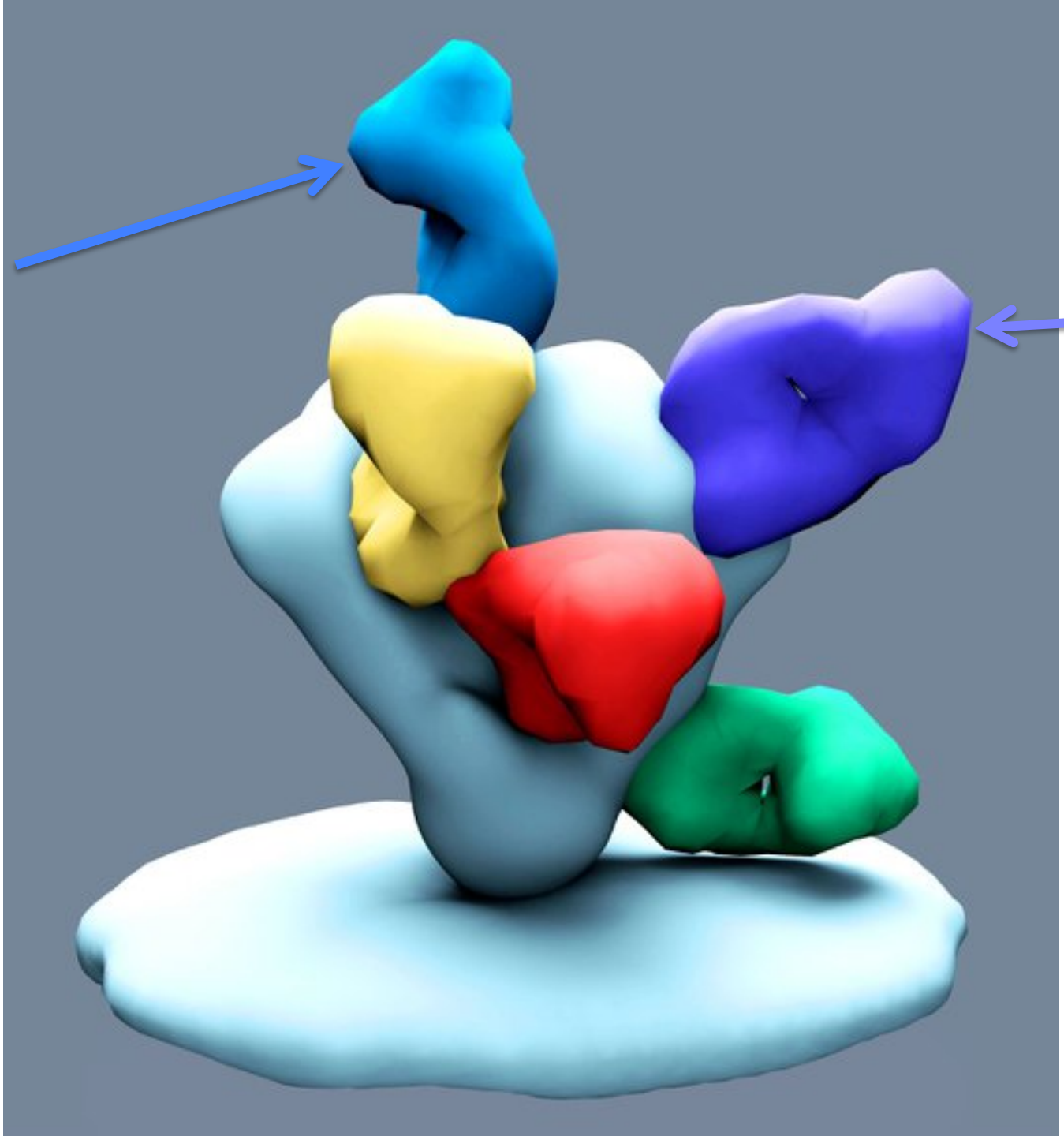
Rescue Ab genes from positive wells

Broad and potent MAbs PG9 and PG16 isolated by direct neutralization screening approach (Walker et al, Science, 2009)



Each dot represents one virus (118 viruses)

Mike Seaman


PGDM1400
PGT121

PGT121 and PGDM1400 neutralization together on 106-virus panel

	PGT121	PGDM1400	PGT121+PGDM1400
Median IC50, µg/ml	0.015	0.005	0.007
% breadth	63	80	98

Sok, van Gils et al, PNAS, in press

PGT 121 effectively protects against high-dose mucosal SHIV challenge in macaques

Challenge SHIV	Challenge route	Complete protection Lowest dose (mg/kg)	50% animals protected dose (mg/kg)	Collabr
162P3	IVAG	1	~0.2	Watkins
162P3	IVAG	2	~0.4	Barouch
AD8E0	IR	1	-	Martin
DH12-V3AD8	IR	0.2	-	Martin
B founder	IR	10	-	Lifson

Potent bnMAbs have therapeutic effects in the SHIV/macaque model

nature

November 2013
Volume 503
Issue 7475

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys

Dan H. Barouch, James B. Whitney, Brian Moldt, Florian Klein, Thiago Y. Oliveira, Jinyan Liu, Kathryn E. Stephenson, Hui-Wen Chang, Karthik Shekhar, Sanjana Gupta, Joseph P. Nkolola, Michael S. Seaman, Kaitlin M. Smith, Erica N. Borducchi, Crystal Cabral, Jeffrey Y. Smith, Stephen Blackmore, Srisowmya Sanisetty, James R. Perry, Matthew Beck, Mark G. Lewis, William Rinaldi, Arup K. Chakraborty, Pascal Poignard, Michel C. Nussenzweig and Dennis R. Burton

nature

November 2013
Volume 503
Issue 7475

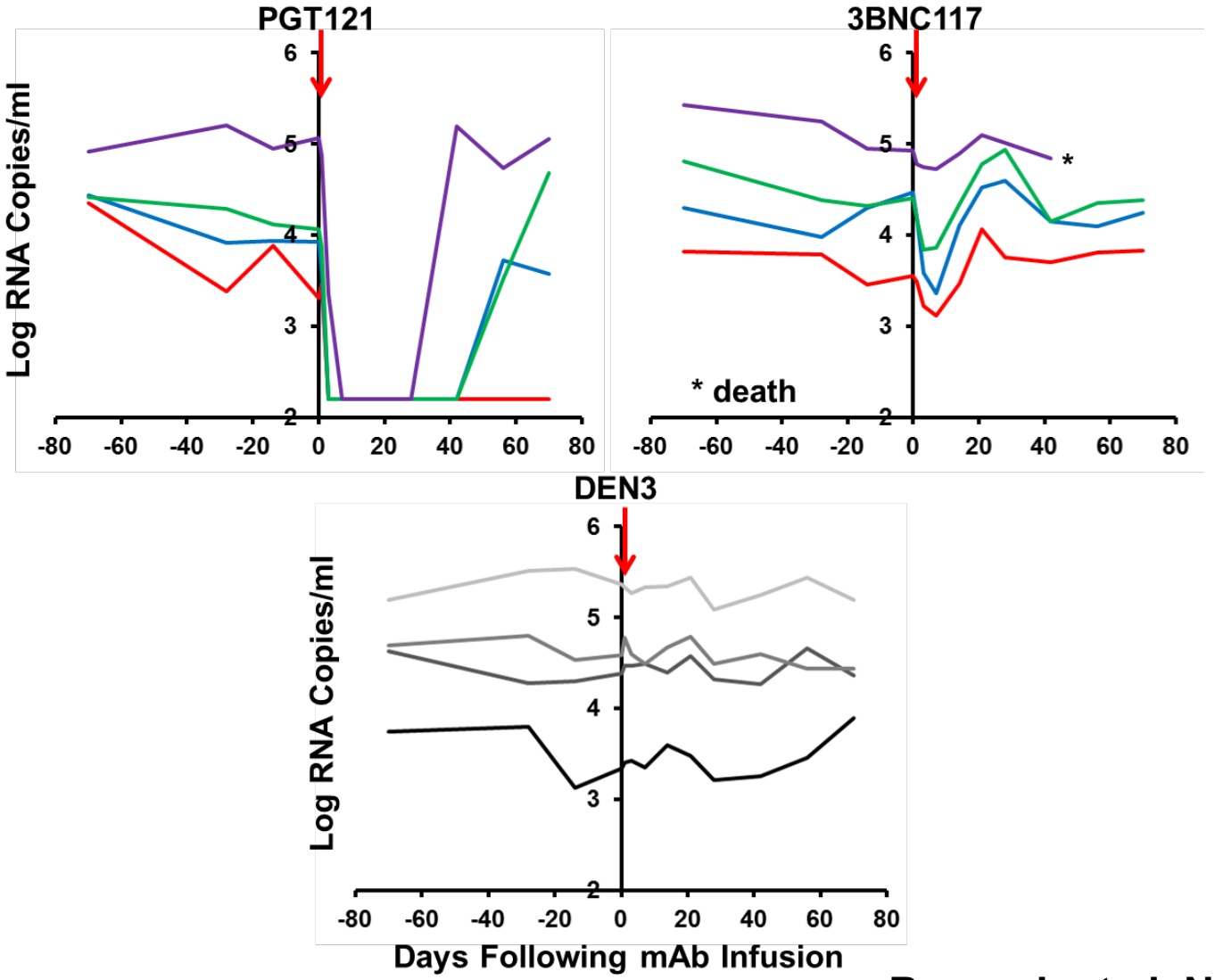
Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia

Masashi Shingai, Yoshiaki Nishimura, Florian Klein, Hugo Mouquet, Olivia K. Donau, Ronald Plishka, Alicia Buckler-White, Michael Seaman, Michael Piatak Jr, Jeffrey D. Lifson, Dimiter S. Dimitrov, Michel C. Nussenzweig, and Malcolm A. Martin

Therapeutic efficacy of PGT121 monotherapy

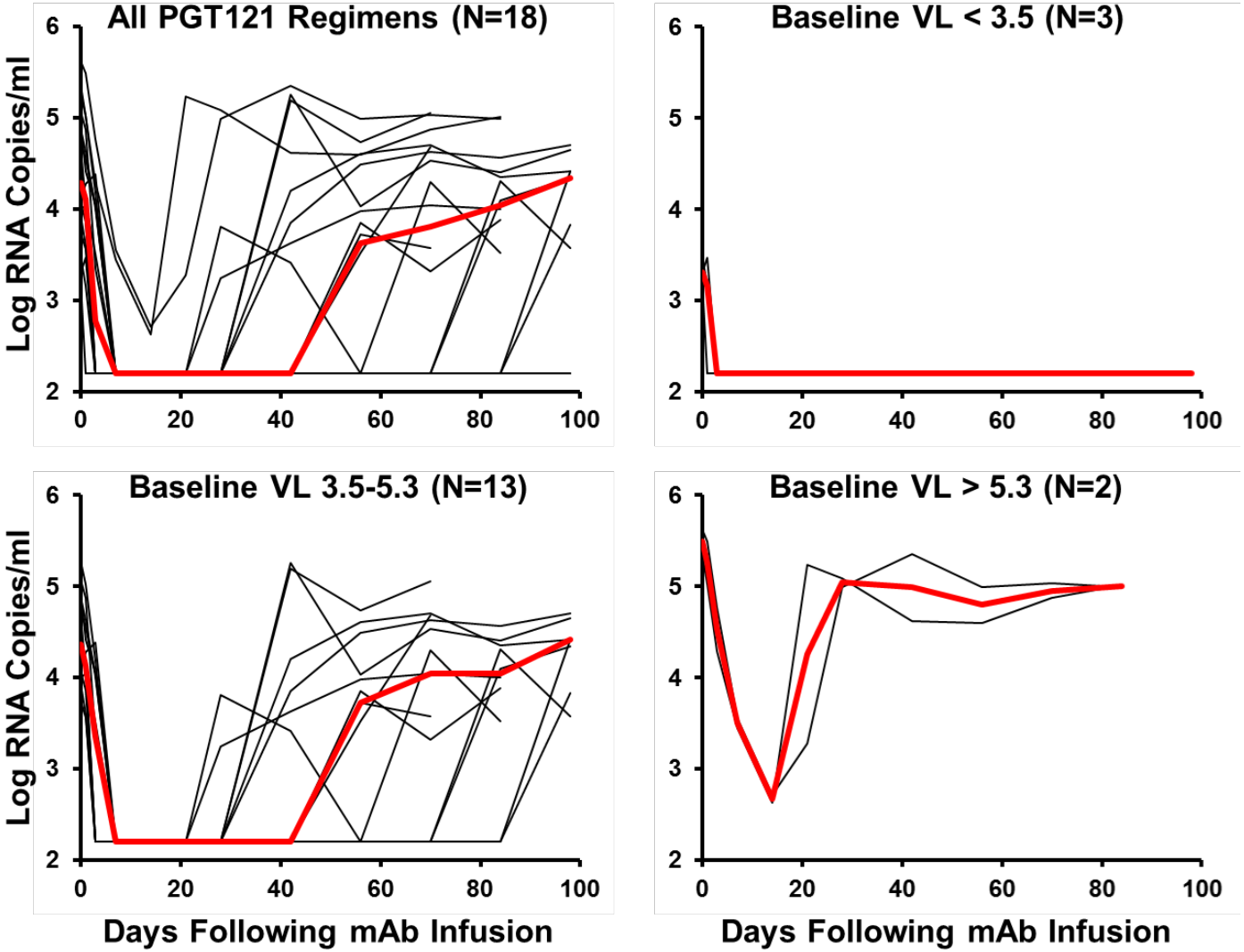
- 12 monkeys infected with SHIV-SF162P3 for 9 months
- Log setpoint viral loads 3.3 - 5.4
- Single IV infusion on day 0
  - PGT121 (10 mg/kg; N=4)
  - 3BNC117 (10 mg/kg; N=4)
  - DEN3 isotype control (10 mg/kg; N=4)

Rapid virologic control following a single infusion of PGT121 alone



Barouch et al. Nature, 2013

Summary of therapeutic efficacy of PGT121 or PGT121-containing mAb cocktails



Barouch et al. Nature, 2013

Perhaps the single largest problem in HIV vaccine design based on Abs is the nature of broadly neutralizing epitopes.

-these epitopes exist in a sea of glycans and variable protein residues, presenting major challenges to recognition by and elicitation of bnAbs.

How do Abs in natural HIV infection deal with glycans and variability?

October 2005
Volume 102
Number 42

PNAS

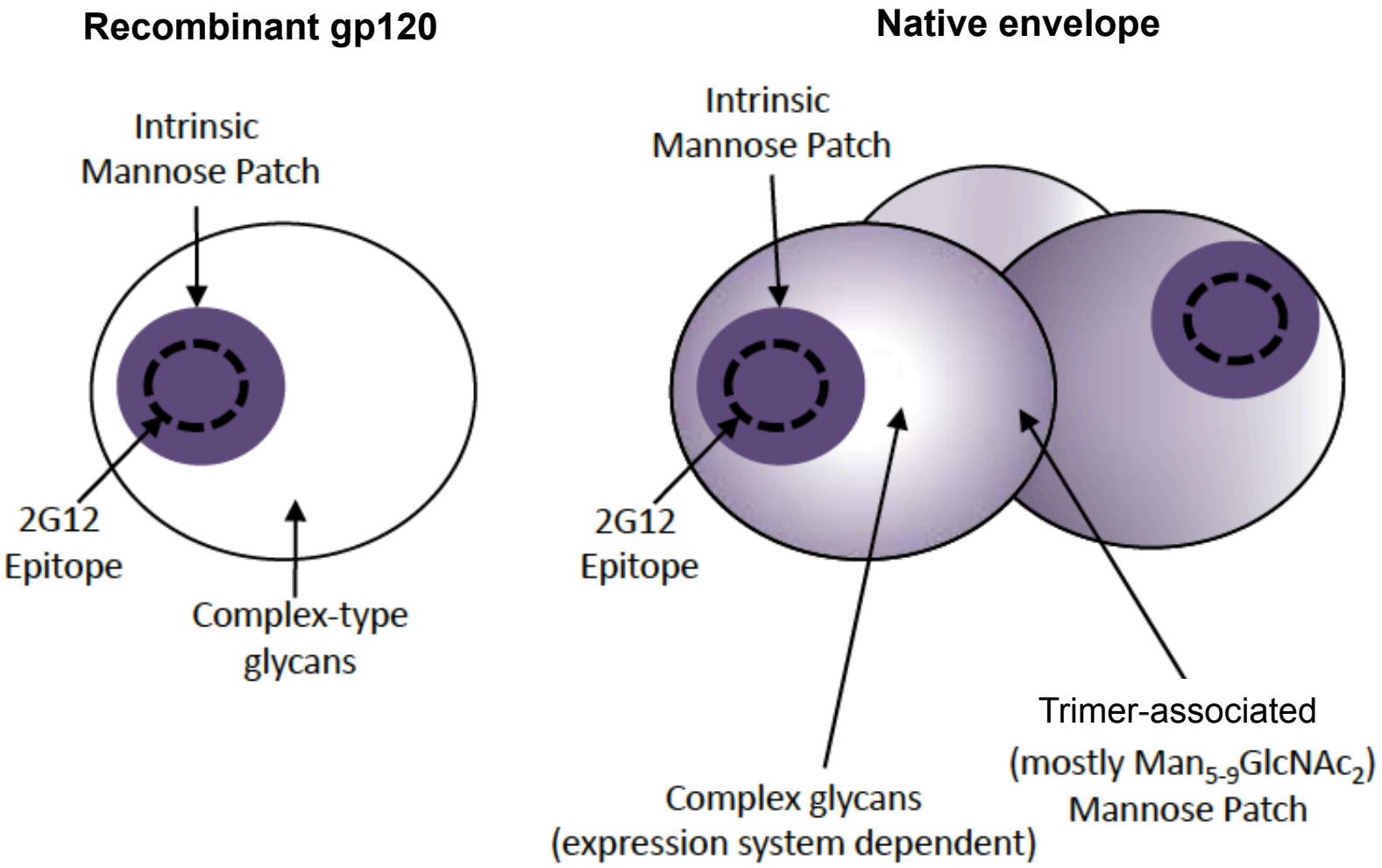
Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

Antibody vs. HIV in a clash of evolutionary titans

Dennis R. Burton, Robyn L. Stanfield, and Ian A. Wilson

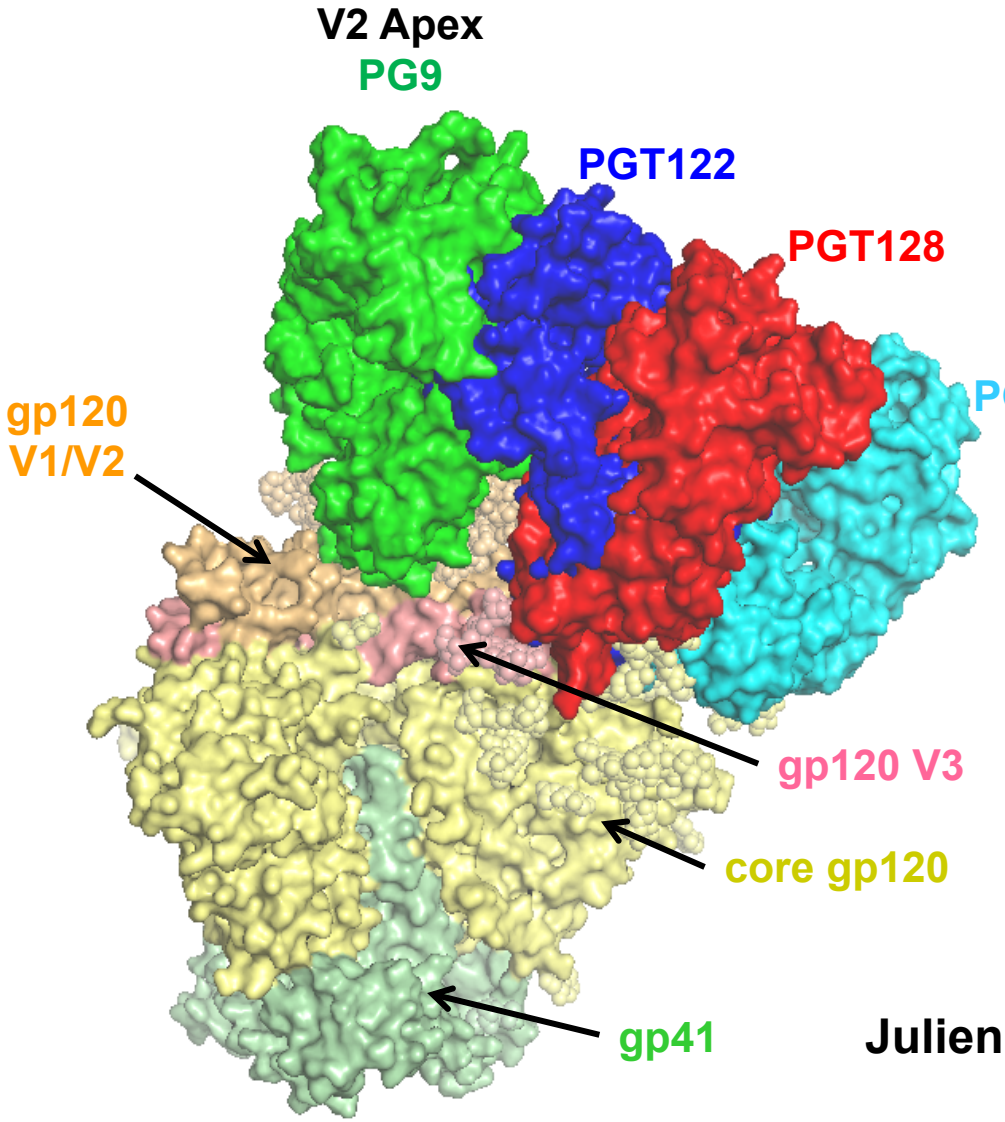
Anti-glycan/protein bnMAbs (V2/apex and high mannose patch)

Model for native envelope glycosylation



Doores, Scanlan et al, PNAS, 2010; Bonomelli, Doores, Scanlan et al, PloS One, 2011.

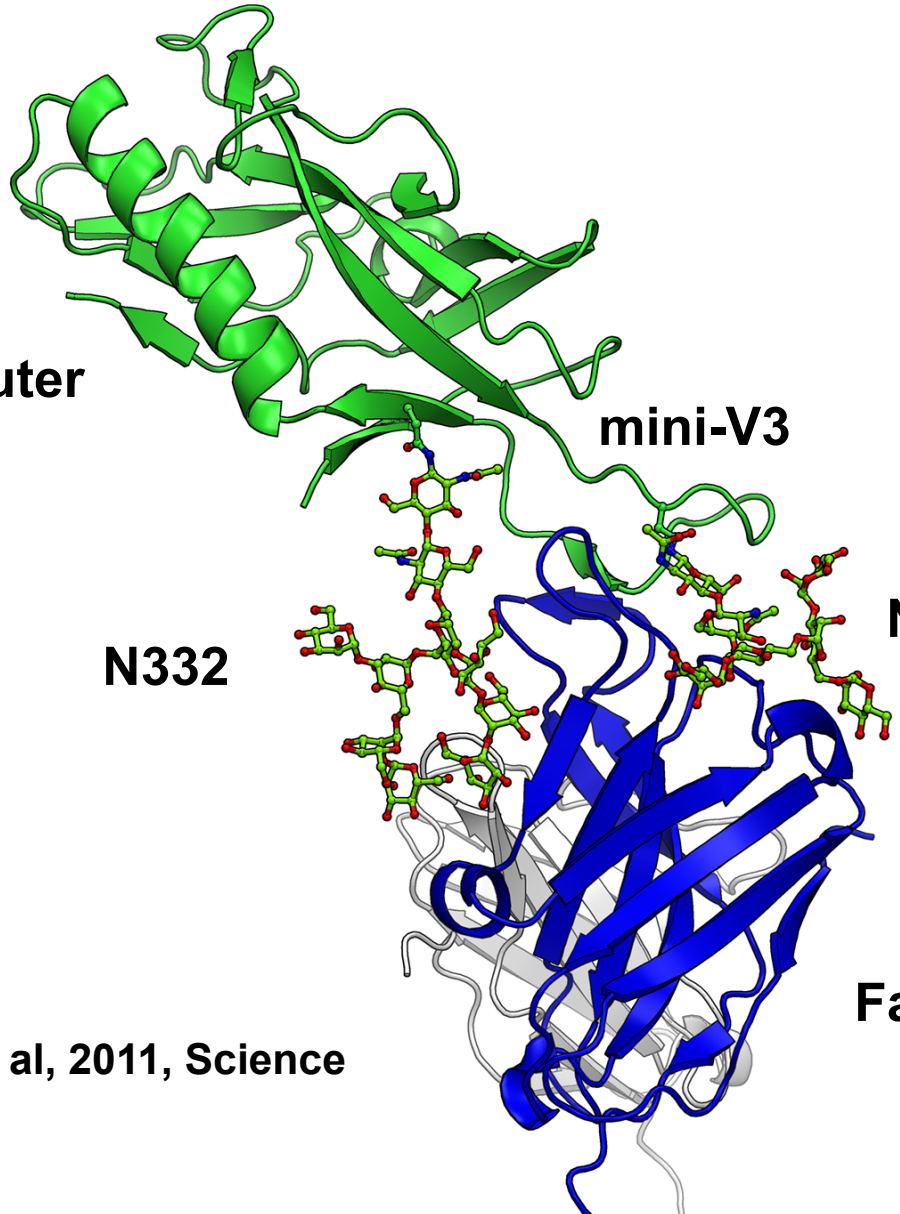
Glycan-dependent bnMAbs bound to SOSIP Env gp140 trimer



High-mannose patch

Julien et al, Science, 2013

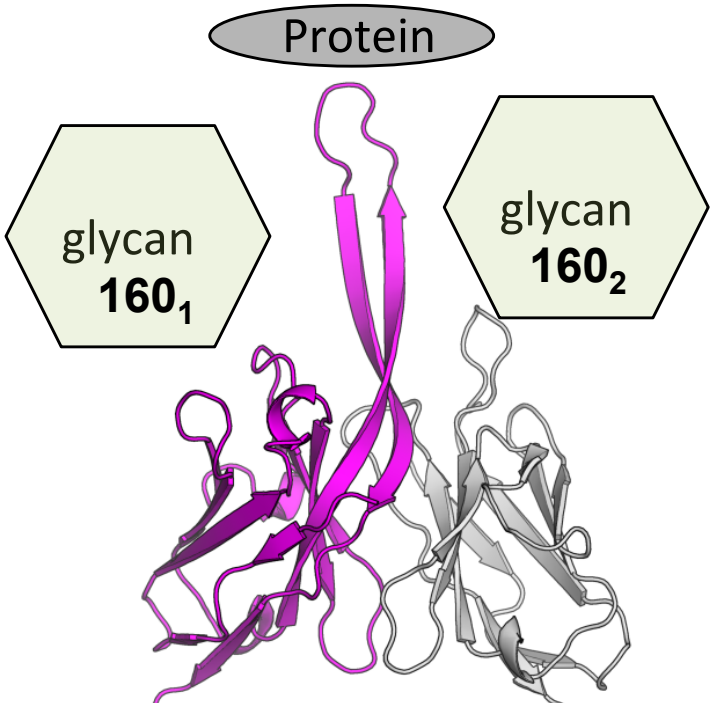
PGT 128 penetrates the glycan shield and accesses the protein surface underneath



Pejchal et al, 2011, Science

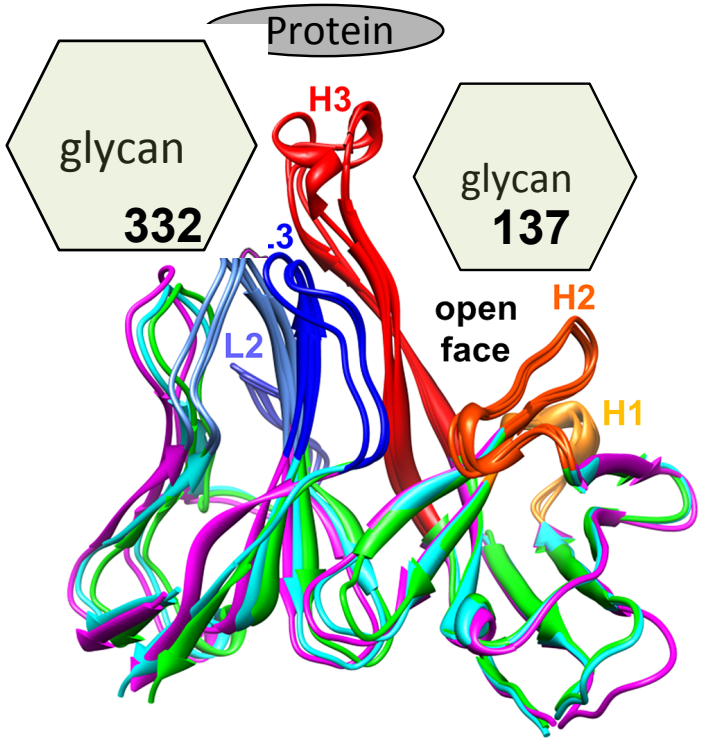
V2 apex and high-mannose patch bnAb recognition

V2 apex



PGT145

High mannose patch

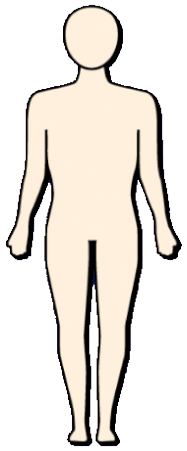


PGT121
PGT124

Leopold Kong

How do we move from data on bnAb-Env interactions to immunogen design?

Reverse engineering a viral vaccine



Infected individual

broadly neutralizing (protective) antibodies

Env

Molecular characterization of Ab-Env

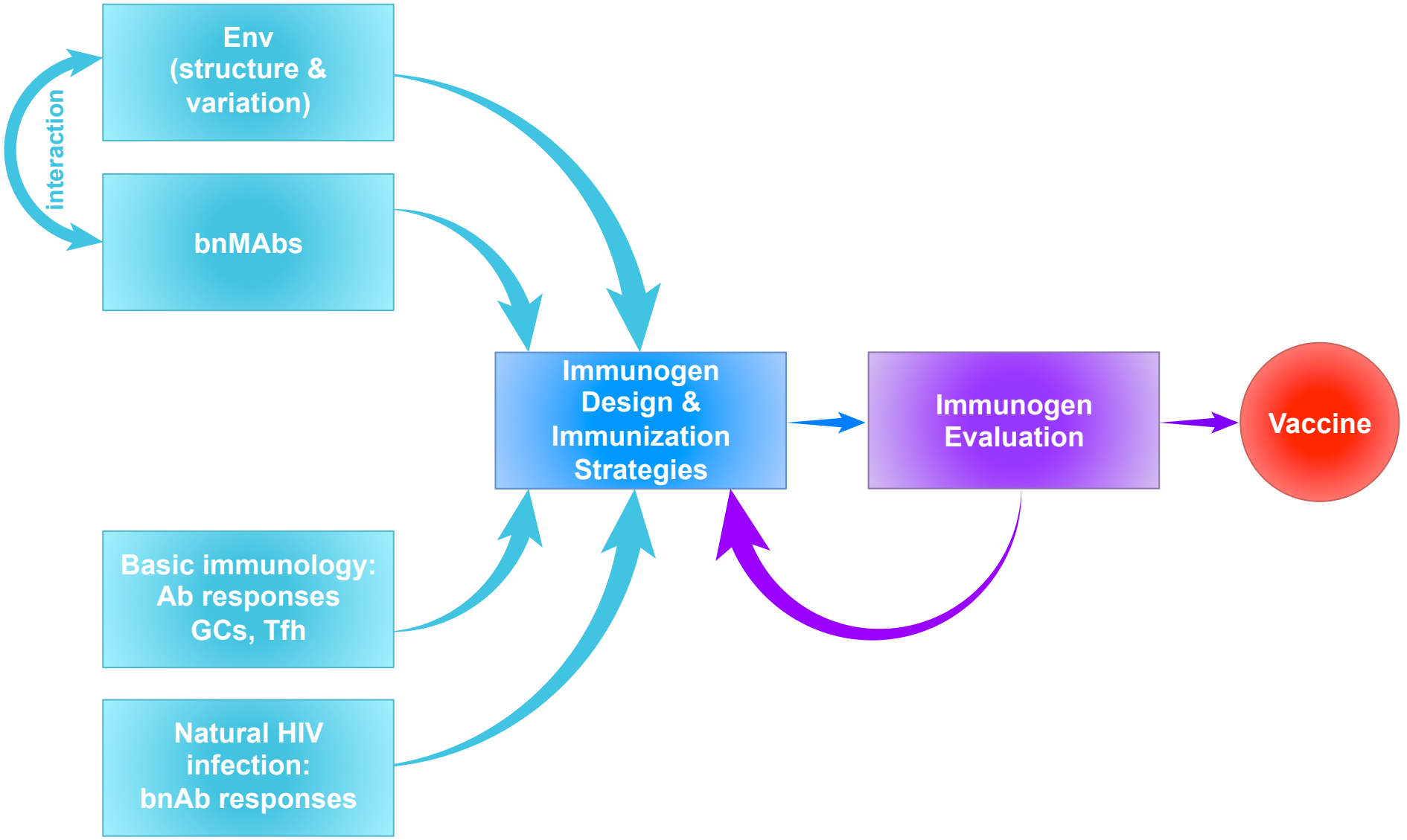
Immunogen design and testing

*modified Env

combination of several immunogens = vaccine

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

Rational Approach to HIV Vaccine Design



SCIENCE
November 2013
Volume 342
Issue 6158

Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus

Jason S. McLellan, Man Chen, M. Gordon Joyce, Mallika Sastry, Guillaume B. E. Stewart-Jones, Yongping Yang, Baoshan Zhang, Lei Chen, Sanjay Srivatsan, Anqi Zheng, Tongqing Zhou, Kevin W. Graepel, Azad Kumar, Syed Moin, Jeffrey C. Boyington, Gwo-Yu Chuang, Cinque Soto, Ulrich Baxa, Arjen Q. Bakker, Hergen Spits, Tim Beaumont, Zizheng Zheng, Ningshao Xia, Sung-Youl Ko, John-Paul Todd, Srinivas Rao, Barney S. Graham, and Peter D. Kwong

nature
March 2014
Volume 507
Issue 7491

Proof of principle for epitope-focused vaccine design

Bruno E. Correia, John T. Bates, Rebecca J. Loomis, Gretchen Baneyx, Chris Carrico, Joseph G. Jardine, Peter Rupert, Colin Correnti, Oleksandr Kalyuzhniy, Vinayak Vittal, Mary J. Connell, Eric Stevens, Alexandria Schroeter, Man Chen, Skye MacPherson, Andreia M. Serra, Yumiko Adachi, Margaret A. Holmes, Yuxing Li, Rachel E. Klevit, Barney S. Graham, Richard T. Wyatt, David Baker, Roland K. Strong, James E. Crowe Jr, Philip R. Johnson and William R. Schief

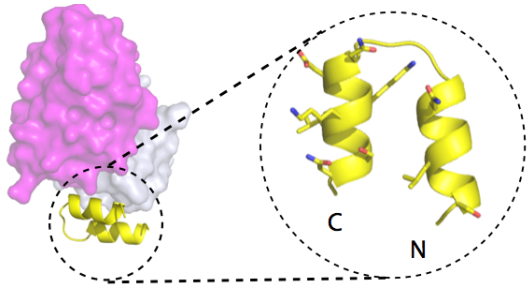
Proof of concept for epitope-focused vaccine design: epitope-scaffolds induce potent neutralization of RSV in NHPs

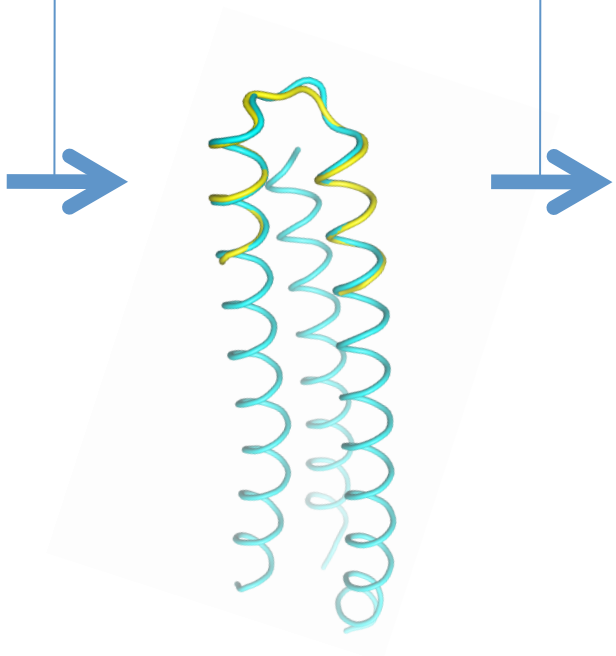
NAb-epitope complex

Computation Design of Epitope-scaffolds

Macaque Immunization

Potent Neutralization of RSV





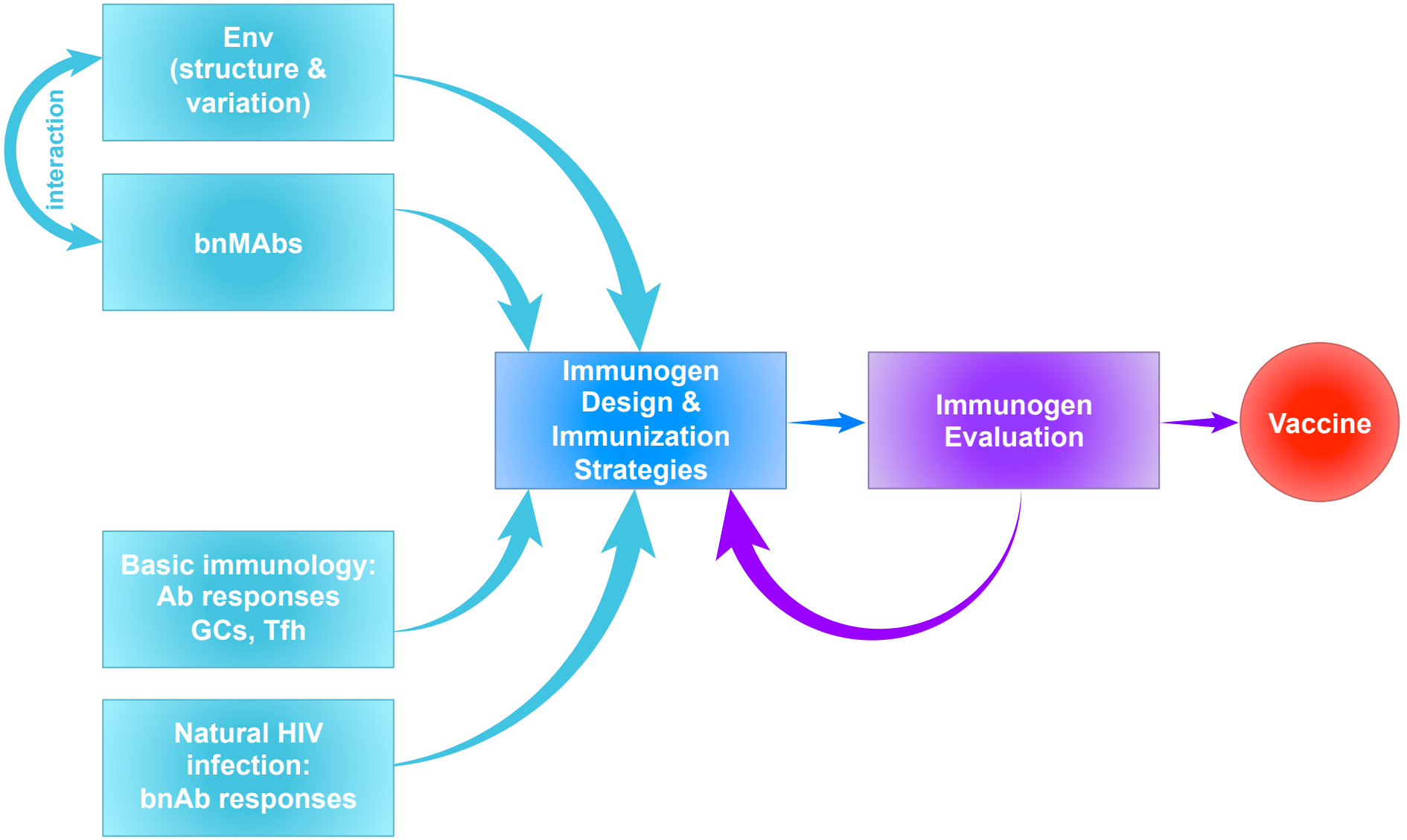
A. Potent polyclonal serum neutralizing responses

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

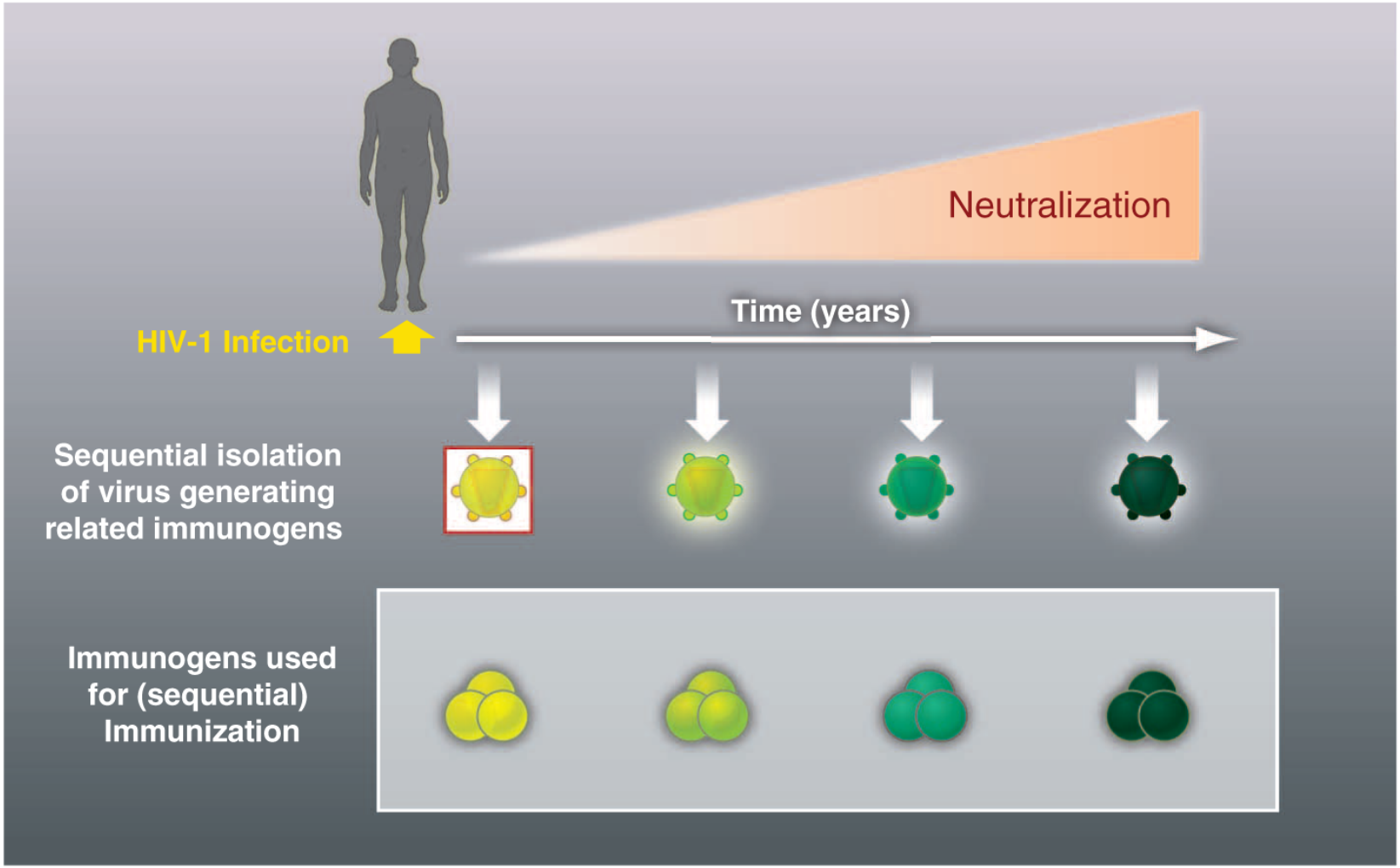
C. Rhesus MAbs recapitulate Mota structural specificity.

Correia et al, Nature, 2014

Rational Approach to HIV Vaccine Design

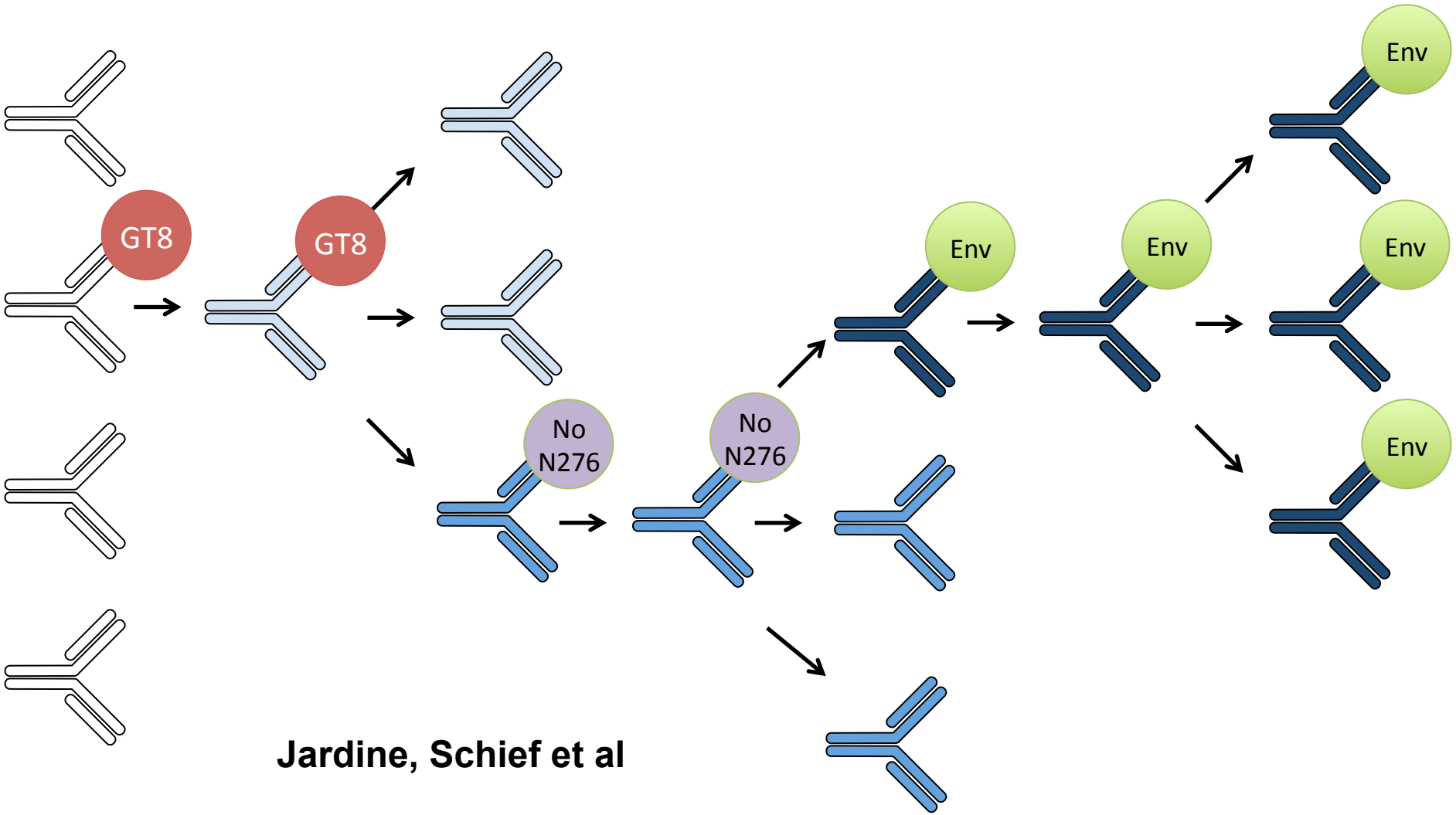


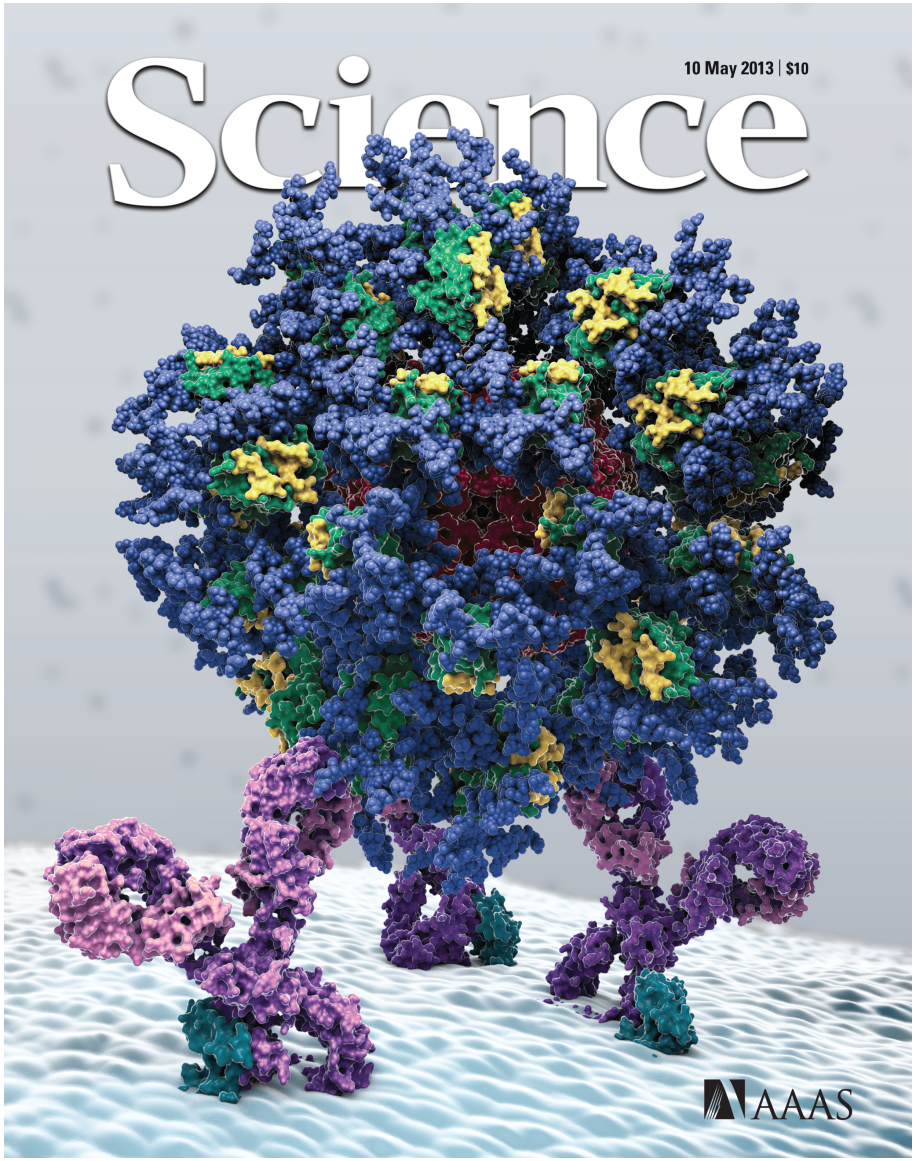
Vaccine Design based on studying Co-Evolution of Antibody and Virus



Klein et al, Science, 2013

The Reductionist Approach: VRC01-like CD4bs Abs-one iteration



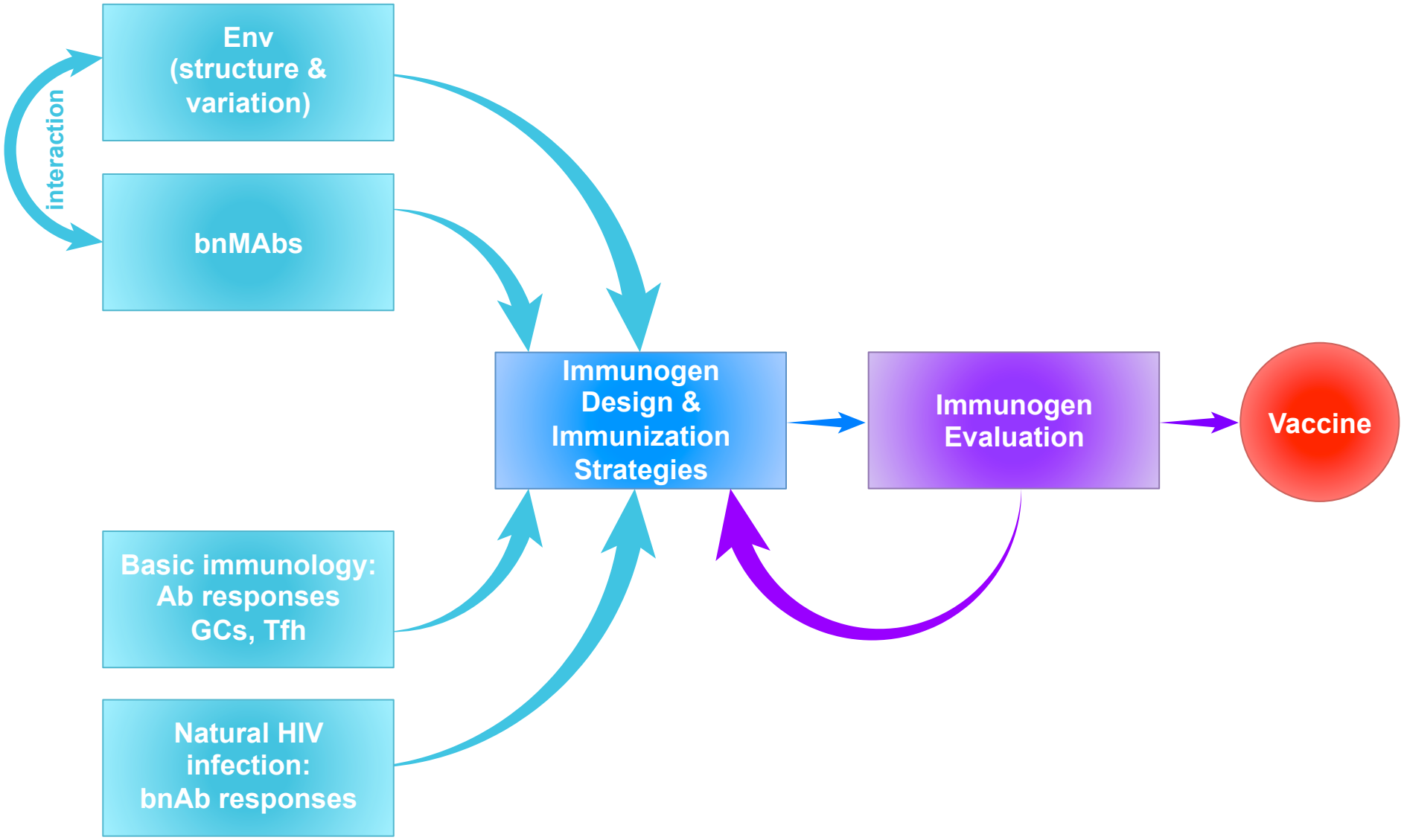


Rational HIV immunogen design to target specific germline B cell receptors.

Jardine J, Julien JP, Menis S, Ota T, Kalyuzhniy O, McGuire A, Sok D, Huang PS, MacPherson S, Jones M, Nieusma T, Mathison J, Baker D, Ward AB, Burton DR, Stamatatos L, Nemazee D, Wilson IA, Schief WR.

Science. 2013 340:711-6

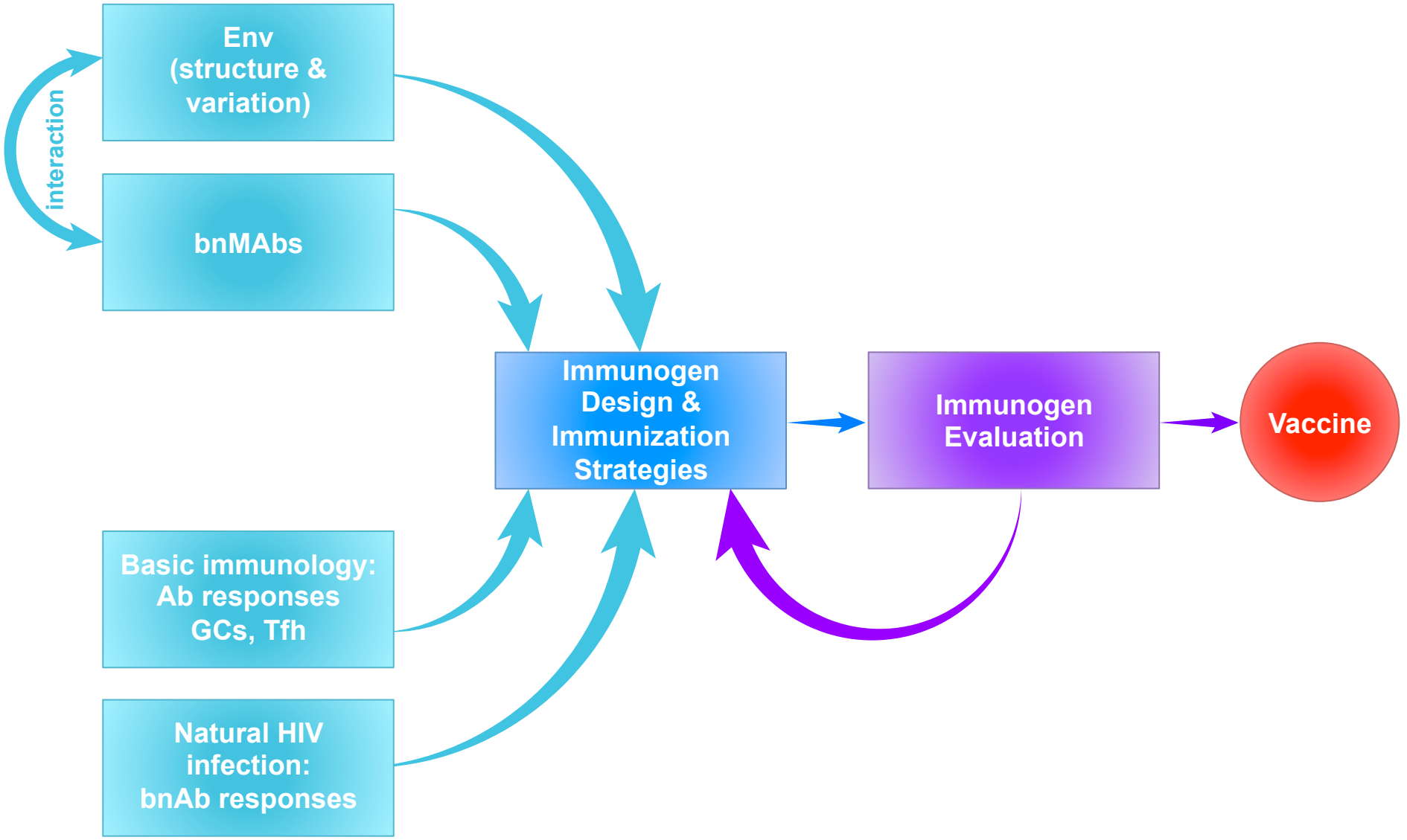
Rational Approach to HIV Vaccine Design



HIV immunogen evaluation

- **Iteration!**
- **Prefer humans! Animal models-macaques, mice expressing human Ab repertoires, germline (GL)-bnAb knockin mice. In vitro models.**
- **Detailed analysis of Ab responses-Next Generation Sequencing, isolation of MAbs, innate signatures, Tfh cells.**

Rational Approach to HIV Vaccine Design



Collaborators

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Guido Silvestri
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Pascal Poignard

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John Mascola
Peter Kwong

Duke CHAVI-ID
Bart Haynes
Bette Korber
Robin Shattock

IAVI
Wayne Koff
Clinical sites

Members of the Neutralizing Antibody Consortium

Protocol G & C scientists & donors

Monogram

Theraclone

Ragon
Bruce Walker
Galit Alter
Dan Barouch
Arup Chakra-borty

Cornell
John Moore

Miami
David Watkins

National Institute of Allergy and Infectious Diseases

Scripps Center for HIV/AIDS Vaccine Immunology & Immunogen Discovery