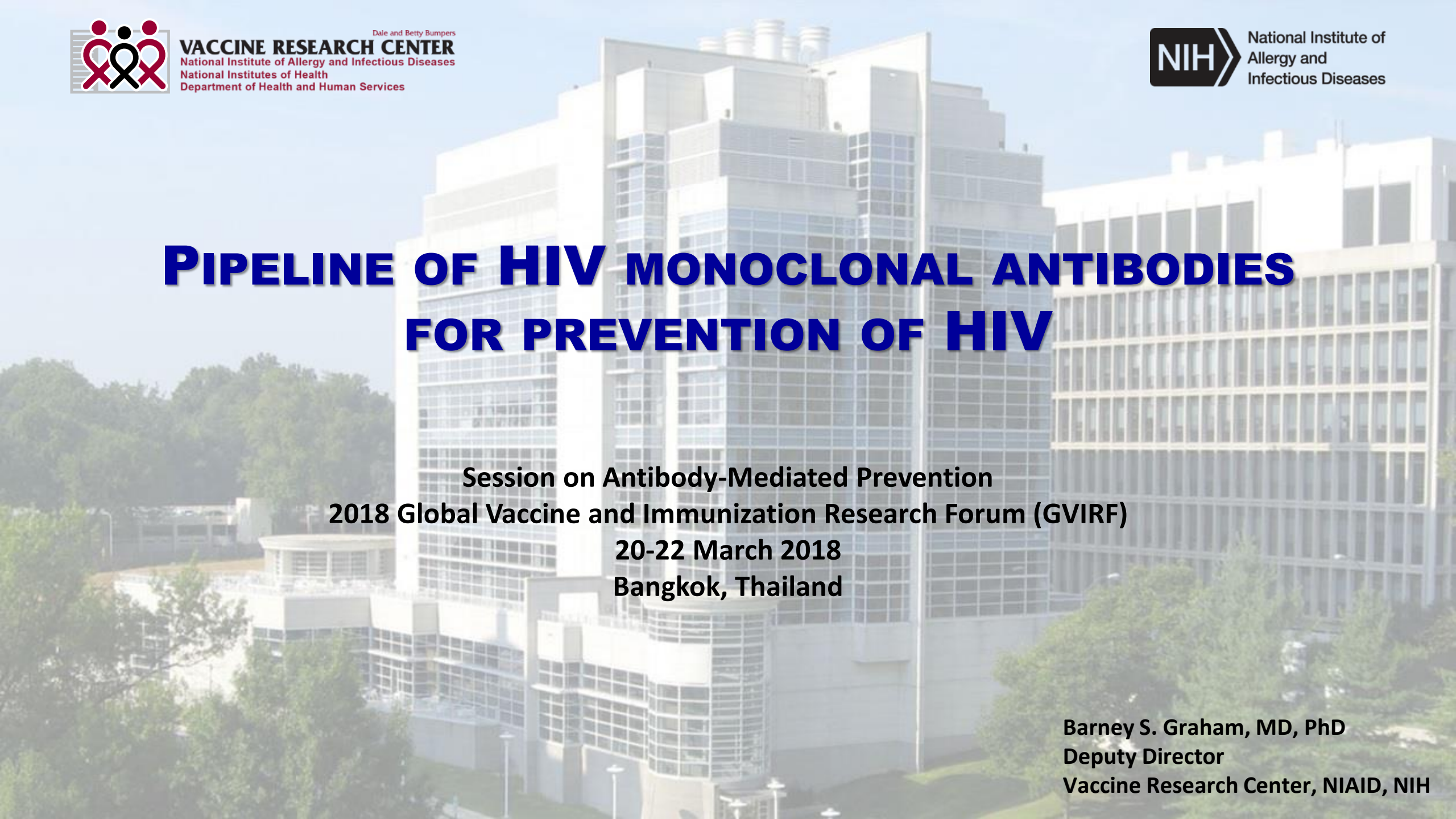


Dale and Betty Bumpers
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

NIH National Institute of Allergy and Infectious Diseases

PIPELINE OF HIV MONOCLONAL ANTIBODIES FOR PREVENTION OF HIV

Session on Antibody-Mediated Prevention
2018 Global Vaccine and Immunization Research Forum (GVIRF)
20-22 March 2018
Bangkok, Thailand

Barney S. Graham, MD, PhD
Deputy Director
Vaccine Research Center, NIAID, NIH

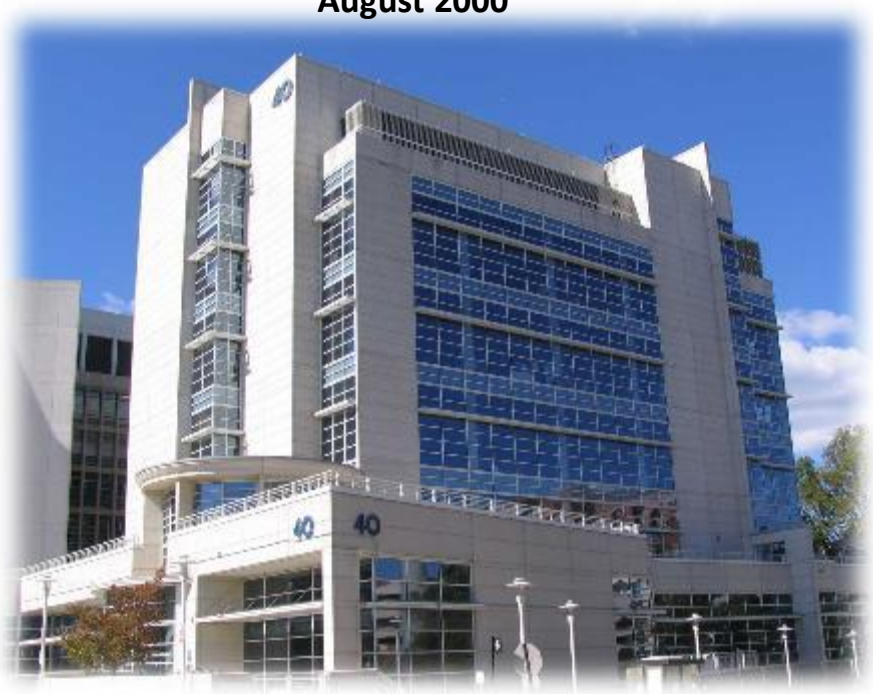
Vaccine Research Center

Dale and Betty Bumpers
Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health

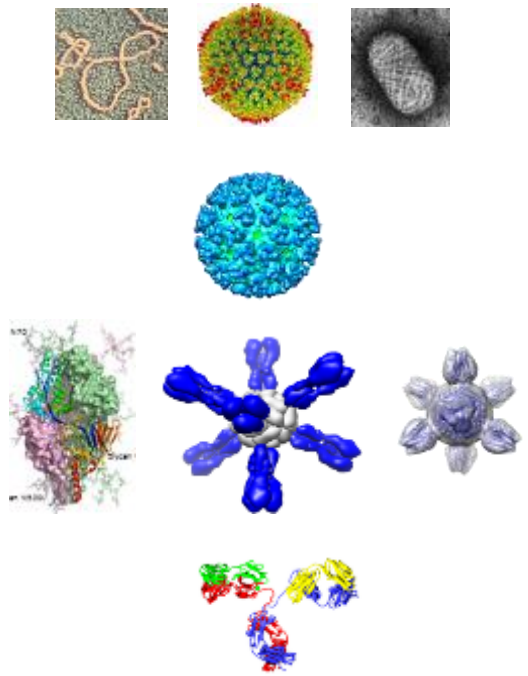
2017 VRC Principal Investigators and Program Directors

VRC Research & Development: From AIDS to Zika

August 2000



- AIDS/HIV
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- MERS-CoV, SARS
- RSV
- Smallpox
- Tuberculosis
- W/E/V equine encephalitis viruses
- West Nile virus, Zika



Engineering Lab

Pilot Plant

Vaccine Evaluation Clinic

Immunology Lab

Partners for Advanced Development

Functional Activity of Anti-Viral Antibodies

- Neutralization
  - Aggregation
  - Attachment blocking
  - Cleavage inhibition
  - Fusion inhibition
  - Preventing particle release
- Fc-mediated functions
  - Antibody dependent cell-mediated cytotoxicity (NK, Macrophage, Neutrophil)
  - Complement binding and activation
- Opsinization and clearance by non-susceptible cells
- Blocking pathogenic immunomodulatory molecules

Long History of Using Antibodies to Treat Infectious Diseases (Serum Therapy)

1890: Emil von Behring and Shibasaburo Kitasato worked on "anti-toxins" for tetanus and diphtheria that led to concept for serum therapy

1901: Emil von Behring - 1901 Nobel Prize in Physiology or Medicine

"For his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths".

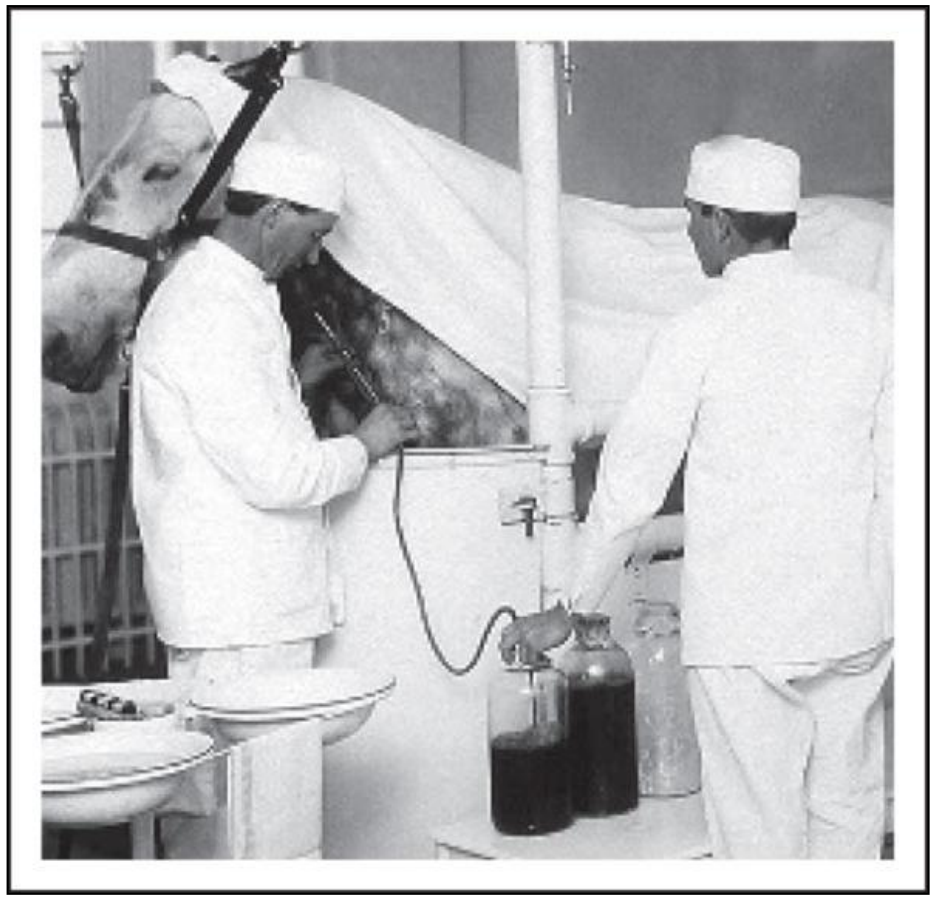
Also worked with Paul Ehrlich on serum therapy for <u>streptococcal infections in pre-antibiotic era</u>

Shibasaburo Kitasato

Wernicke, Frosch, and Behring in Koch's Berlin Lab

Balto's route

Application and Regulation of Serum Therapy



Collection of blood for production of anti-diphtheria horse serum. Jin was the horse associated with the deaths of 13 children treated with immune serum collected near the time of his death from tetanus in 1901. The 1902 Biologics Control Act established standards for the processing and labeling of biological products for human use.

Graham & Ambrosino. **History of passive antibody administration for prevention and treatment of infectious diseases.** Current Opinion in HIV & AIDS. 2015; 10:129-134.

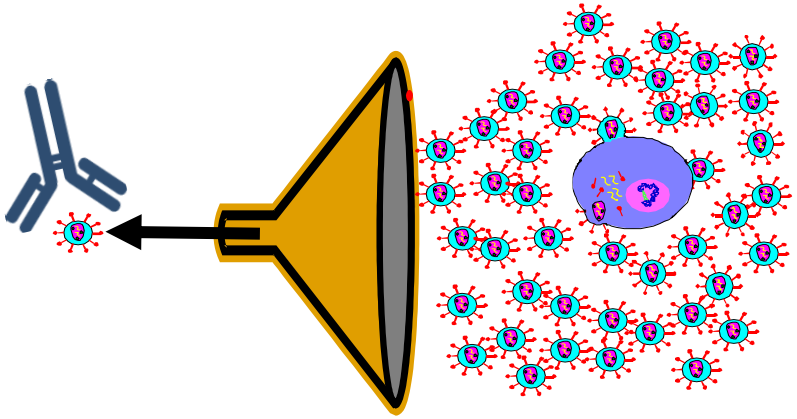
Clinical Use of Antibodies

Prevention and Treatment are Different

Prevention

- Prevent acquisition of infection

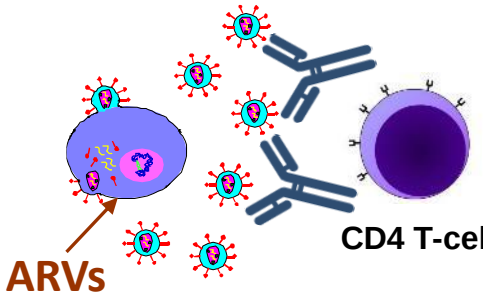
Block
Transmission event



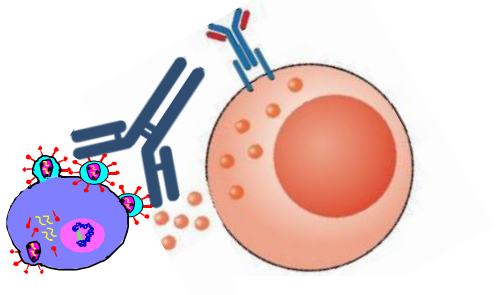
Treatment

- Different mechanism of action
- Eliminate infected cells; reduce viral reservoir
- Maintain viral suppression induced by ARV

Block viral entry



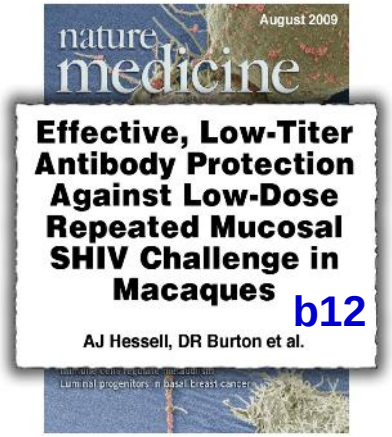
Cell killing

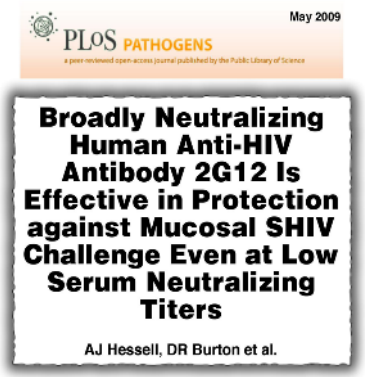


NK cell directed elimination of infected cells

Passive Antibody Prevention of HIV/SHIV in NHP for > 25 years

- 1990 - polyclonal IgG protects Chimps from HIV
- 1998 - polyclonal IgG protects against SHIV
- 2000 - first use of use of mAbs (2F5, 2G12, F105) and protection against mucosal challenge
- 2009 - Low-dose mucosal SHIV challenge
- 2012 - Protection with newer generation mAbs (PGT121, 3BNC117, 10-1074, VRC01, VRC07)
- 2016 – Clearance of SHIV infection in neonatal macaques when treated with mAbs post-challenge





Key Sites of Neutralization-Sensitivity on HIV-1 gp160

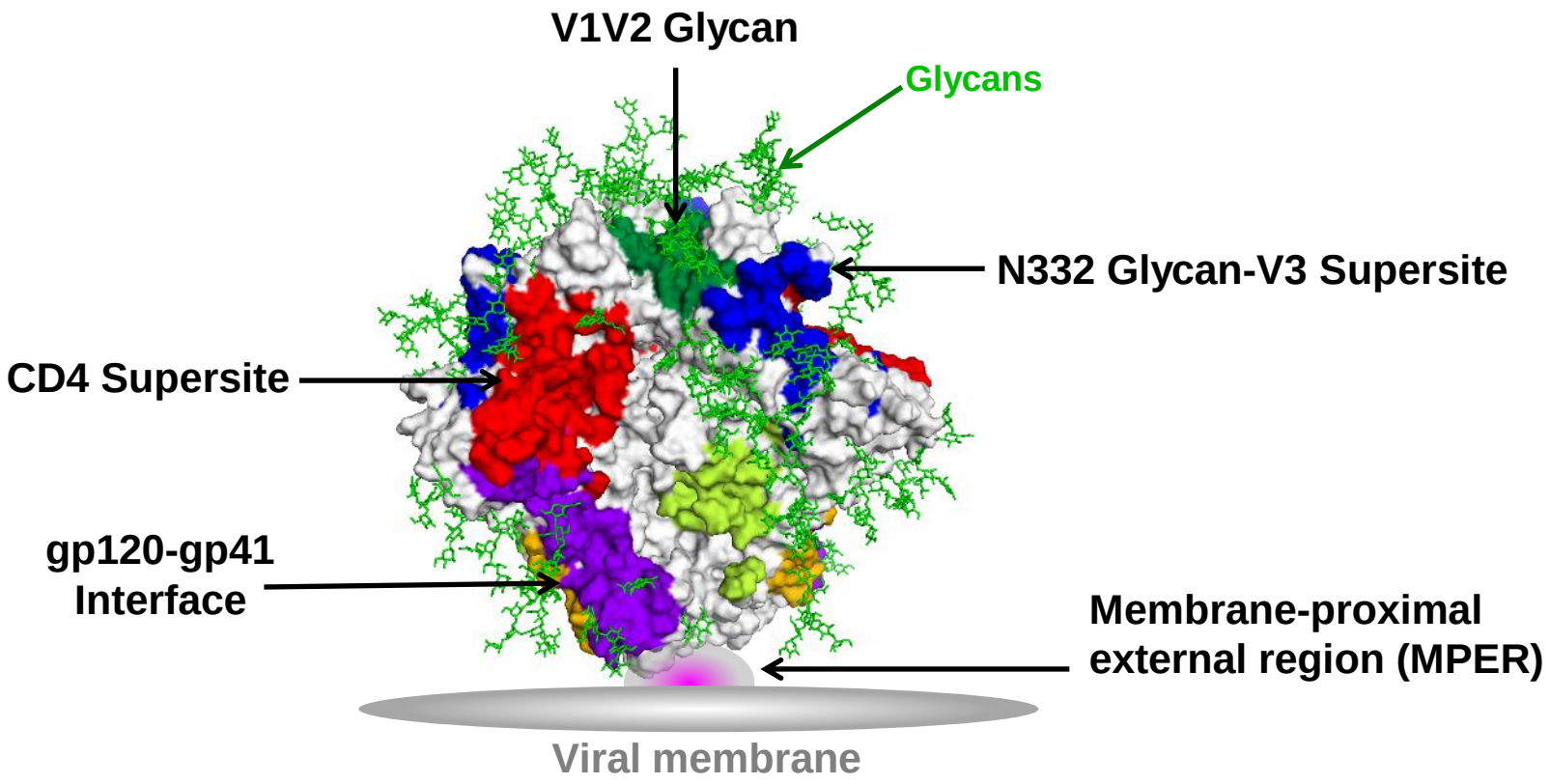
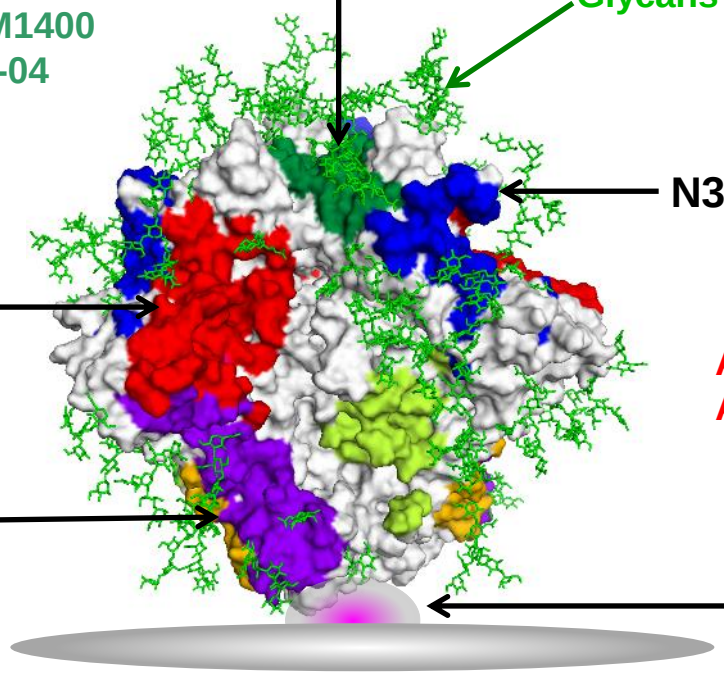


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

Broadly Neutralizing mAbs in Development



PG9, PG16
PGT141-145
CAP256-VRC26
PGDM1400
CH01-04

V1V2 Glycan

Glycans

VRC01, VRC01-LS, PG04,
CH31, 3BNC117, CH103,
12A12, VRC13, VRC07
VRC07-523-LS
Z258-N6, DH270,
BANC131, CH235

CD4 Supersite

N332 Glycan-V3 Supersite

PGT121
PGT128
10-1074
DH270

Anti-CD4-BS/10e8 bi-specific
Anti-CD4-BS/ anti-V2/ anti-MPER tri-specific

35022
PGT151
8ANC195

gp120-gp41
Interface

Membrane-proximal
external region (MPER)

2F5
4E10
10e8v5R

Viral membrane

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

Broadly Neutralizing mAbs in Development

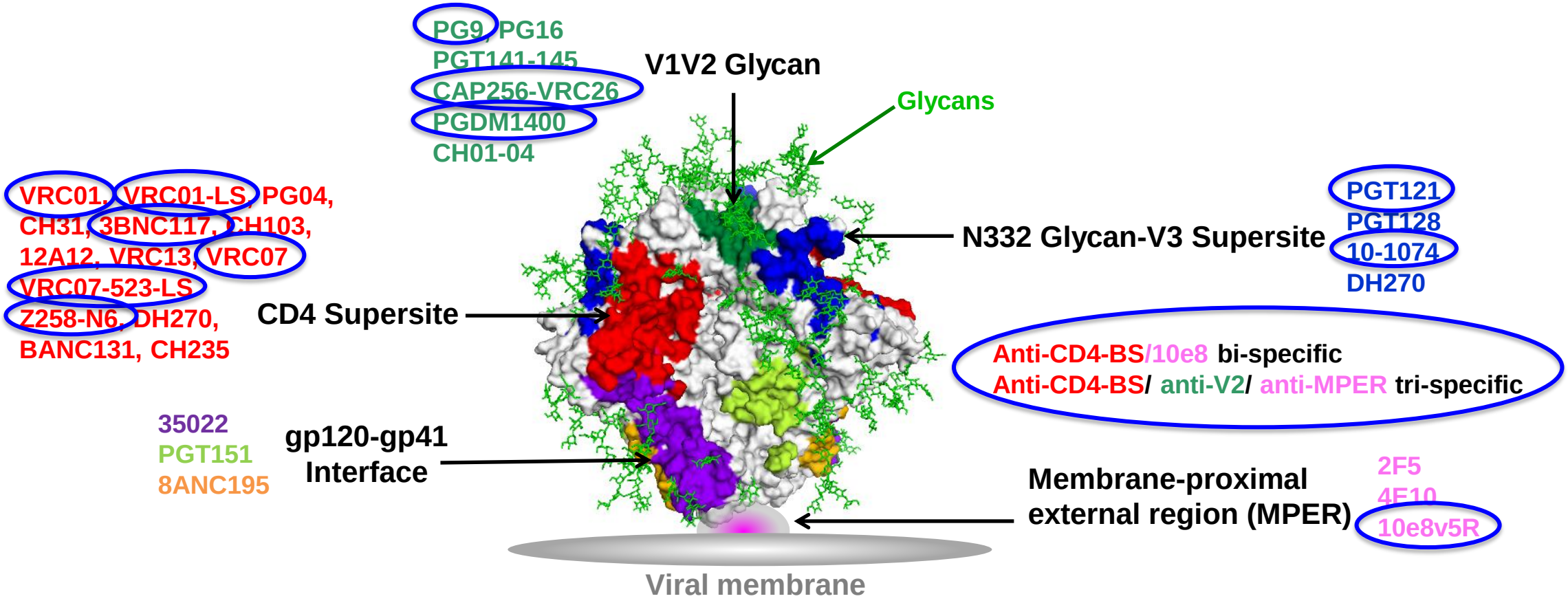


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

Target Product Profile for mAb Prevention

Product	**Two (possibly 3) IgG mAbs (or one bi-/tri-specific)**
Indication	**Prevention of HIV infection**
Efficacy Profile	**Prevents infection by >98% strains**
Target Population	**Adolescents/adults: high-risk of HIV infection** **Infants of HIV^{+} mothers: at birth; during breastfeeding**
Dosage Administration	**Adolescents/adults: 5 mg/kg SQ q3-6 months** **Infants: one birth dose ~20 mg/kg SQ**
Safety/Tolerability	**Adverse event frequency – rare**
Cost of Goods	**<$50 per person, per year**

Hinges on human efficacy data,
commercial interest in producing mAbs for broad use

AMP = Antibody Mediated Prevention Studies

VRC01 administered at 30 mg/kg, or 10 mg/kg, vs placebo

Administered once every 8 weeks by IV infusion

Two harmonized studies

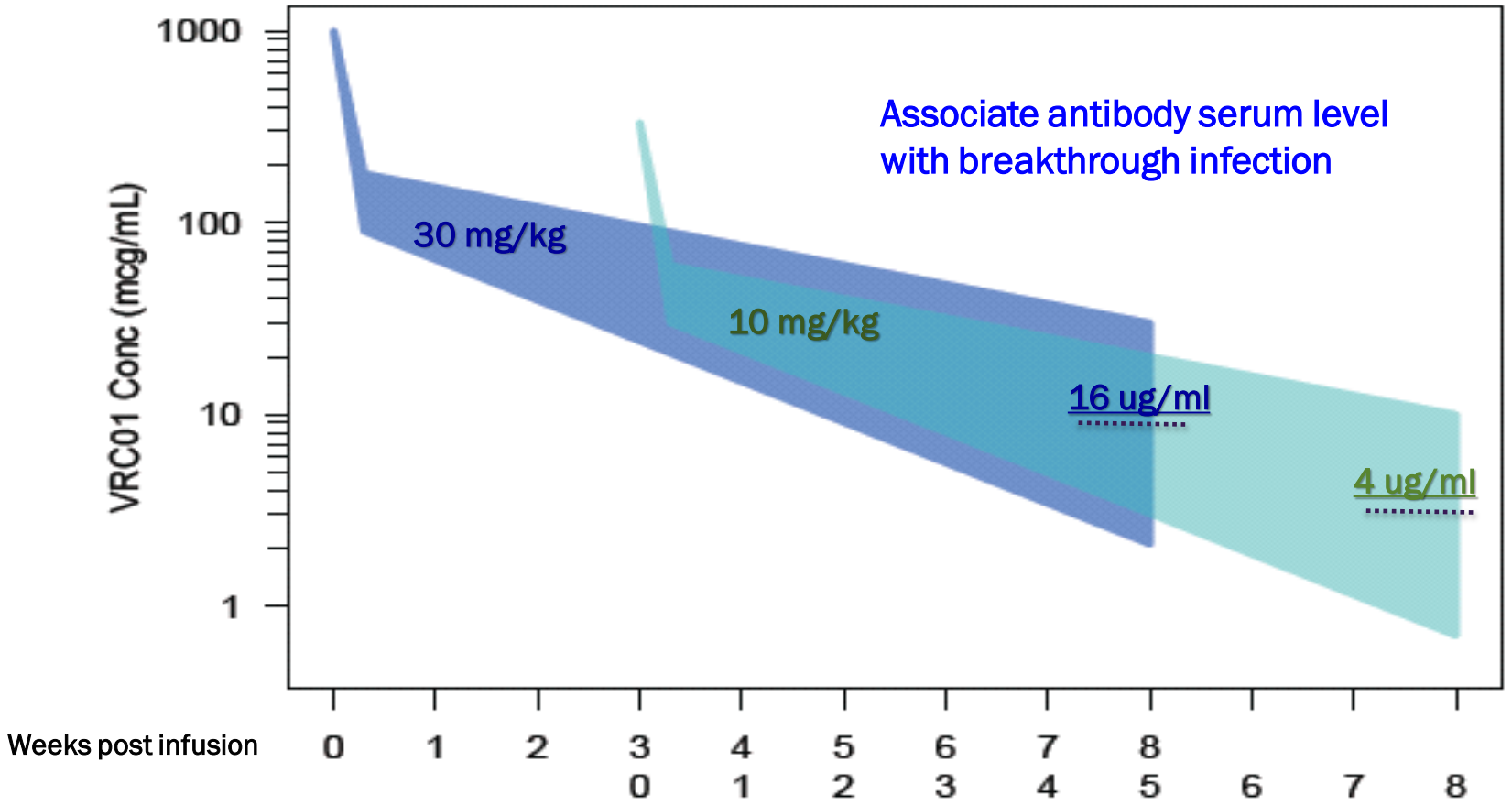
- **High risk men in North and South America**
- **High risk women in South and East Africa**

4600 subjects
3725 enrolled as of March 19, 2018

What serum level of mAb is associated with protection?
Powered to define an overall 60% efficacy

VRC01 Concentrations Over Time

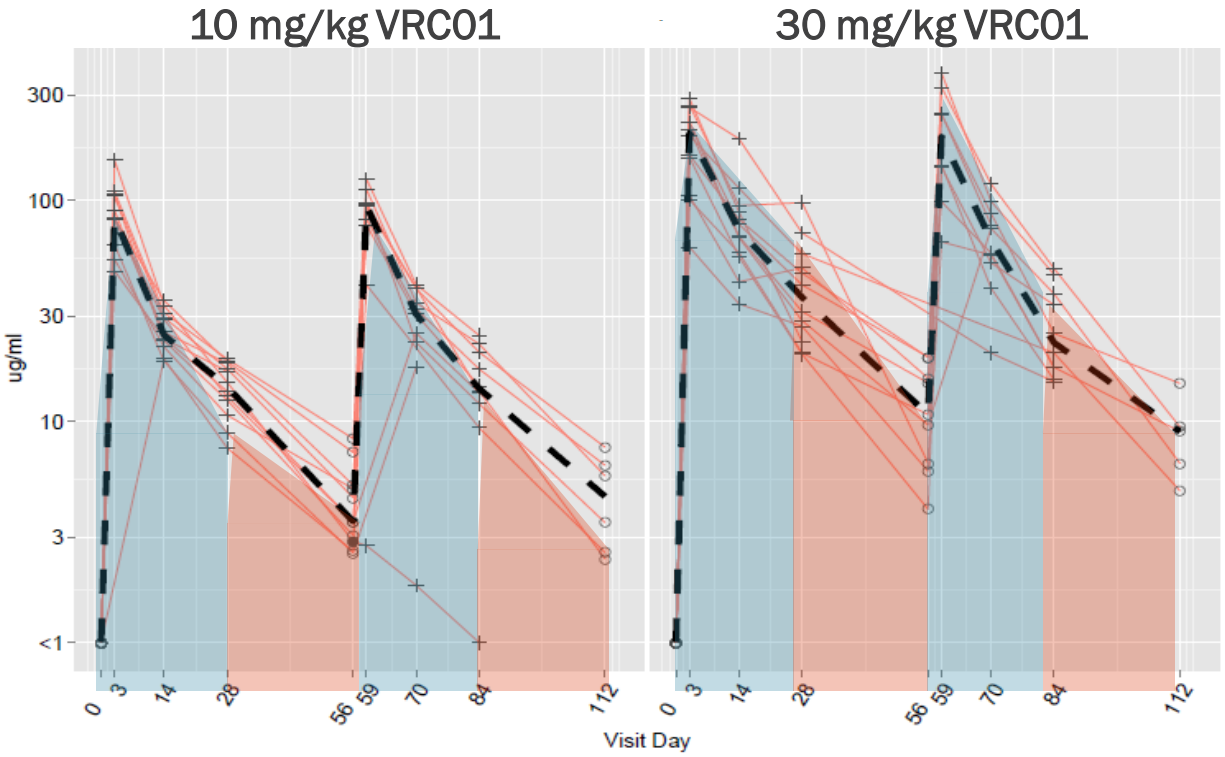
HVTN104: Mayer et al. PLoS Medicine (2017)



- Follow monthly
- Associate serum level with breakthrough infection

AMP Approaches to Learning About Correlates of Prevention Efficacy (PE)

1. **Compare VRC01 dose groups**
   - Compare PE of the 10 vs. 30 mg/kg VRC01 dose groups
2. **Case-control VRC01 marker analysis**
   - Assess how HIV-1 risk and PE varies over subgroups defined by VRC01 markers
3. **Sieve analysis (VRC01 vs. placebo)**
   - Assess how PE varies with AA sequence and phenotypic characteristics of breakthrough founder HIV-1s



- HIV-1 Dx tests included between peaks and troughs

Improving HIV mAbs for Prevention

- **Longer half-life = VRC01 is I.V. every 2 months**
  Goal: SQ injection once every 3 - 6 months
- **More potent (10x) = protect at lower concentration**
  Goal: Use less mAb - SQ injection
- **Broader coverage = VRC01 breadth 80-90%**
  Goal: 98% circulating viruses in all regions of world

LS Modification Prolongs Half-Life of VRC01

PLOS | MEDICINE January 24, 2018

RESEARCH ARTICLE

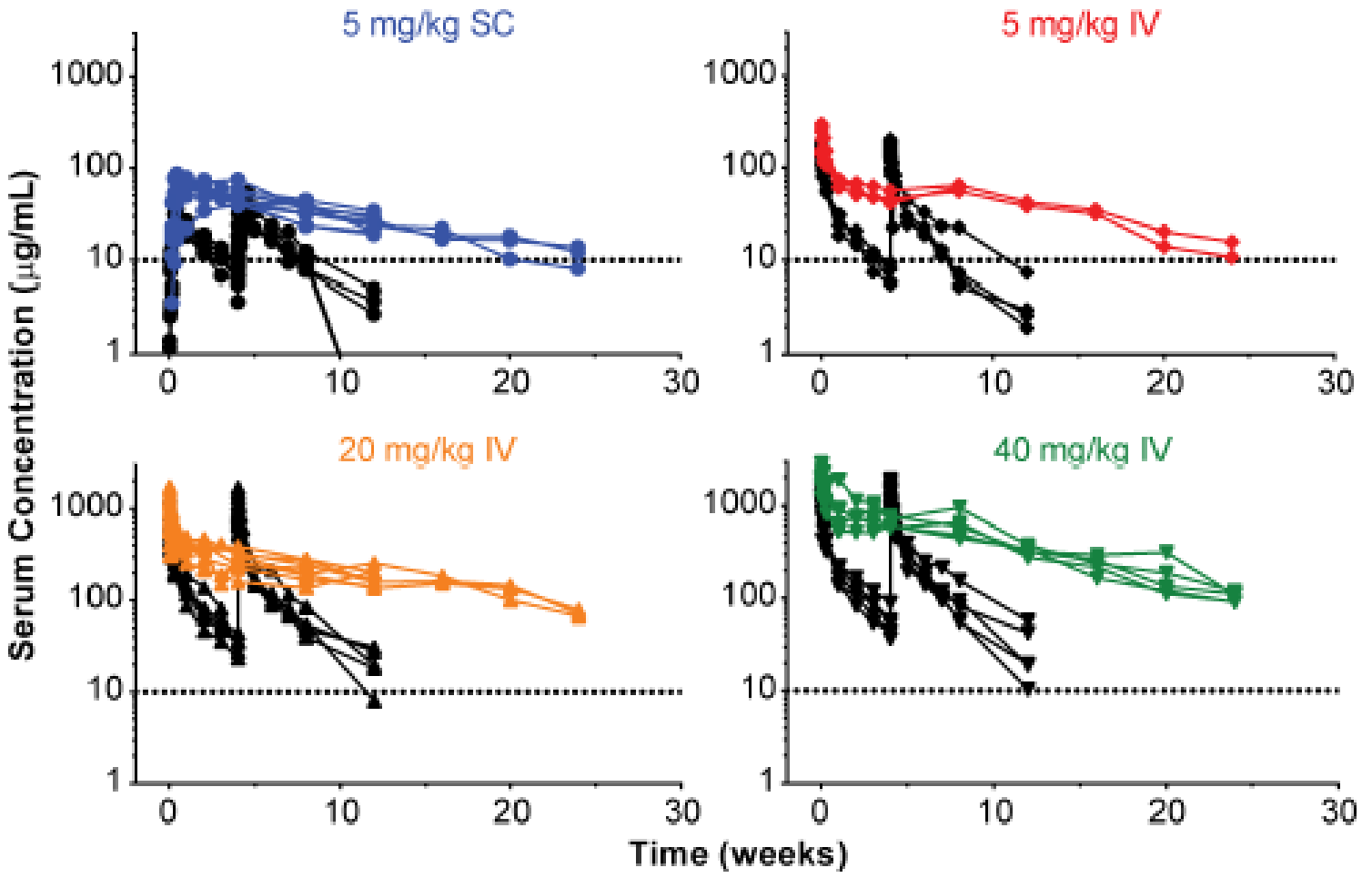
Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults

Martin R. Gaudinski[1☯], Emily E. Coates[1☯], Katherine V. Houser[1], Grace L. Chen[1], Galina Yamshchikov[1], Jamie G. Saunders[1], LaSonji A. Holman[1], Ingelise Gordon[1], Sarah Plummer[1], Cynthia S. Hendel[1], Michelle Conan-Cibotti[1], Margarita Gomez Lorenzo[2], Sandra Sitar[1], Kevin Carlton[1], Carolyn Laurencot[1], Robert T. Bailer[1], Sandeep Narpala[1], Adrian B. McDermott[1], Aryan M. Namboodiri[3], Janardan P. Pandey[3], Richard M. Schwartz[1], Zonghui Hu[4], Richard A. Koup[1], Edmund Capparelli[5], Barney S. Graham[1], John R. Mascola[1], Julie E. Ledgerwood[1]*, the VRC 606 Study Team[¶]

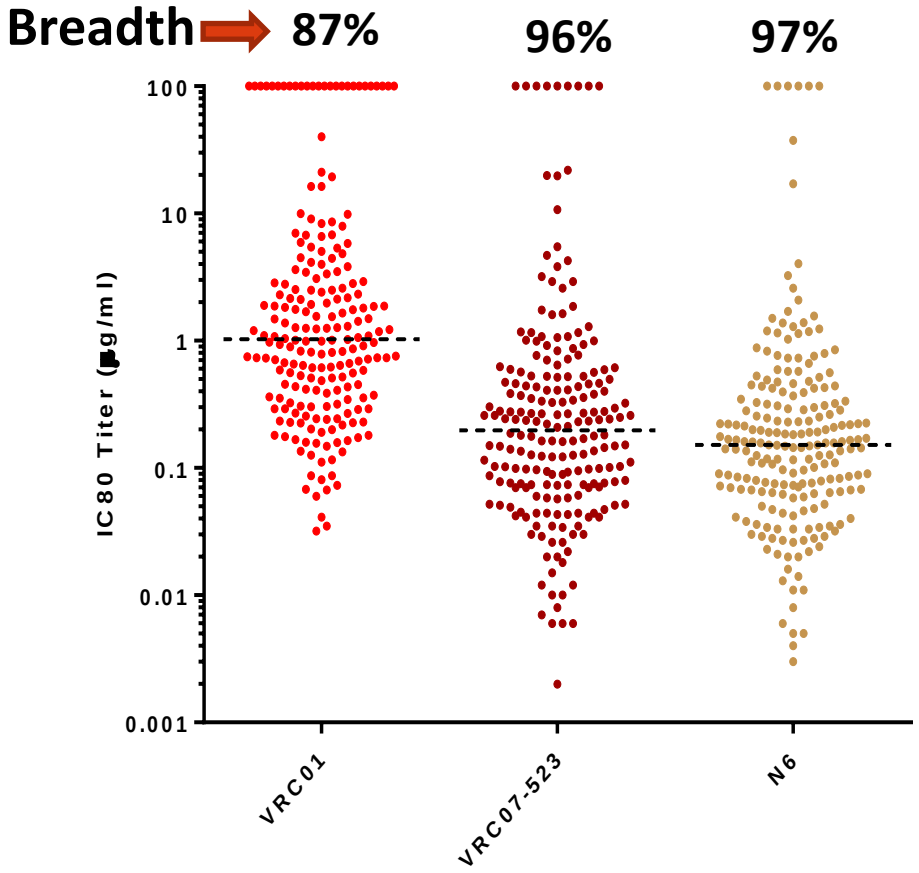
Dose/Route VRC01LS

- 5 mg/kg SC
- 5 mg/kg IV
- 20 mg/kg IV
- 40 mg/kg IV

Black symbols indicate serum concentrations of corresponding VRC01 infusions from Ledgerwood JE, Clin Exp Immunol. 2015;182(3):289-301.



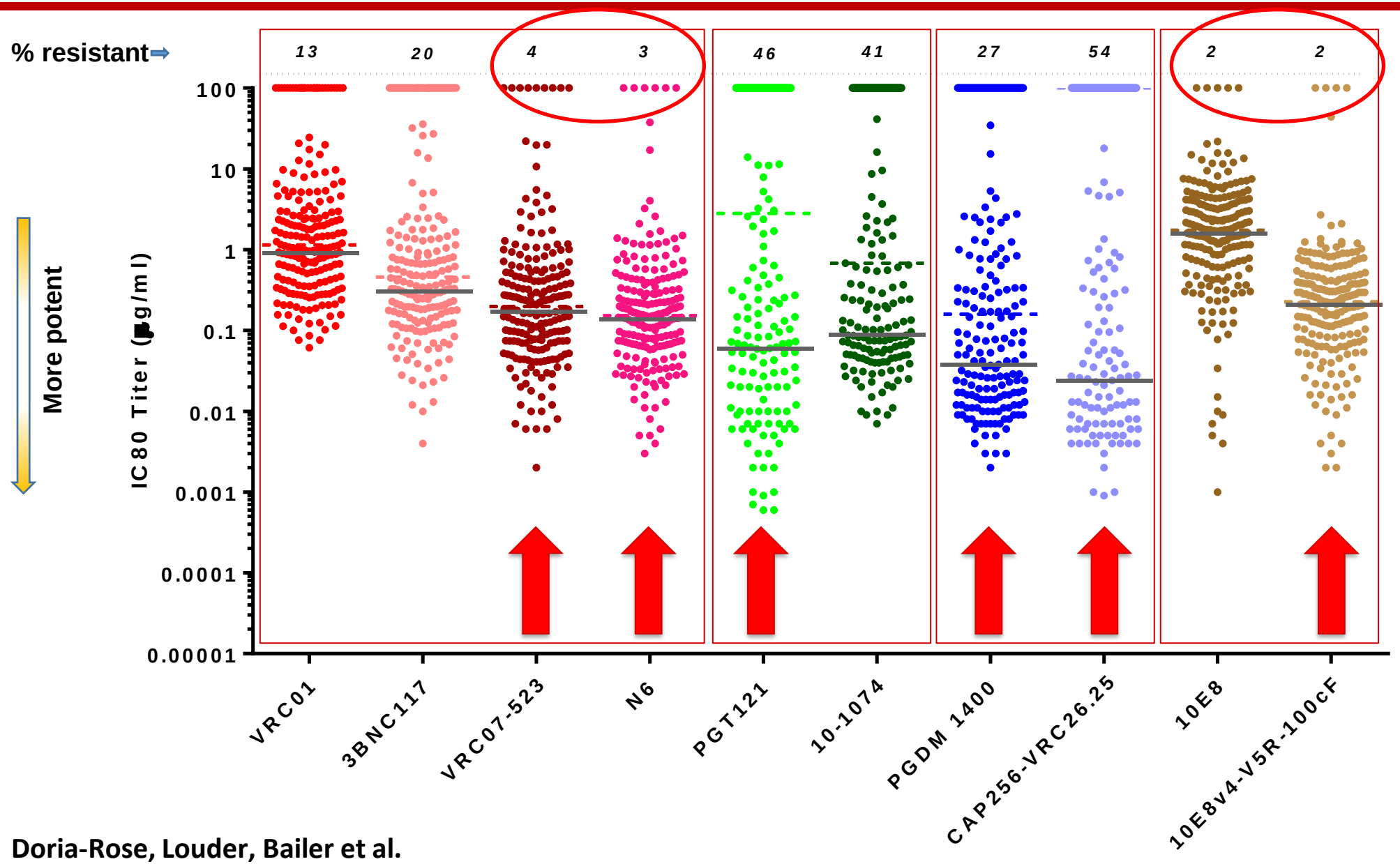
Improve Potency and Breadth of CD4-BS mAbs



- VRC 07-523 is 5-fold more potent than VRC01
- Coverage improves to >96%
- VRC07-523-LS phase 1 fully enrolled/ HVTN 127 written
- N6 phase I in spring 2018

Panel of 206 Env-pseudoviruses:
Doria-Rose, Louder, Bailer et al.

Other Antibodies with Improved Potency/Breadth



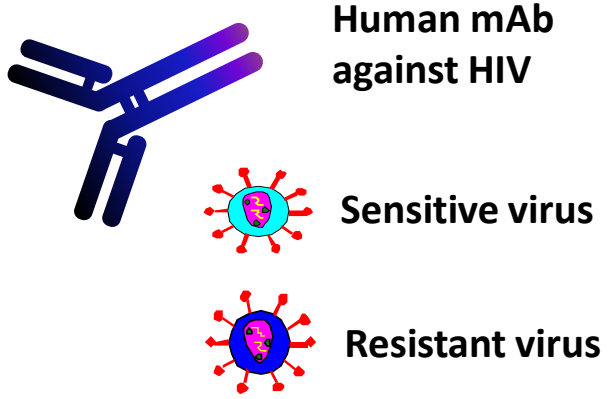
Doria-Rose, Louder, Bailer et al.

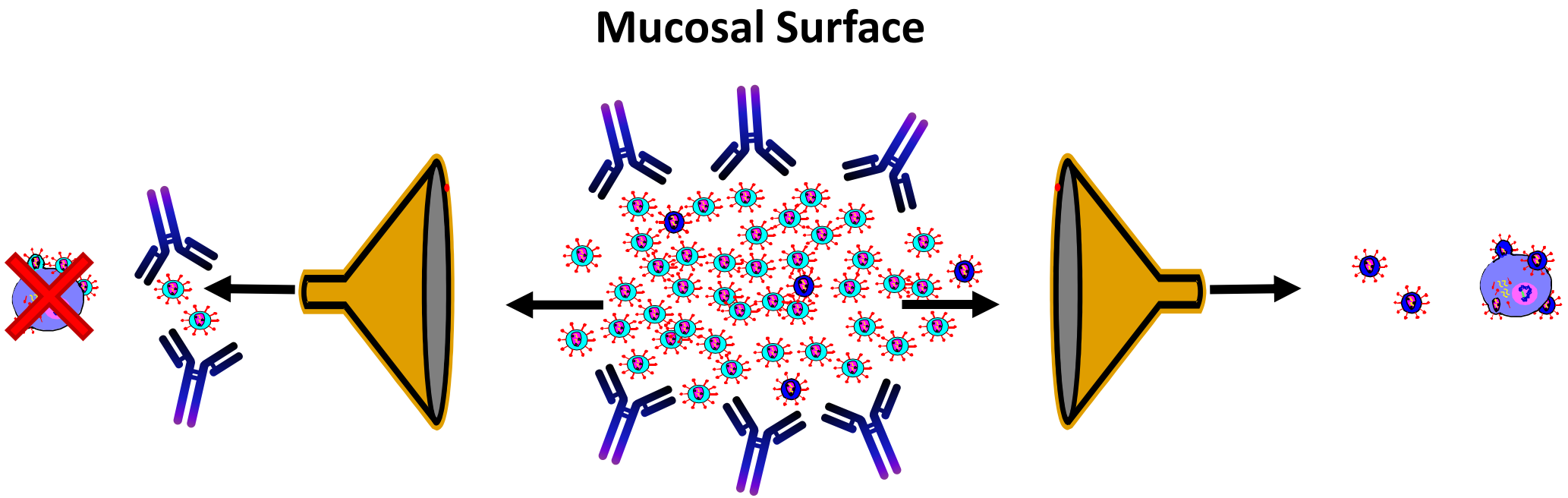
Panel of 208 Env-pseudoviruses

Other considerations: How transmission occurs

How transmission occurs may impact antibody efficacy

How does antibody block HIV-1 transmission event?

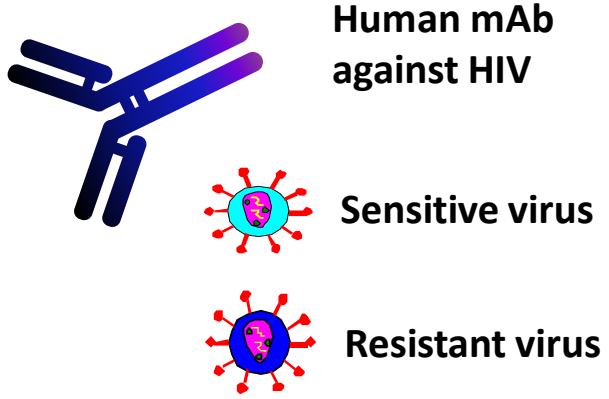




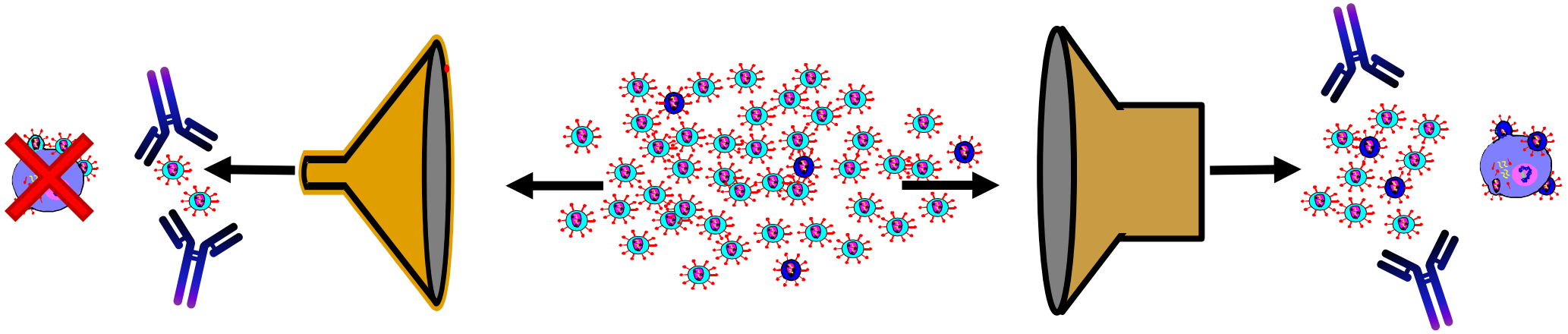
Other considerations: How transmission occurs

How transmission occurs may impact antibody efficacy

How does antibody block HIV-1 transmission event?



May differ by route and target population



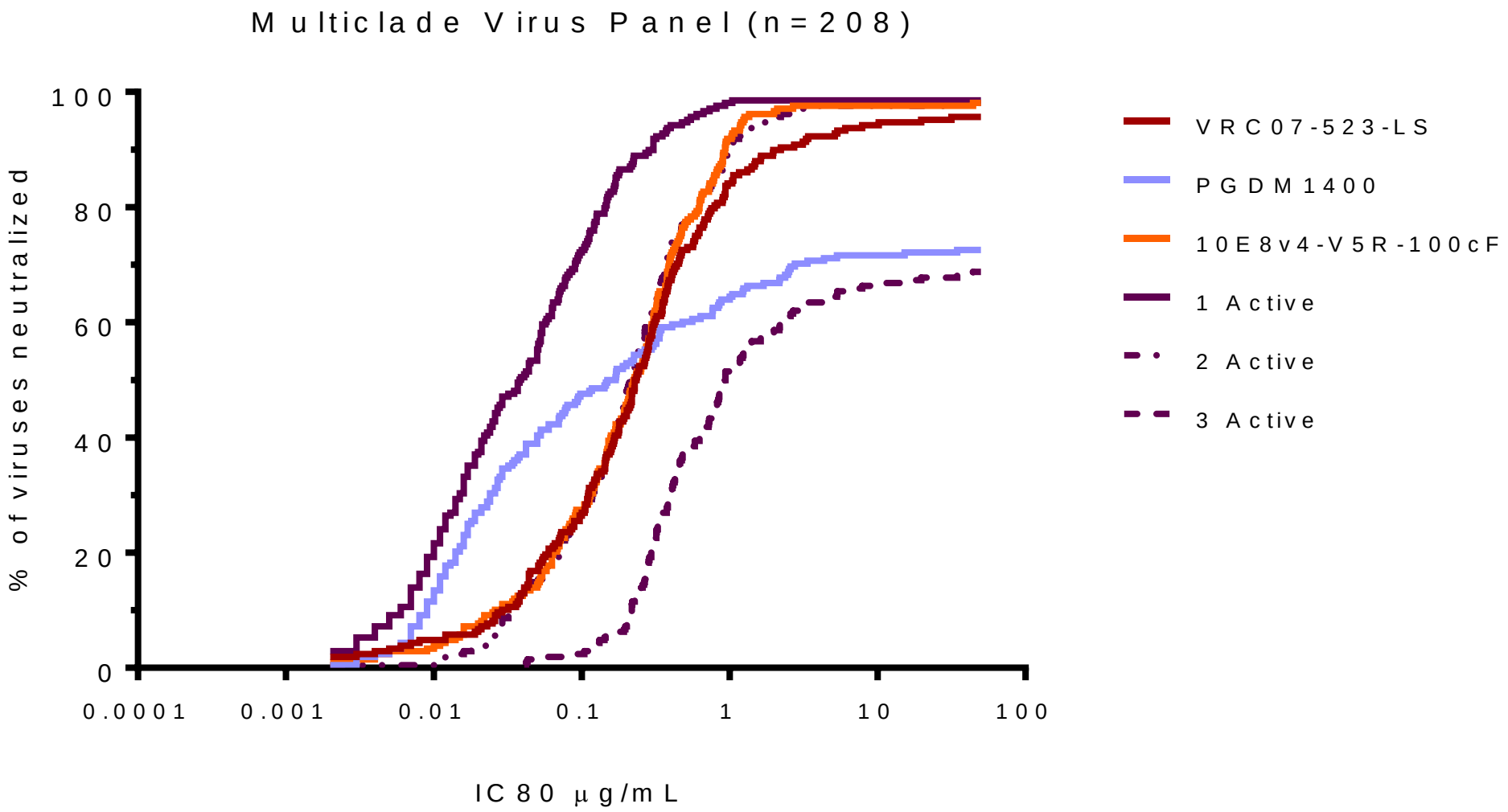
Advanced Development and Implementation

- Development of a preventive mAb combination product would be greatly facilitated by big Pharma interest/investment
- Big Pharma mostly interested if there is a therapeutic indication
- Therapeutic product could then be used as a preventive agent
- TPP for therapeutic agent will be different from that of preventive agent
- Alternatively, need government of NPO to establish manufacturing and distribution capacity

Will likely require coverage of viruses by at least two mAbs to avoid escape

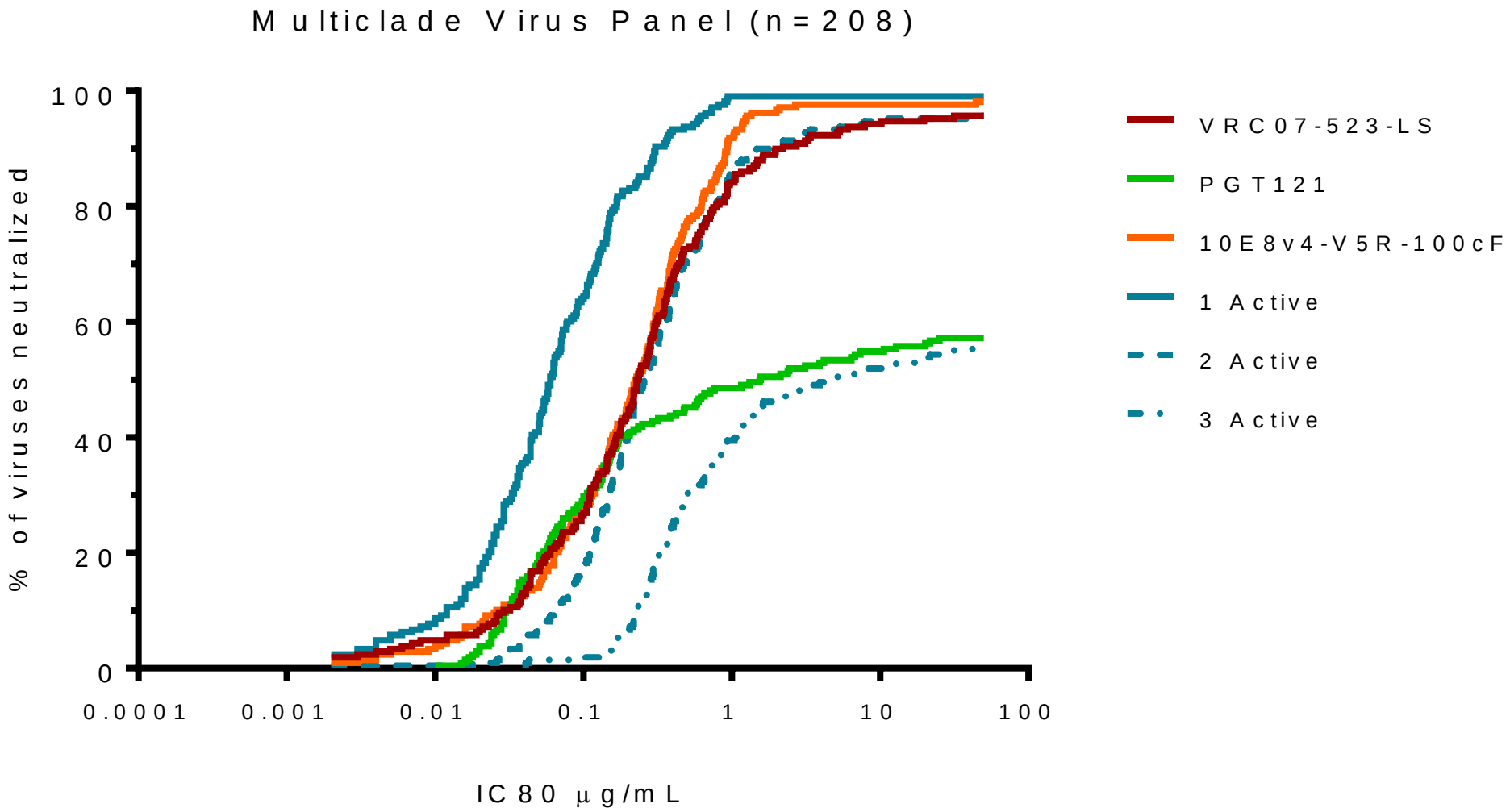
Achieving dual coverage in combination mAb Rx

Theoretical Combinations of VRC07-523-LS+10E8v4-V5R-100cF+PGDM1400



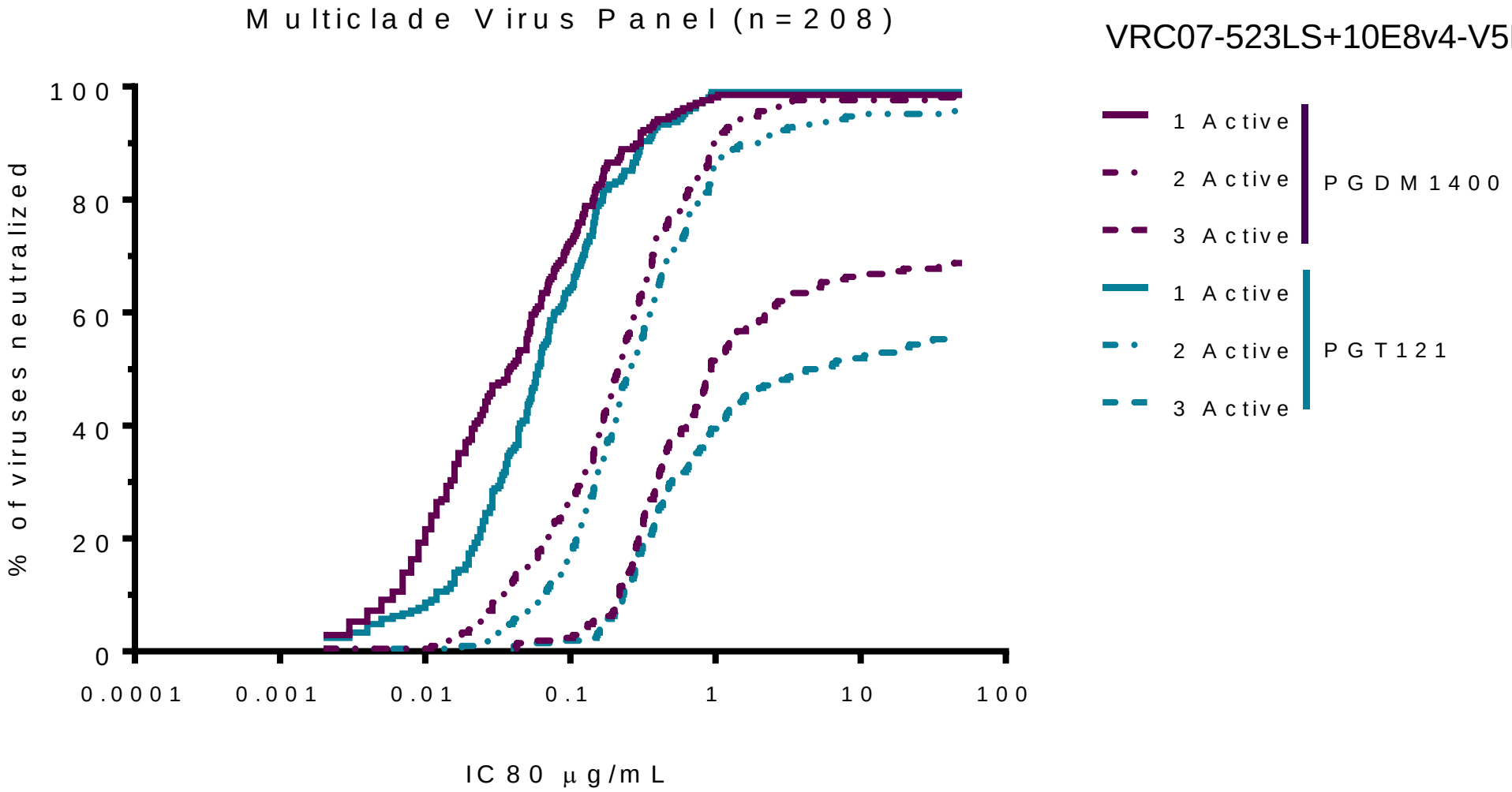
Achieving dual coverage in combination mAb Rx

Theoretical Combinations of VRC07-523-LS+10E8v4-V5R-100cF+PGT121

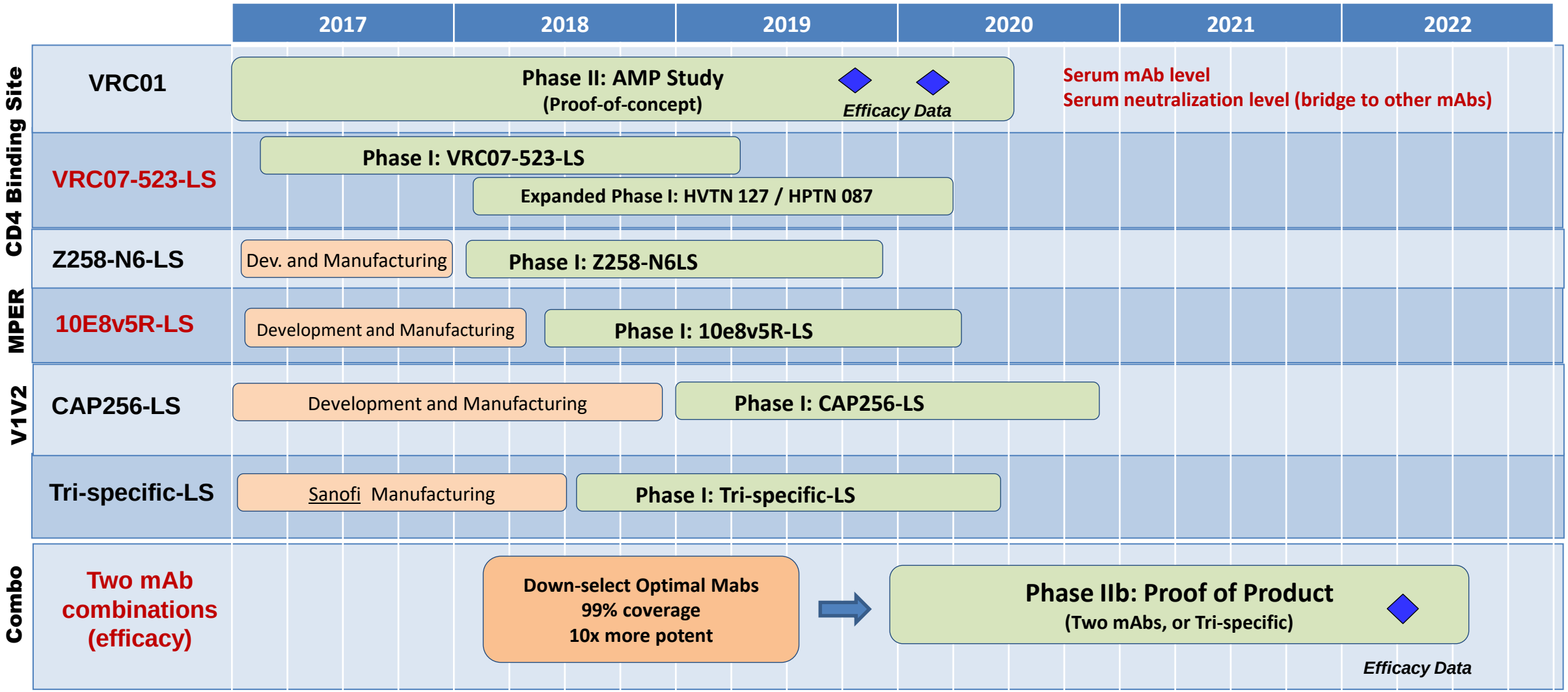


Achieving dual coverage in combination mAb Rx

Theoretical Combinations of VRC07-523-LS+10E8v4-V5R-100cF+ either PGDM1400 or PGT121



VRC HIV-1 mAb Portfolio and Timelines



Summary

- Passive immunization with immunoglobulins for prevention and treatment of viral diseases has a long successful history
- mAbs can prevent SIV/SHIV infections in NHP
- Using mAbs for HIV prevention is becoming a practical option
  - engineering potency, breadth, and extended half-life
  - manufacturing advances
- Proof-of-concept for prevention of HIV infection with neutralizing mAb will be available in ~2 years
- Planning for success should include developing new business plans for large scale manufacturing and product deployment

Dale and Betty Bumpers
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

Acknowledgements

National Institute of Allergy and Infectious Diseases

VRC Clinical Trials
Grace Chen
Ingelise Gordon
Martin Gaudinski
Emily Coates
Katherine Houser
Sandra Sitar
Pamela Costner
Jamie Saunders
Sarah Plummer
Lasonji Holman
Cynthia Hendel
Floreliz Mendoza
Laura Novik
Brenda Larkin
Galina Yamshchikov
Nina Berkowitz
Olga Vasilenko
Iris Pittman
Pernell Williams
Stephen Migueles
Adam DeZure

Study Volunteers!

VRC PIs
John Mascola
Richard Koup
Peter Kwong
Mario Roederer
Bob Seder
Danny Douek
Eli Boritz
Nancy Sullivan

VRC Program Heads
Julie Ledgerwood – clinical trials
Adrian McDermott – vaccine immunology
Diana Scorpio – Preclinical studies
Frank Arnold – manufacturing
David Lindsey & VCMP

VRC Regulatory Affairs
Carrie Laurencot
Michelle Conan-Cibotti
Mary Enama
Flo Kaltovich

VRC Product Management & Strategic Development
Jason Gall
Kevin Carlton
Judy Stein
Marybeth Daucher
Abe Mittelman
Lucio Gama
Karin Bok

NIAID, Biostatistics Research Branch
Zonghui Hu
Martha Nason
Dean Follman

VRC Virology & Immunology Labs
Nicole Doria-Rose
Amarendra Pegu
Rebecca Lynch
Keyun Wang
Xuejen Chen
Mangai Asokan
Misook Choe
Joe Casazza
Kathy Foulds
Richard Nguyen
David Ambrozak
Mark Louder
Robert Bailer
Sandeep Narpala
Many others

UCSD
Edmund Capparelli

HVTN, HPTN
Many investigators
Larry Corey
Mike Cohen
Peter Gilbert

DAIDS
Carl Dieffenbach
Mary Marovich
Sarah Read
Sheryl Zwerski
Diana Finzi

Mark Connors NIAID Lab
Leo Laub
Jinghe Huang

CAVD, VIMC
Michael Seaman
David Montefiori

HVTN 703/HPTN 081 Protocol Team

- Chairs: Larry Corey & Mike Cohen
- Co-Chairs: Nyaradzo Mgodi & Sri Edupuganti
- Protocol Team Leader & Core Medical Monitor: Shelly Karuna
- DAIDS Medical Officers: Marga Gomez & David Burns
- Statisticians: Allan DeCamp, Deborah Donnell, Peter Gilbert, Michal Juraska, Nidhi Kochar
- Laboratory Representatives: John Hural, Sue Eshleman, On Ho, David Montefiori, Vanessa Cummings, Estelle Piwowar-Manning
- VRC Representatives: Julie Ledgerwood, Barney Graham, John Mascola
- Investigator Representatives: Ken Mayer, LaRon Nelson, Manuel Villaran, Sinead Delaney-Moretlwe
- Social & Behavioral Scientist: Michele Andrasik
- DAIDS Protocol Pharmacist: Scharla Estep
- Regional Medical Liaison: Simba Takuva
- Clinical Safety Specialist: Maija Anderson
- Protocol Development Manager: Carter Bentley
- FHI360/HPTN LOC Director: Niru Sista
- Senior Research Clinician: Phil Andrew
- Clinical Trials Manager: Carissa Karg
- Clinical Research Manager: Liz Greene
- SDMC Representatives: Gina Escamilla, Lynda Emel
- Regulatory Affairs Representative: Meg Brandon
- Communications Representatives: Jim Maynard & Eric Miller
- Community Engagement Representatives: Gail Broder, Jonathan Lucas, Jontraye Davis
- Clinic Coordinators: Christie Heiberg, Deb Dunbar, Ana Ramachi
- CAB Representatives: Likhapha Faku, Mark Hubbard, Jim Wick
- Community Educators/Recruiters: DaShawn Usher & Luciana Kamel
- Technical Editor: Erik Schwab

Decision to Proceed with Proof-of-Product Trial

VRC01 Phase 2b AMP study (proof-of-concept)

Efficacy	Selection for (R)	Phase 2b/3 study
None: < 30%	Weak* →	Do not proceed
	Mod/Strong** →	Possibly proceed with 2 or 3
Low: 30-40%	Weak →	Do not proceed
	Mod/Strong →	Probably Proceed with 2 or 3
Moderate: 40 – 60%	Weak →	Proceed, possibly with 2 or 3
	Mod/Strong →	Proceed with 2 or 3
High: 60 – 80%	Weak →	Proceed, possibly with 2
	Mod/Strong →	Proceed with 2

*Weak selection for NT escape suggests need for improved potency, dose, or distribution

**Moderate to strong selection suggests need for more targets and improved breath