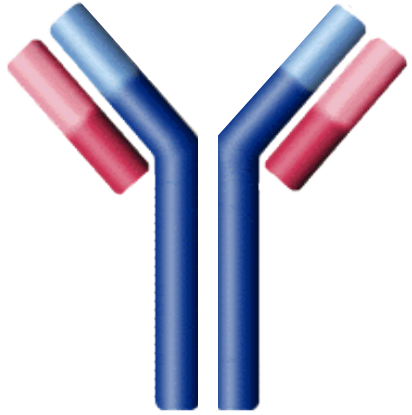
Overview of the Joint HVTN/HPTN Research Portfolio

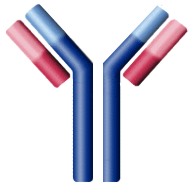


Theresa Gamble, PhD
HPTN LOC
May 15, 2018

Joint HVTN/HPTN mAb Portfolio

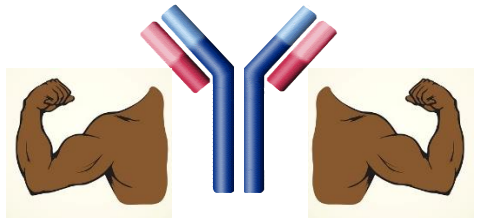
HVTN 703/HPTN 081
HVTN 704/HPTN 084

AMP
(VRC01)



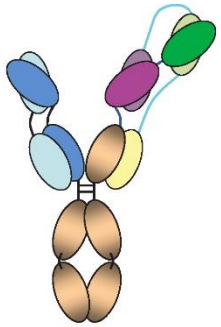
HVTN 127/HPTN 087

VRC07-
523LS



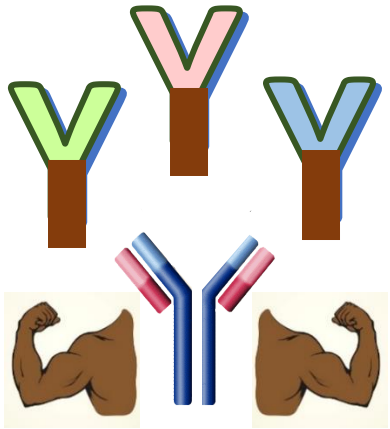
HVTN 129/HPTN 088

Trispecifc
(1 mAb, 3 targets)



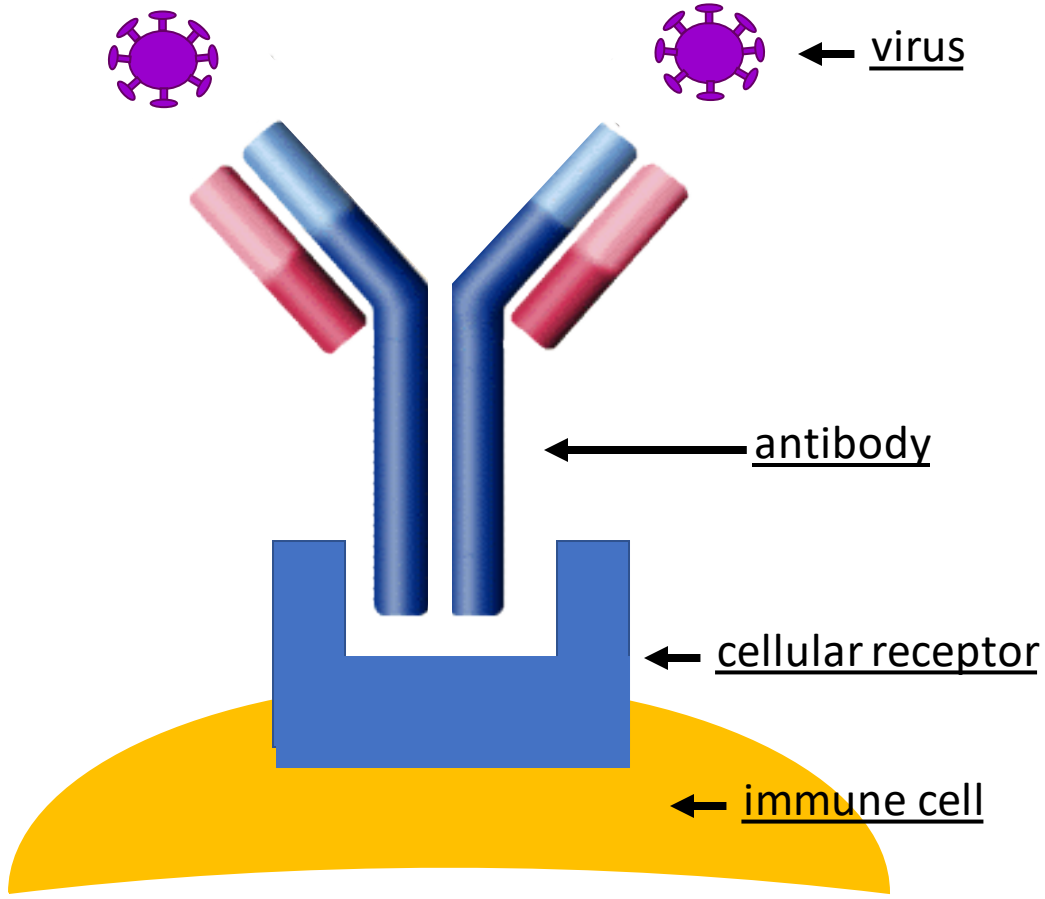
HVTN 130/HPTN 089

Combo mAbs
(multiple
mAbs/targets)



What is an antibody?

- A complex protein molecule made by the immune system
- Found free-floating in the bloodstream and lymphatic system or bound to B-cells
- "Sticky" on both ends – binding to foreign targets (like viruses) on one end and cellular receptors on the other



What do antibodies do?

- Normally humans make their own antibodies to ward off disease
- It is also possible to give someone antibodies to prevent or treat disease

VIRUS	*PRODUCT DESCRIPTION*	*INDICATION*
Measles	Concentrated human gamma globulin	Prevention
Polio	Concentrated human gamma globulin	Prevention
CMV	Cytomegalovirus Immune Globulin	Prevention
Hepatitis A	Immune serum globulin (ISG)	Prevention (travel)
Hepatitis B	Hepatitis B Immune Globulin	Post Exposure
Rabies	Rabies Immune Globulin	Post Exposure
RSV	mAb (palivizumab) for prophylaxis of high risk infants	Prevention in High Risk Infants
VZ	Varicella Zoster Immune Globulin	Post Exposure

The Great Race of Mercy

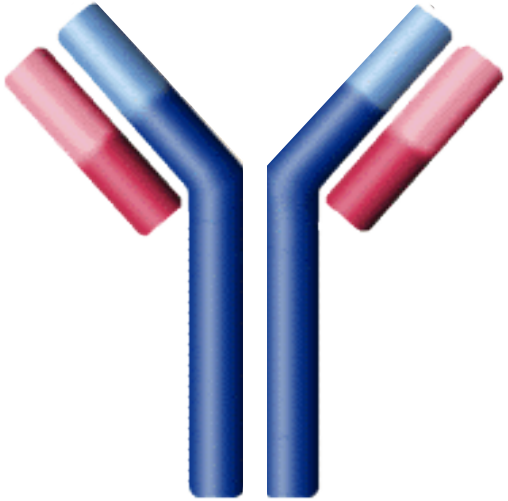
- In 1925, 20 mushers and 150 sled dogs raced 674 miles in 5.5 days to bring frozen antibodies to Nome, Alaska, saving the town from a diphtheria epidemic.

That's Togo, the lead sled dog, good boy!

Antibodies and HIV

- Antibody Mediated Prevention

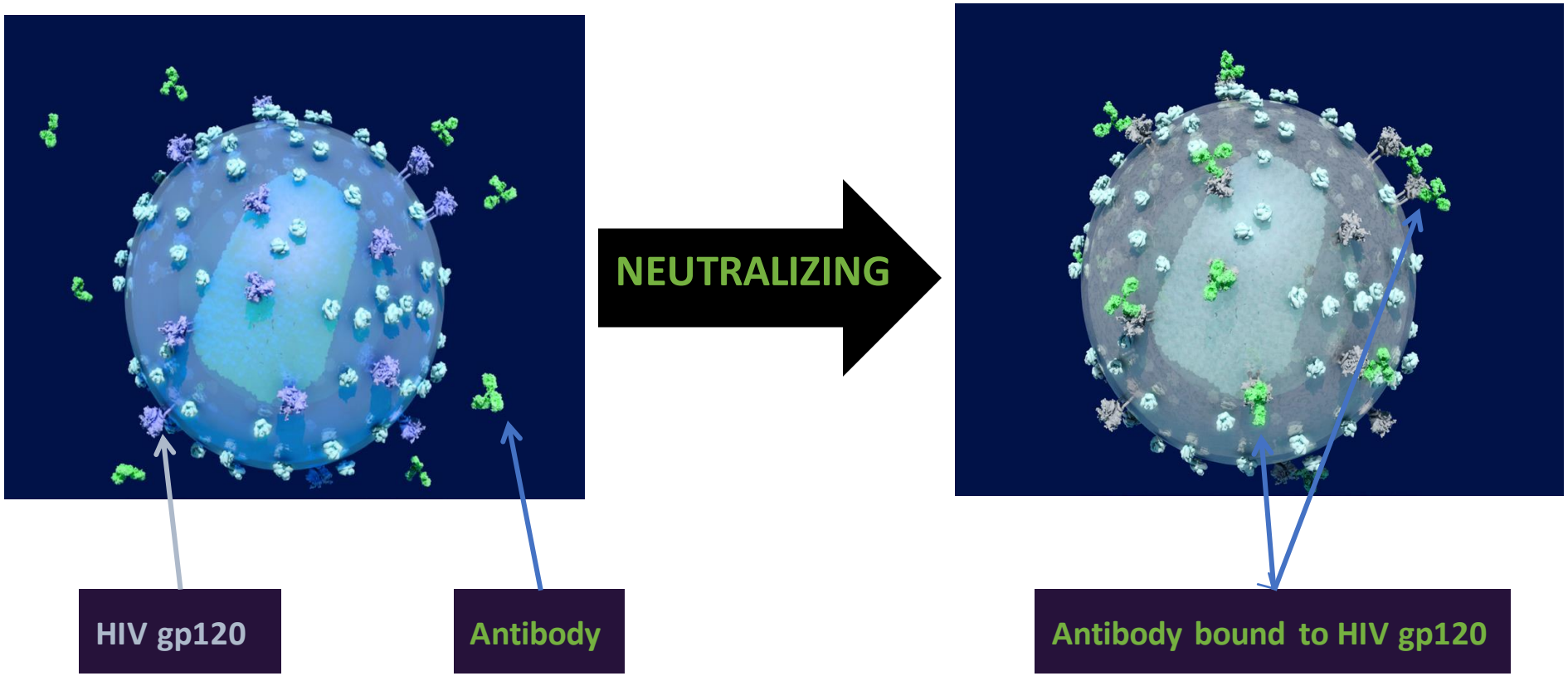
- This is the idea of using an antibody made in the lab and giving it to people directly, i.e. using an intravenous (IV) infusion, to prevent HIV infections



How could antibodies work against HIV?

NEUTRALIZATION

Antibodies bind to HIV & blocks its attachment to host cells



Thanks to Lisa Donohue for these images.

How could antibodies work against HIV?

OPSONIZATION
("buttering the toast")

Antibodies bind to HIV, then binds to macrophages;
the macrophages then eats the HIV

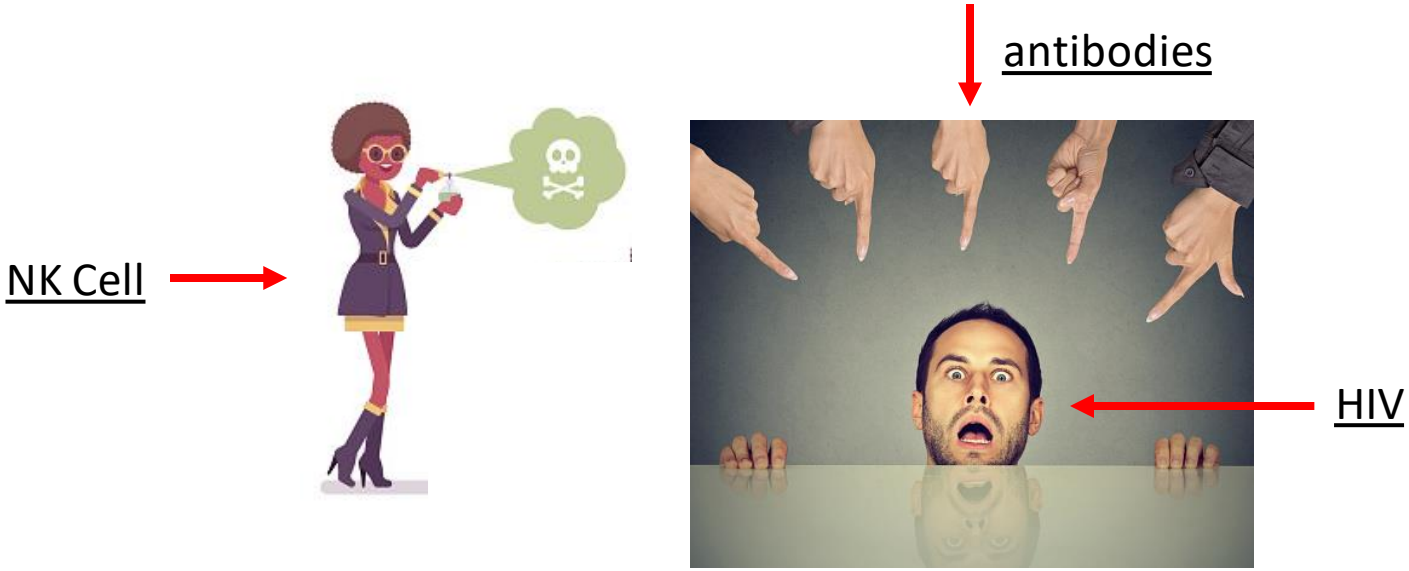
macrophage

antibody bound to HIV

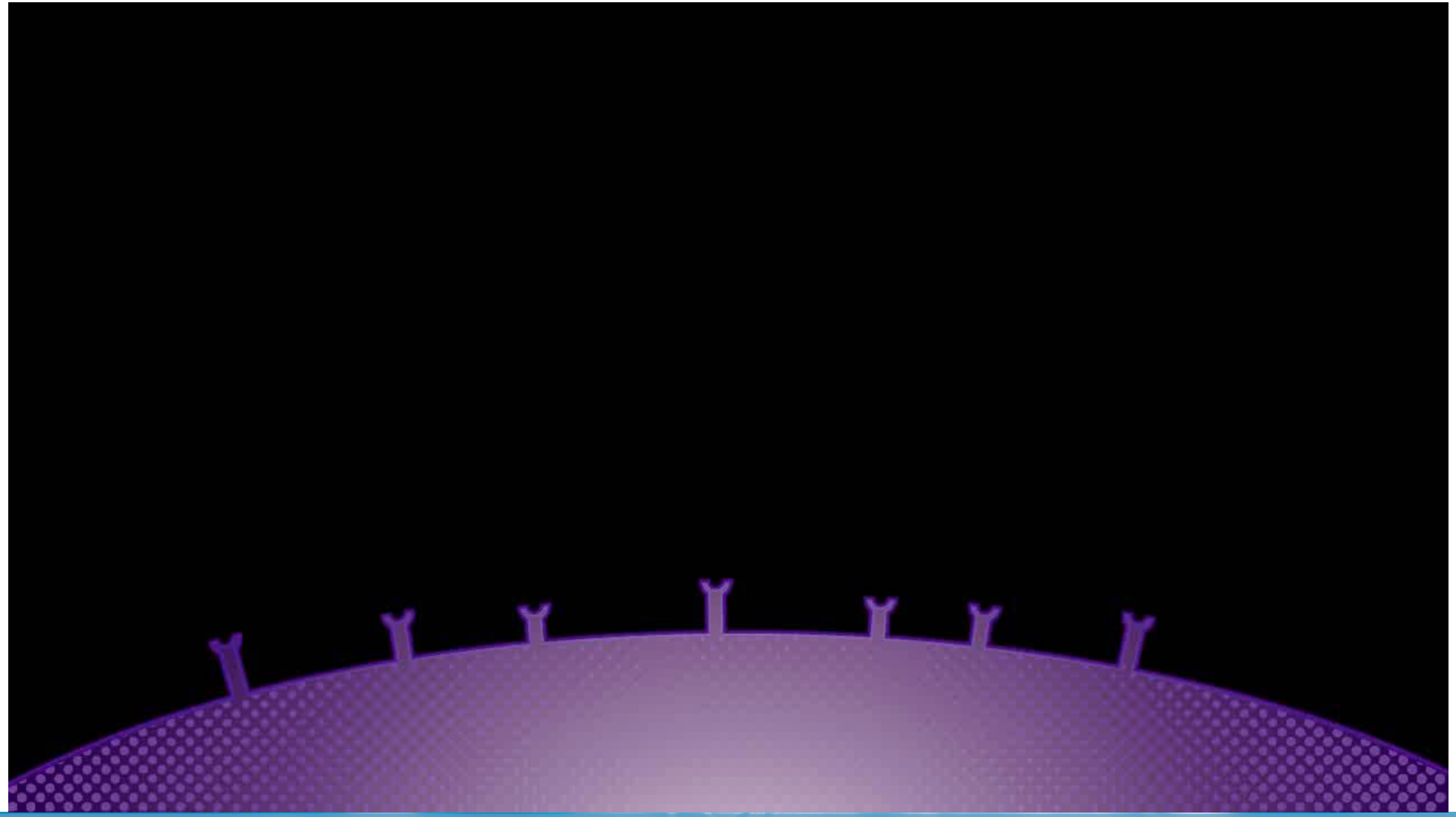
How could antibodies work against HIV?

SENSITIZATION
("the lookout for the hitman")

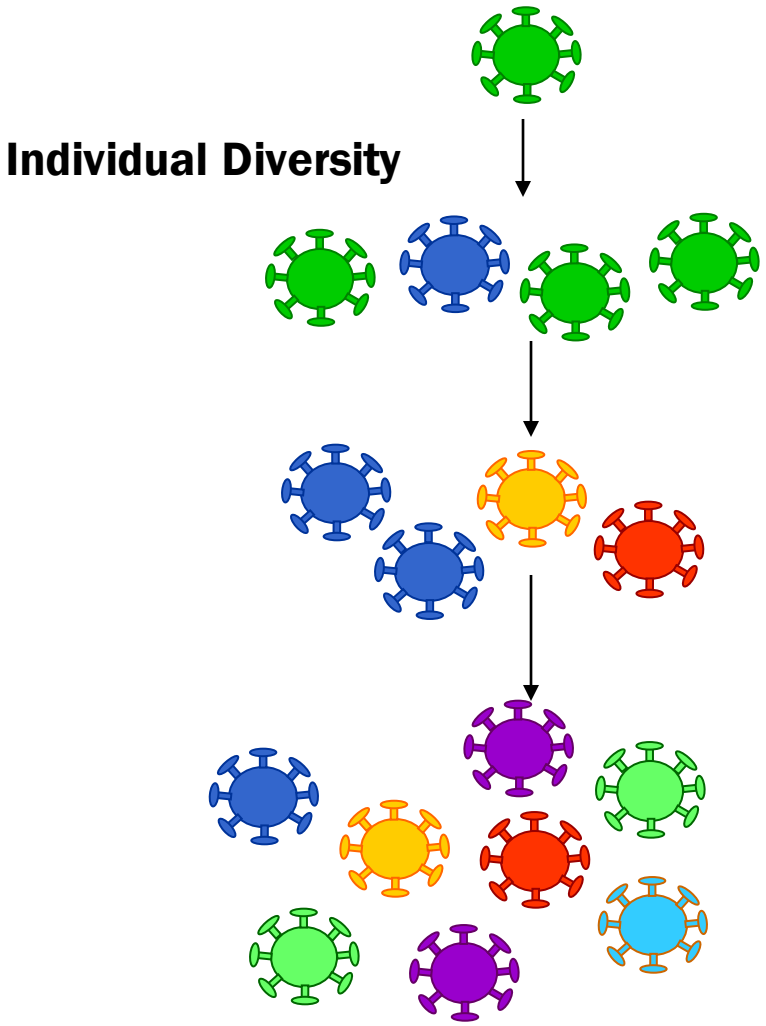
Antibodies bind to HIV, then bind to natural killer (NK) cells; the NK cells then spill their "poison" to kill HIV



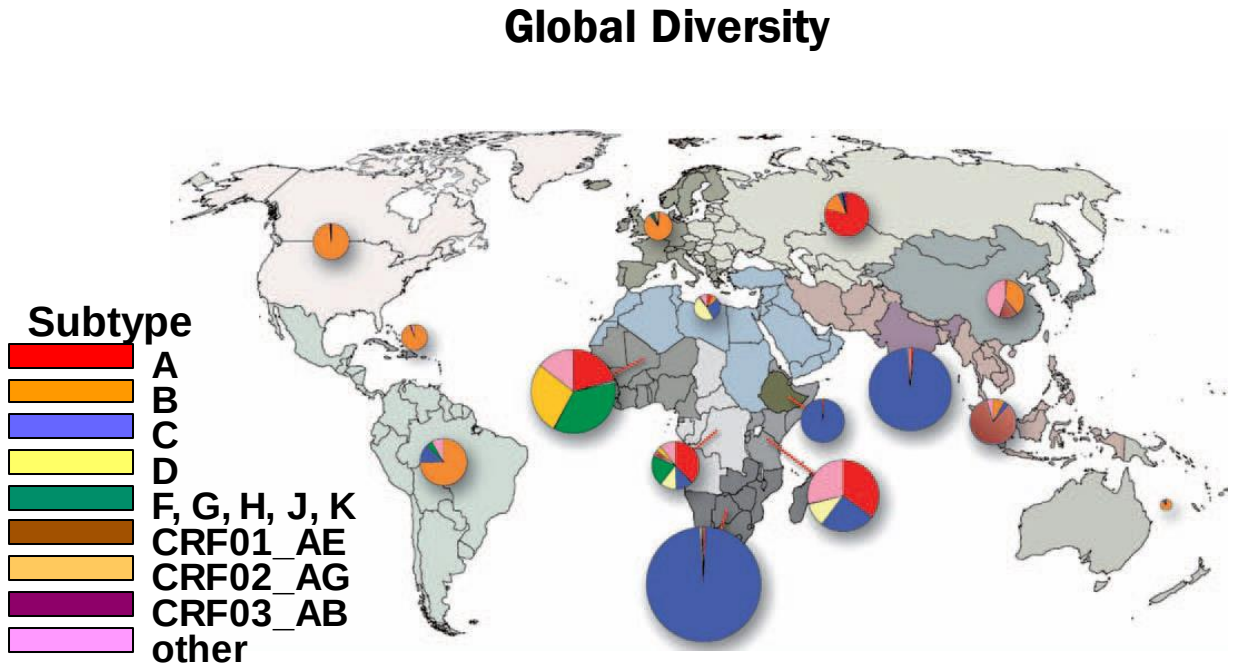
Antibody neutralization against HIV



What is a broadly neutralizing antibody (bnAb)?



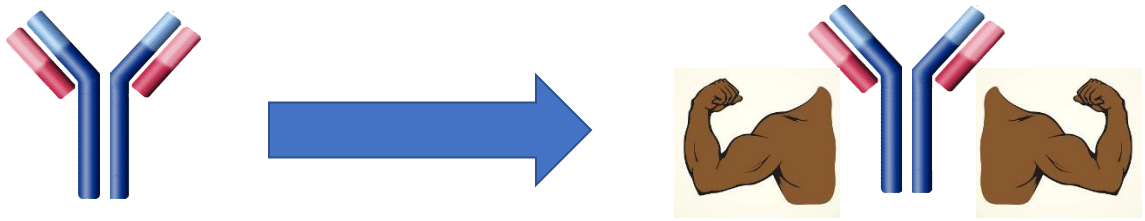
An antibody that neutralizes a lot of different types or strains of HIV.



Where do bnAbs come from?

- Some individuals eventually make bnAbs against HIV, but it is too late to prevent infection.

- These human-generated bnAbs can be used as they are or can be modified to improve their breadth and potency (better binding to a larger number of viral variants)



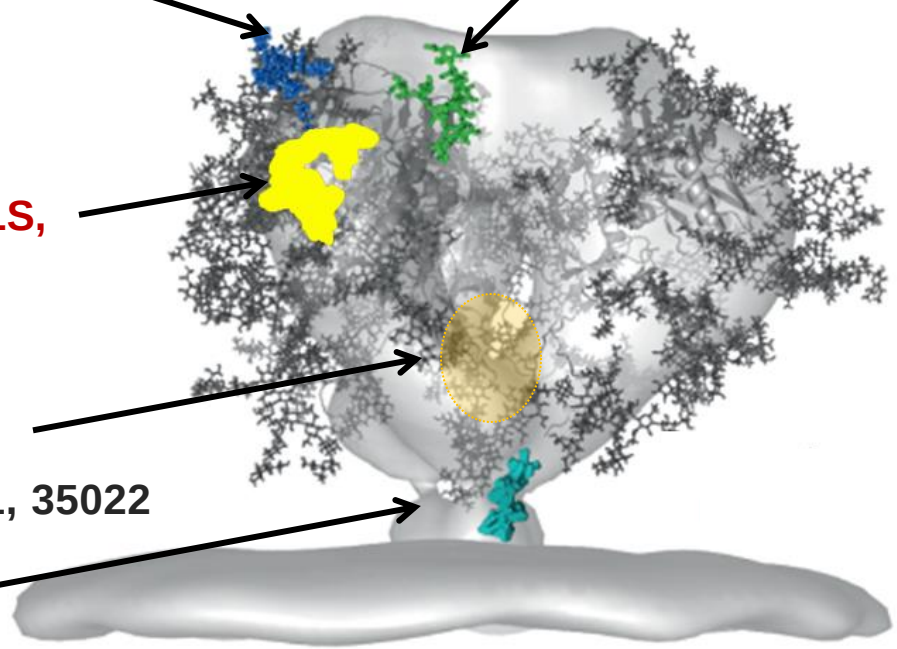
What is a monoclonal antibody (mAb)?

- A single type ("clone") of antibodies often found in the blood of long-term non-progressors, then made in a lab
- Bind to different parts of the HIV gp120 envelope protein

N332 Glycan Supersite:
PGT121, PGT128, 10-1074

V1V2 Glycan:
PG6, PG16, CH01-04, PGT141-45, PGDM1400, CAP256-VRC26

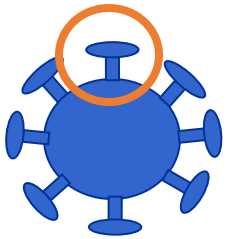
CD4 Binding Site:
VRC01, PG04, CH31, VRC07-523LS, 3BNC117, 12A12, CH103



Trimer (gp120/41)
8ANC195, PGT151, 35022

gp41 MPER:
2F5, 4E10, 10e8

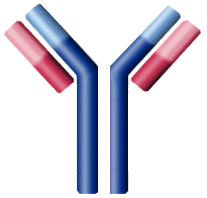
HIV gp160 envelope protein



Thanks to the Subramaniam, Kwong, and Wilson groups.

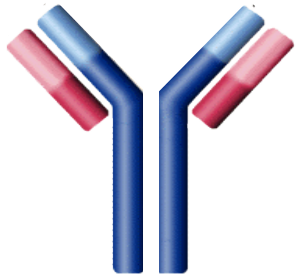
The AMP Studies: VRC01

In the lab, VRC01 has been able to block HIV in about 90% of the different types by binding to the CD4 binding site.



Key Elements	Key Information
Purpose	• Safety and tolerability • Efficacy
What's Special	• First efficacy study using mAbs for HIV prevention
Study Design	• Randomized, controlled, double-blind, 10 doses (1 every 8 weeks) via IV (10-30 mg/kg)
Participants	• 1900 women or 2700 MSM or transgender (at risk for HIV)
Sites	• 46 globally
Study Duration: 60 months (includes enrollment and follow-up)	

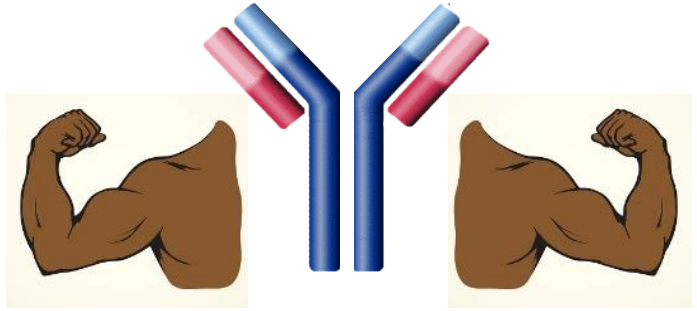
HVTN 127/HPTN 087: VRC07-523LS



VRC01

~10-fold more potent
(better binding, need less of it)

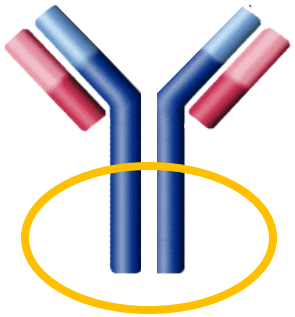
Neutralizes 96% of viral strains



VRC07-523LS

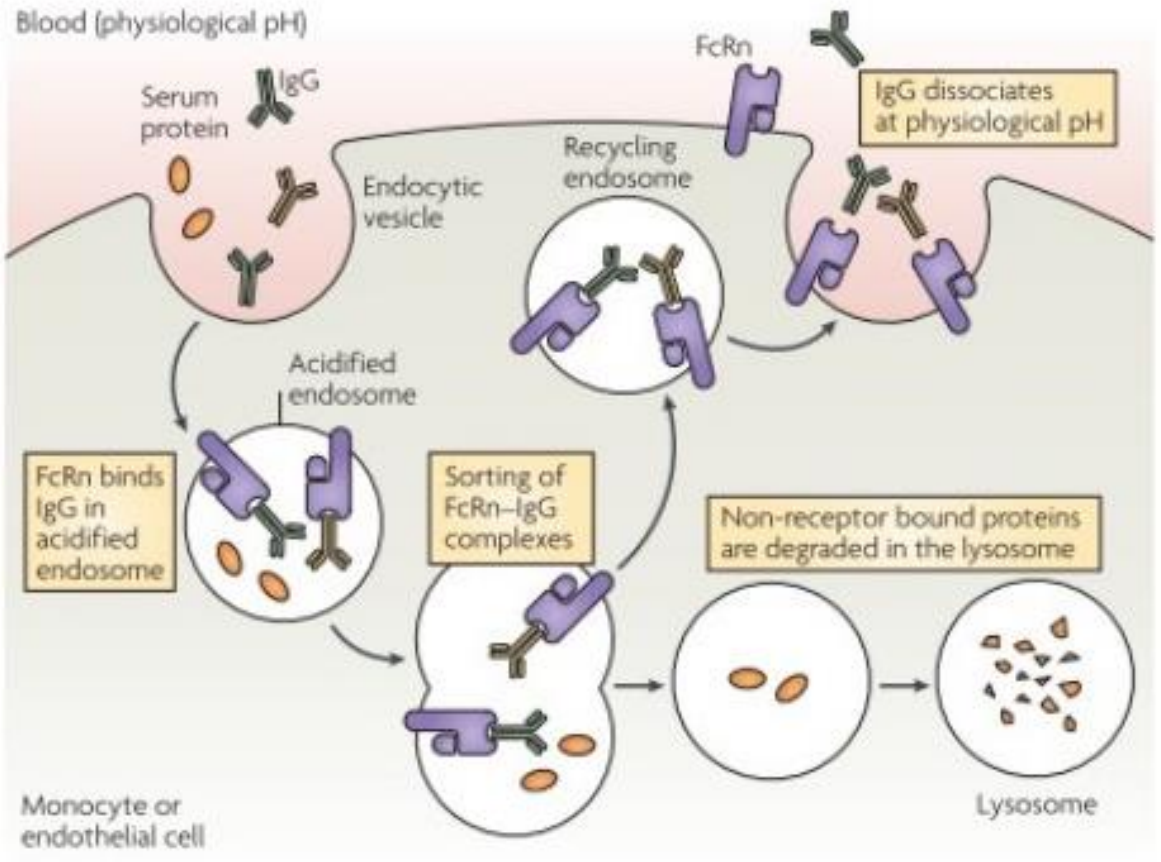
Extended half-life (LS mutation) – so it lasts longer in the bloodstream

HVTN 127/HPTN 087: VRC07-523LS



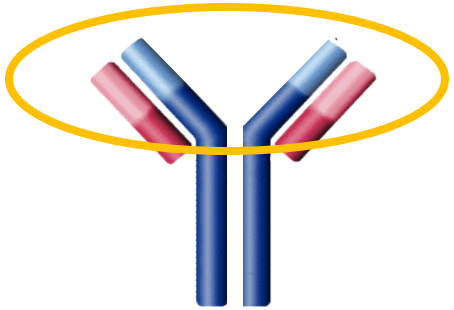
The LS mutation takes place here

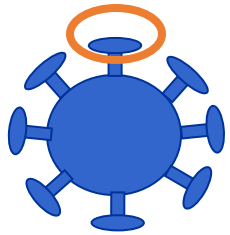
Now the mAb can bind to the neonatal FC receptor (FcRn), which recycles the mAb back to the bloodstream.



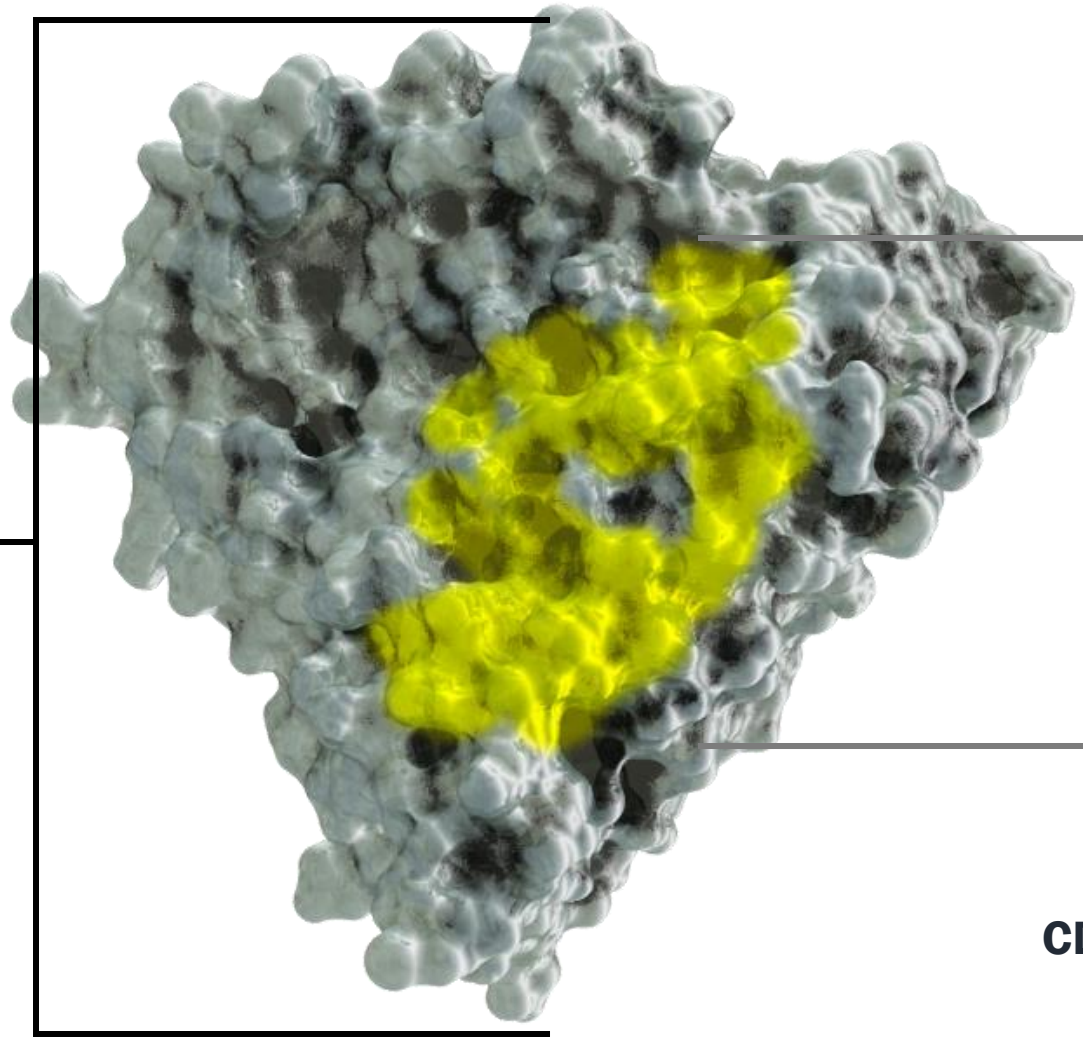
gp120 CD4 Binding Site

Binding mutations takes place here



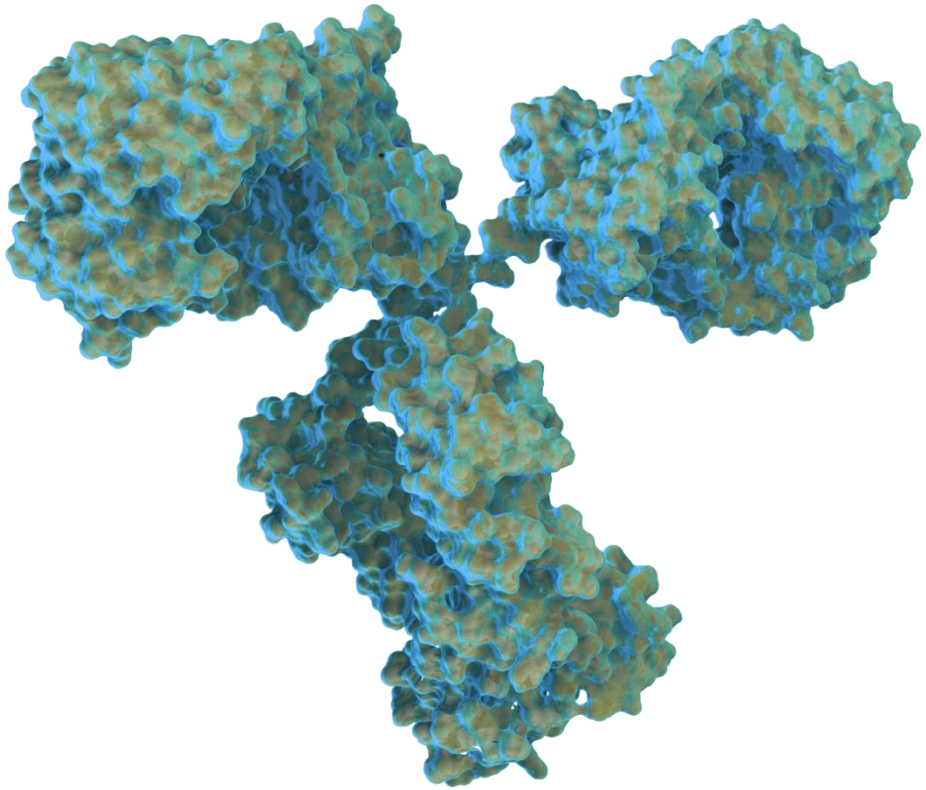


gp120

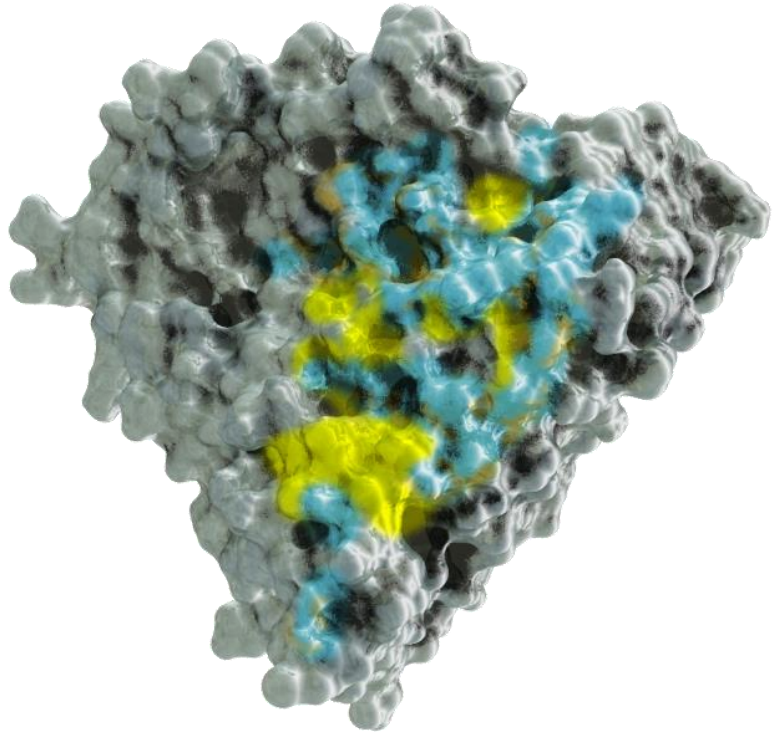


VRC01 Footprint

VRC01 mAb

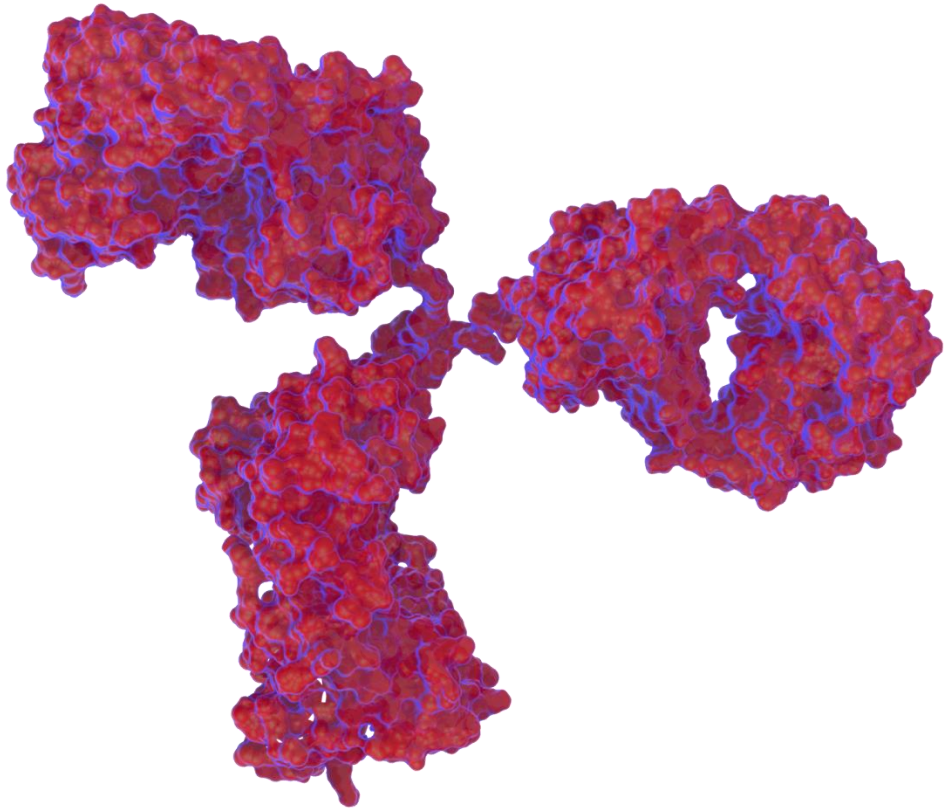


gp120

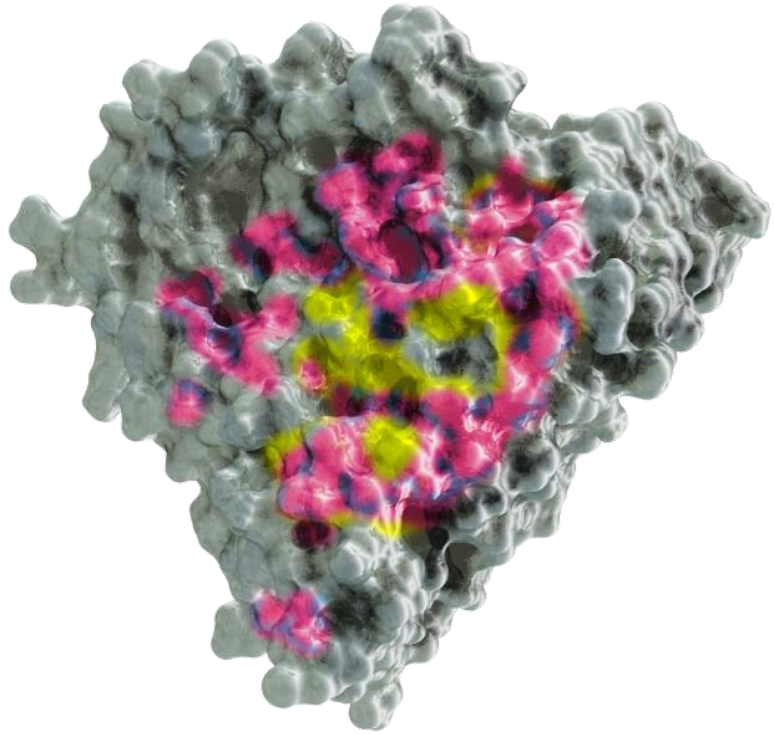


VRC07-523LS Footprint

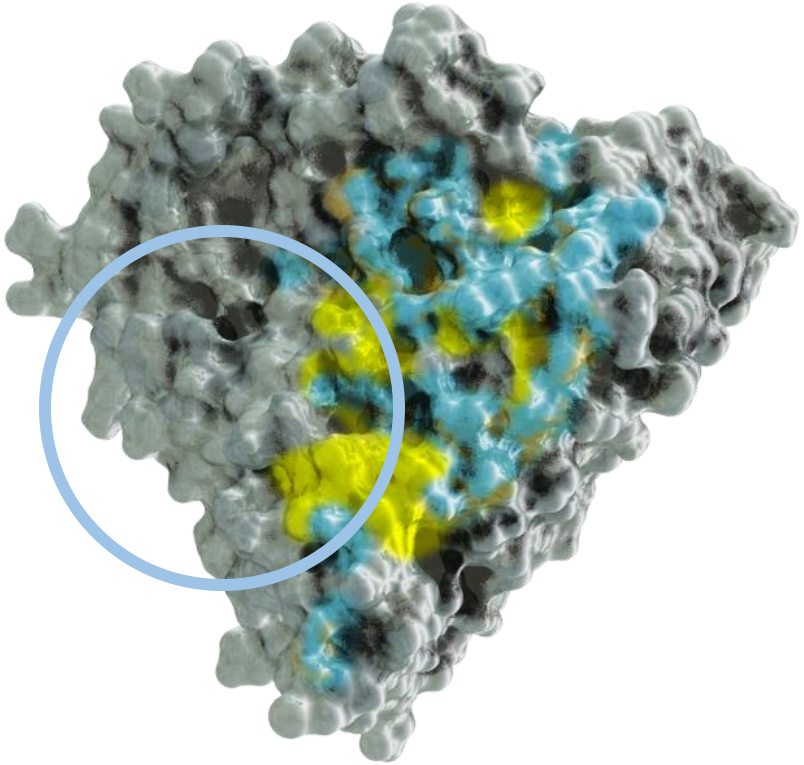
VRC07-523LS
mAb



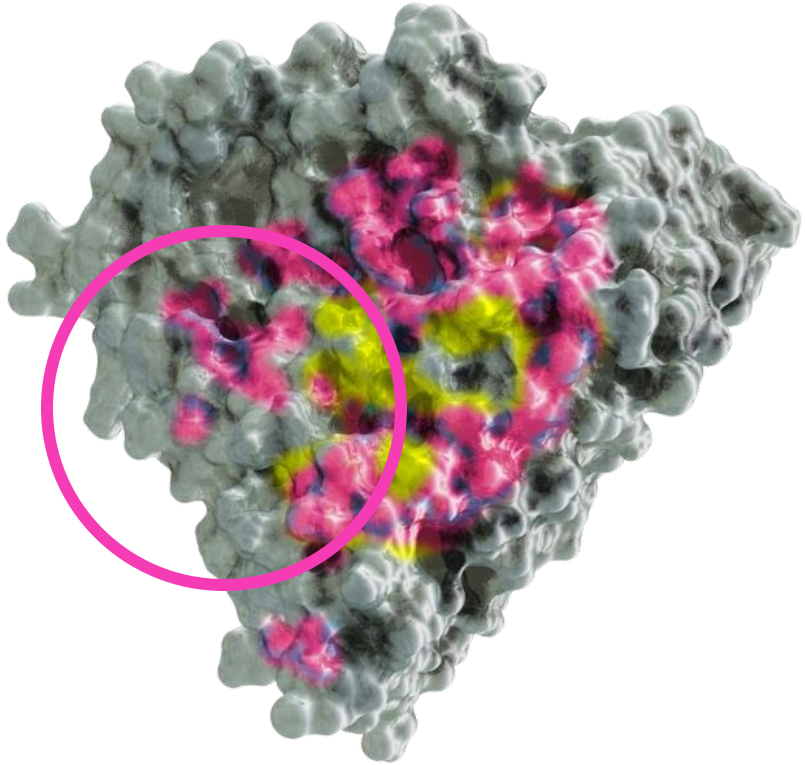
gp120



VRC01 vs VRC07-523LS Coverage



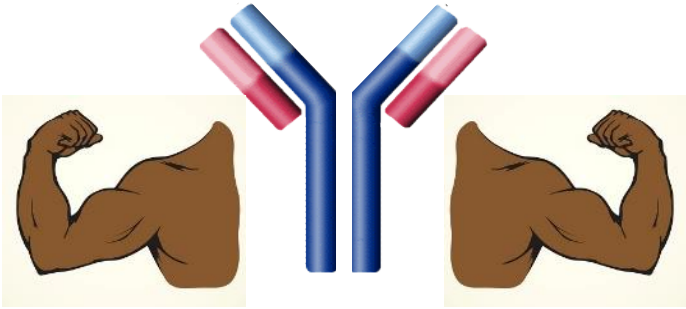
VRC01 mAb



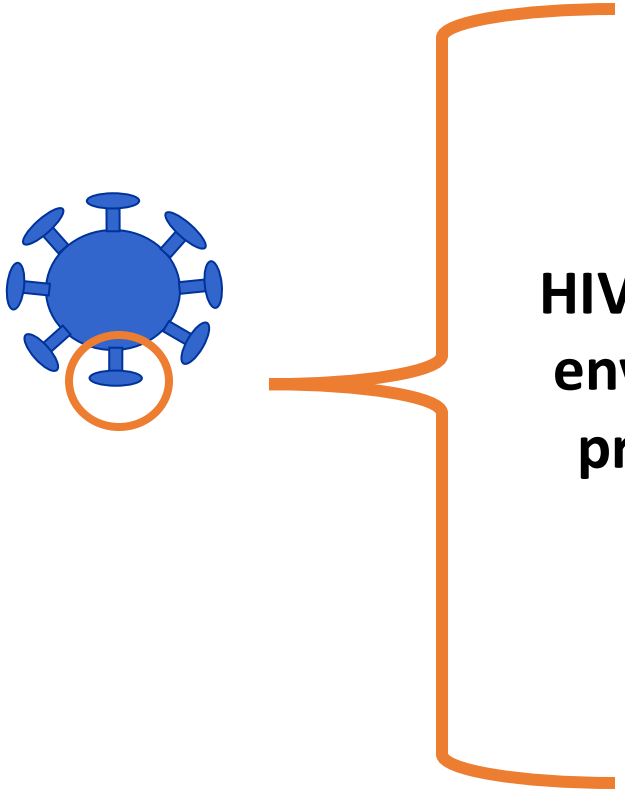
VRC07-523LS mAb

HVTN 127/HPTN 087: VRC07-523LS

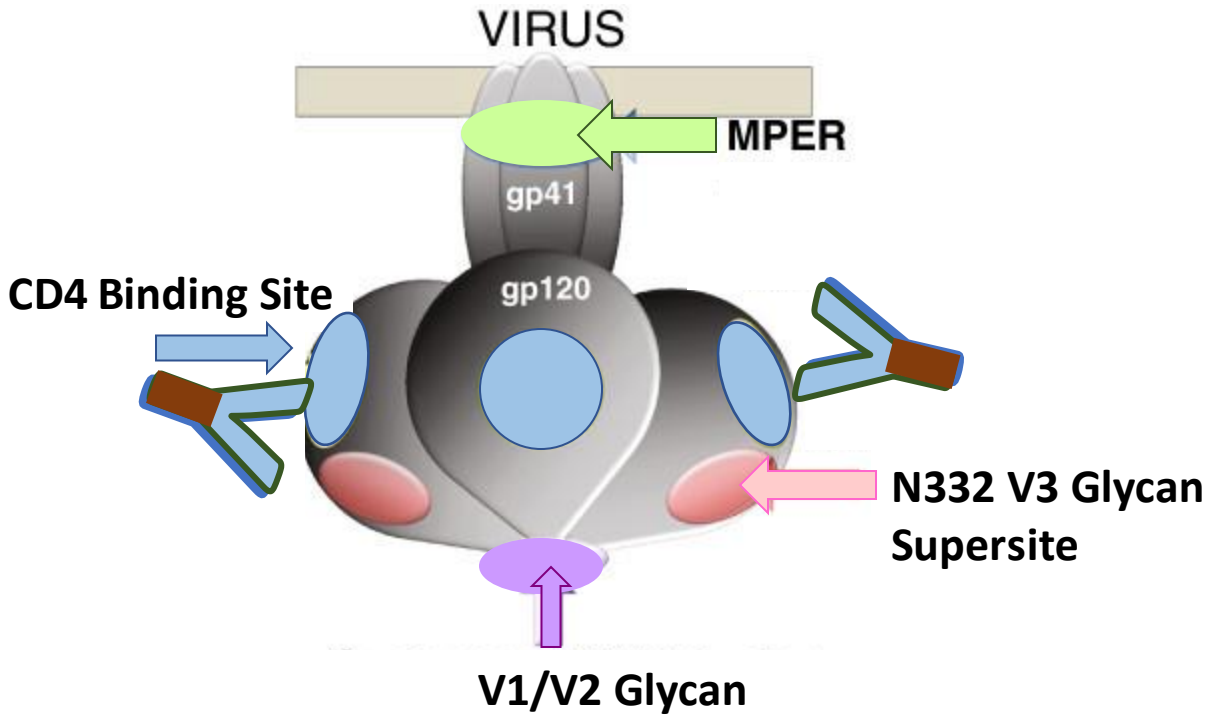
Key Elements	Key Information
Purpose	• Safety and tolerability • Serum concentrations (pK, binding, neutralizing activity) and development of anti-drug antibodies (ADA)
What's Special	• Broader (neutralizes more HIV-1 isolates), more potent and longer half-life than VRC01
Study Design	• Randomized, multi-dose (5 doses 16 weeks apart), dose ranging via IV (2.5 – 20 mg/kg), SC (2.5 – 5.0 mg/kg) and IM (2.5 mg/kg)
Participants	• 124 healthy adults at low risk for HIV
Sites	• 7 sites (Switzerland, Atlanta, Birmingham, Boston (2), Chapel Hill and New York)
Study Duration: 32 months (includes enrollment and follow-up)	



VRC01 and VRC07-523LS bind to the CD4 binding site

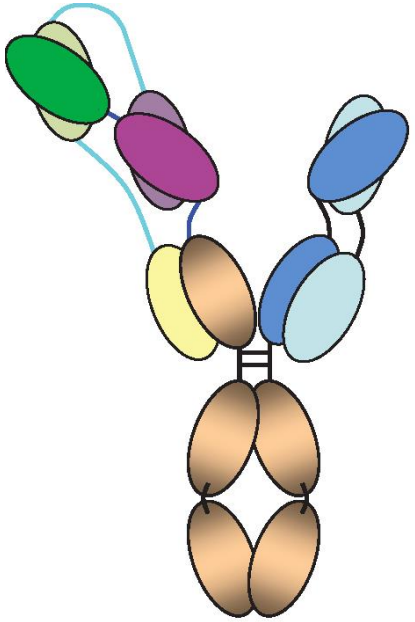


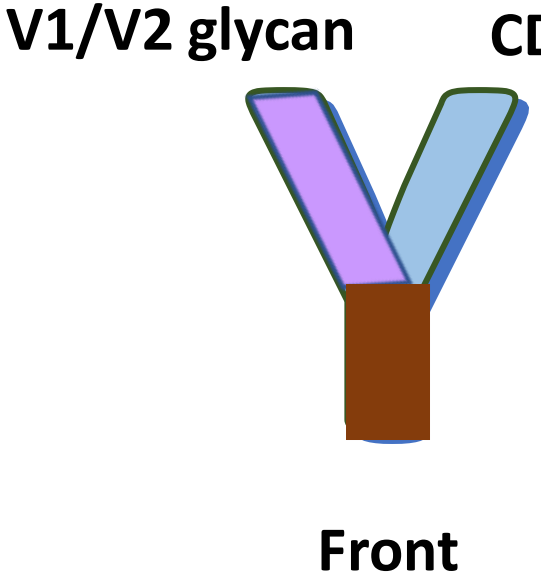
HIV gp160 envelope protein

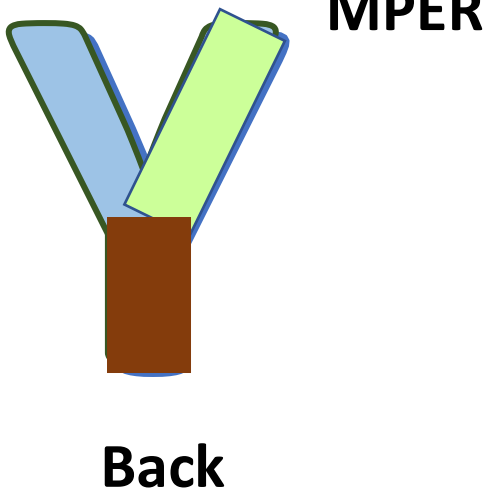


SAR441236 (trispecific mAb)

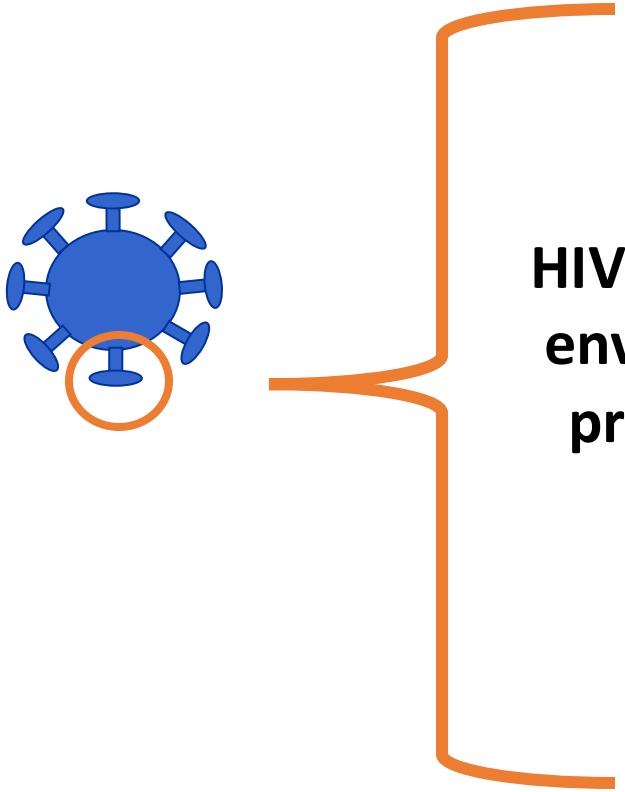
- Made up of pieces from three different mAbs
- Binds to HIV in three unique locations



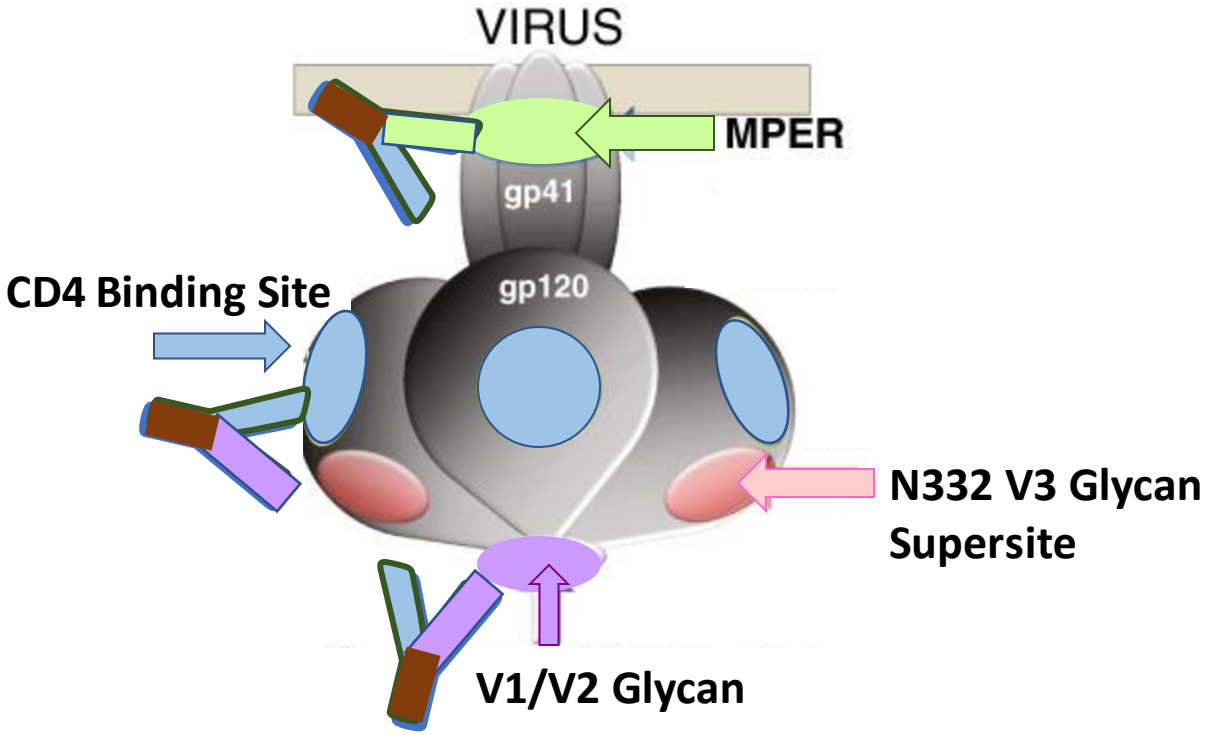




SAR441236 (trispecific mAb) binds in 3 unique locations

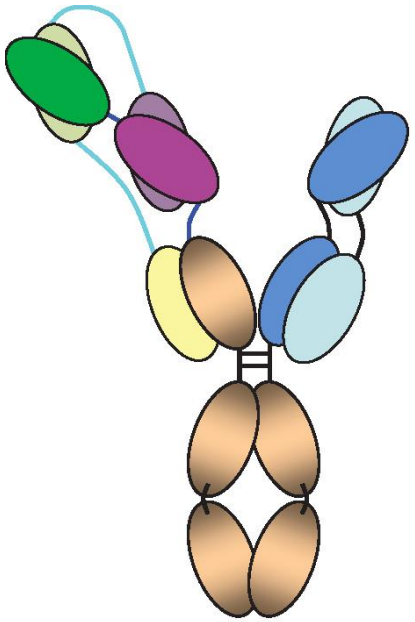


HIV gp160 envelope protein

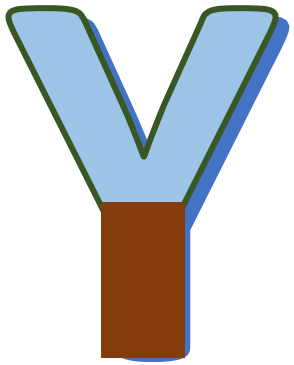


HVTN 129/HPTN 088: Trispecific mAb

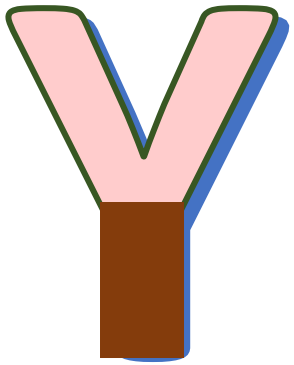
Key Elements	Key Information
Purpose	• Safety and tolerability (first in human) • Serum concentrations (pK, binding) and development of anti-drug antibodies (ADA)
What's Special	• Single mAb engineered to bind HIV in three locations (CD4 binding site, MPER epitope and V1/V2 epitope)
Study Design	• Part A: Randomized, single dose escalation (1-30 mg/kg IV and 3 mg/kg SC), no placebo (30 participants) • Part B: Randomized, three doses (12 weeks apart) of 3 and 30 mg/kg (IV), includes placebo (48 participants)
Participants	• 78 healthy adults at low risk for HIV
Sites	• 6 US sites (Los Angeles, Atlanta, Newark, Philadelphia, San Francisco and Rochester)
Study Duration: Part A: 12 M follow-up, Part B: 18 M follow-up	



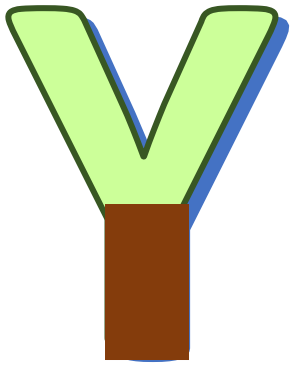
Another way to bind more HIV sites is to use more mAbs



CD4

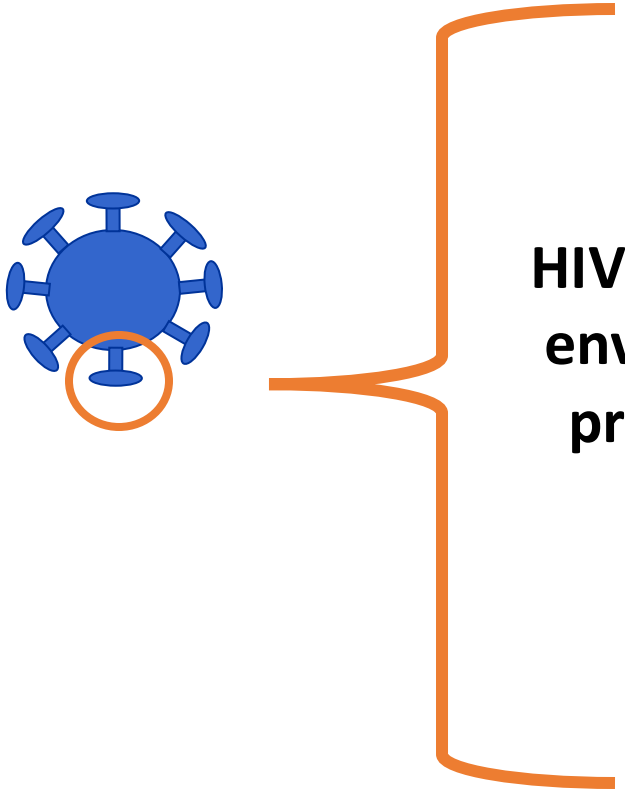


N332 glycan supersite (V3)

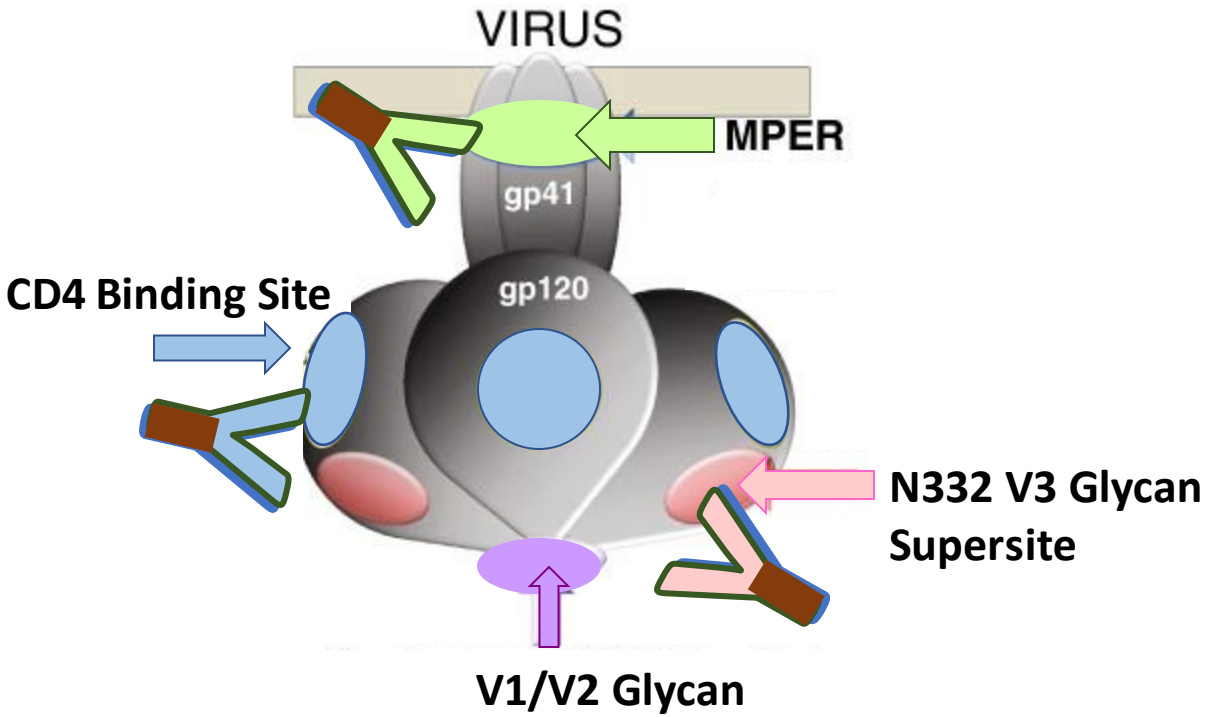


MPER

Multiple mAbs binding in multiple locations



HIV gp160 envelope protein

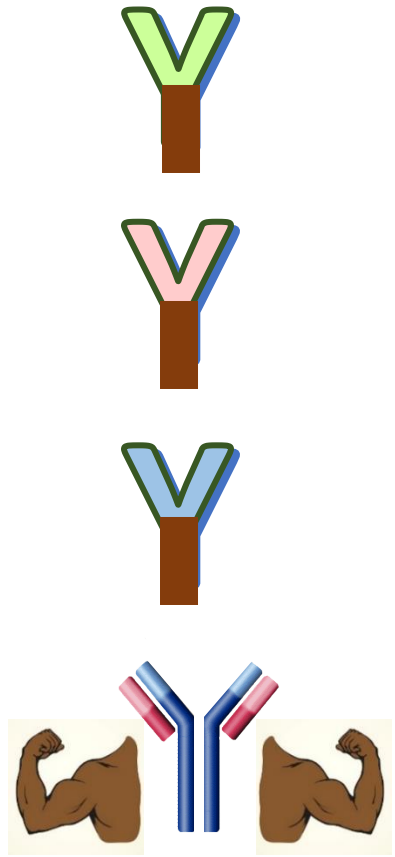


Potential advantages of the trispecific and combination mAb approach

- mAbs or mAb fragments can be chosen so that HIV strains resistant to one are sensitive to the others
- Increase breadth - theoretically, these could be effective against 99% of HIV strains
- May prevent viral escape (the virus mutates and the mAbs no longer work)

HVTN 130/HPTN 089: Triple Combo

Key Elements	Key Information
Purpose	• Safety and tolerability of dual (VRC07 -523LS with PGT121, PGDM1400 or 10-1074) or triple (first in human for all combinations) • Serum concentrations (pK, binding and neutralizing activity) of dual and triple combinations via IV and SC
What's Special	• Many HIV strains that are resistant to one are sensitive to the other(s) • Theoretically, could be effective against 99% of HIV-1 strains
Study Design	• Part A: Double-blind, randomized, single dose of dual combinations (20 + 20 mg/kg), IV only (18 participants) • Part B: Open label, triple combinations, two doses (4 months apart) (10+10+10 [IV], 20+20+20 [IV] or 5+3+3 [SC]) (36 participants)
Participants	• 54 healthy adults at low risk for HIV
Sites	• 4 US sites (New York (x2), Nashville and Boston)
Study Duration: Part A: 12 M follow-up, Part B: 16 M follow-up	



Questions and Discussion