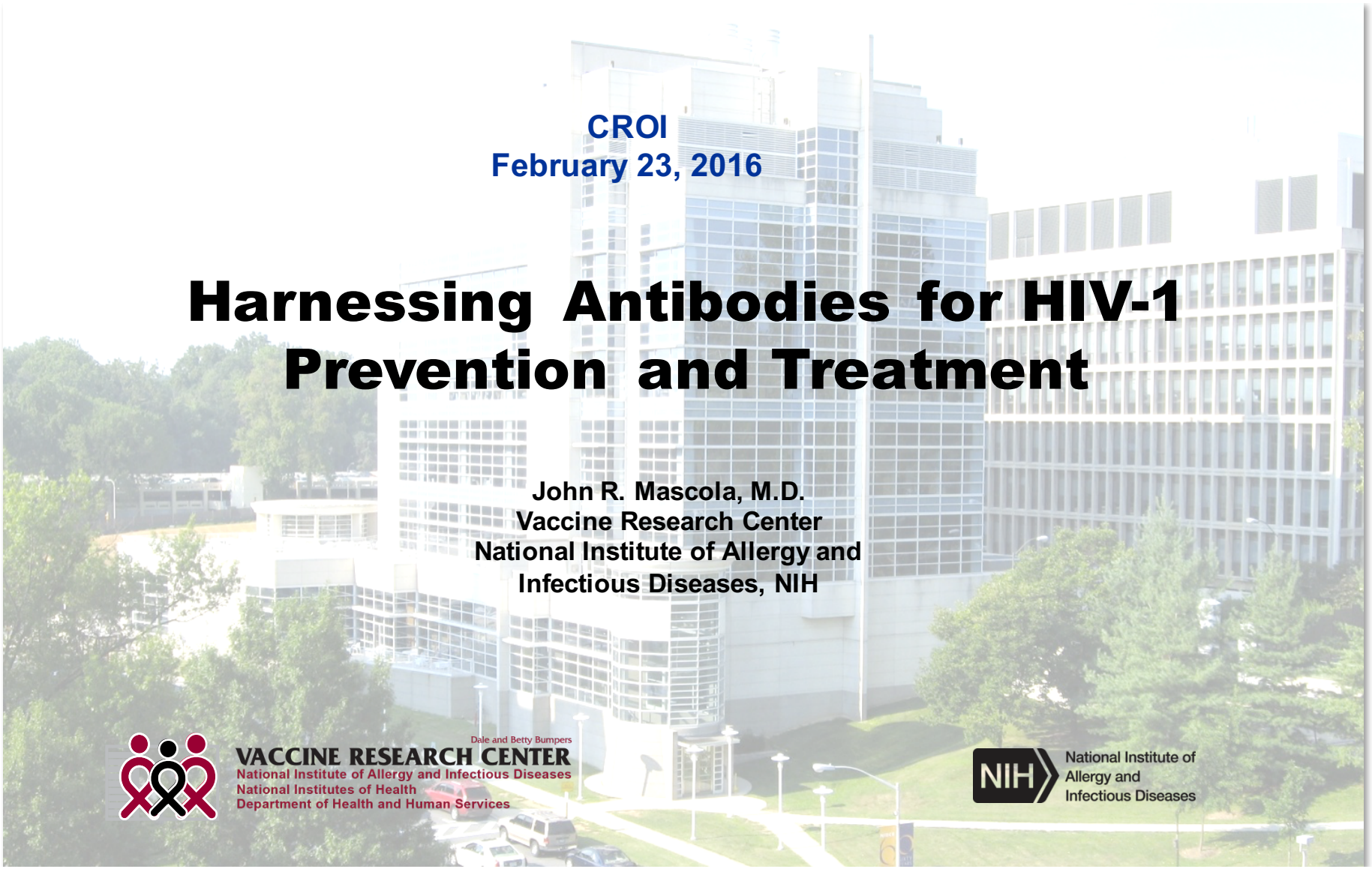

CROI
February 23, 2016

Harnessing Antibodies for HIV-1 Prevention and Treatment

John R. Mascola, M.D.
Vaccine Research Center
National Institute of Allergy and Infectious Diseases, NIH

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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

Harnessing Antibodies for HIV-1 Prevention and Treatment

- Background on HIV-1 Antibodies: Why are we currently focusing on using antibodies clinically?
- Can antibodies be used to prevent HIV-1 infections; i.e., as a means of PreP?
- Do antibodies have a role in treatment of HIV-1 infection?

Long History of Antibodies to Treat Infections Disease (Serum Therapy)

Behring together with his colleagues Wernicke (left) and Frosch (center) in Robert Koch's laboratory in Berlin.
Photo: Courtesy of Aventis Behring
WWW.nobelprize.org

The Nobel Prize in Physiology or Medicine 1901 to Emil von Behring: "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".

Pre-Antibiotic Era: Bering and Paul Ehrlich pioneered serum therapy for diseases such as diphtheria, tetanus, streptococcal infections

Nobel Prizes awarded for discoveries related to antibodies in infectious diseases

- **1901: Serum therapy for dipthereria (Behring),**
- **1908: Describing humoral immunity (Mechnikov, Ehrlich),**
- **1972: Defining the chemical structure of antibodies (Edelman, Porter)**
- **1984: Production of monoclonal antibodies (mAbs) (Jerne, Köhler, Milstein)**
- **1987: explaining the mechanism for antibody diversity (Tonegawa)**

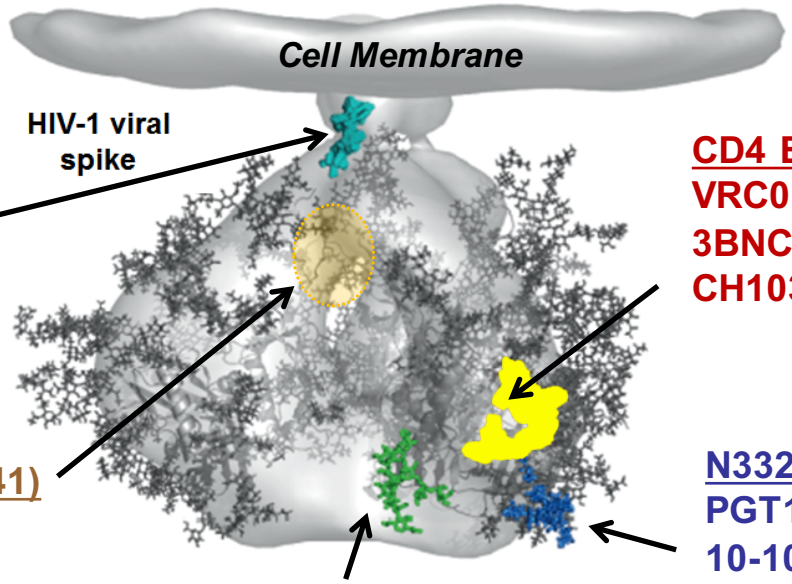
Antibodies use For Viral Infections

Current clinical use

Pathogen	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
VZIG	Varicella Zoster Immune Globulin	Post Exposure

Concept of using antibodies against HIV-1 follows naturally from knowledge gained from many viral diseases

Neutralizing Monoclonal Antibodies Discovered since 2009



gp41 MPER:
2F5, 4E10
10e8

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

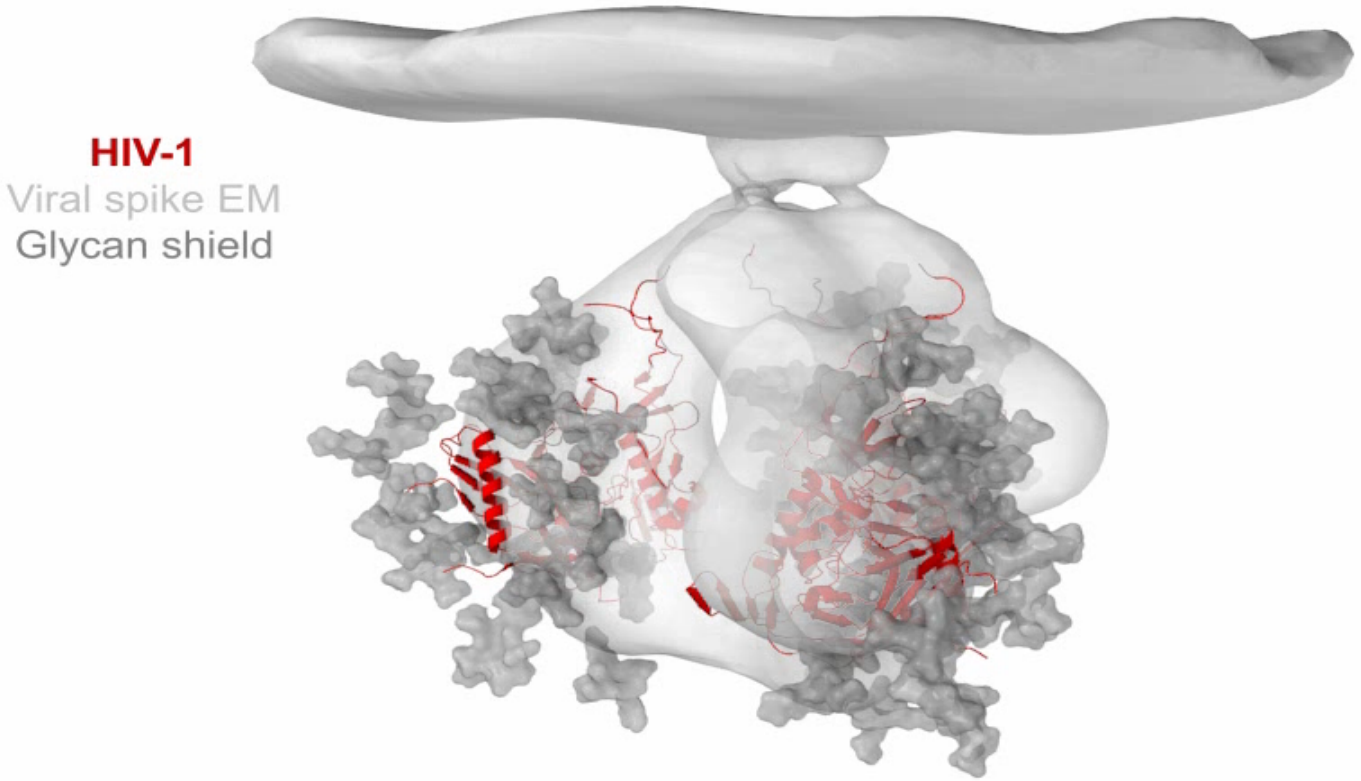
Trimer (gp120/41)
8ANC195
PGT151
35022

N332 Glycan Supersite:
PGT121, PGT128
10-1074

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

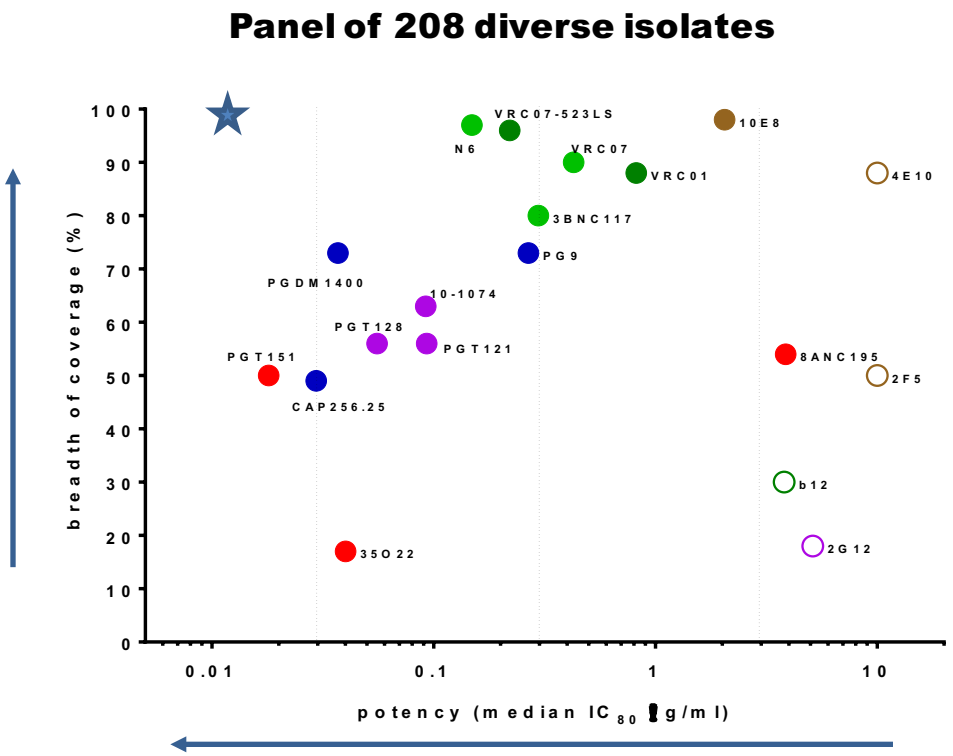
Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups

Sites of Vulnerability on HIV



From: Jonathan Stuckey, Peter Kwong and colleagues

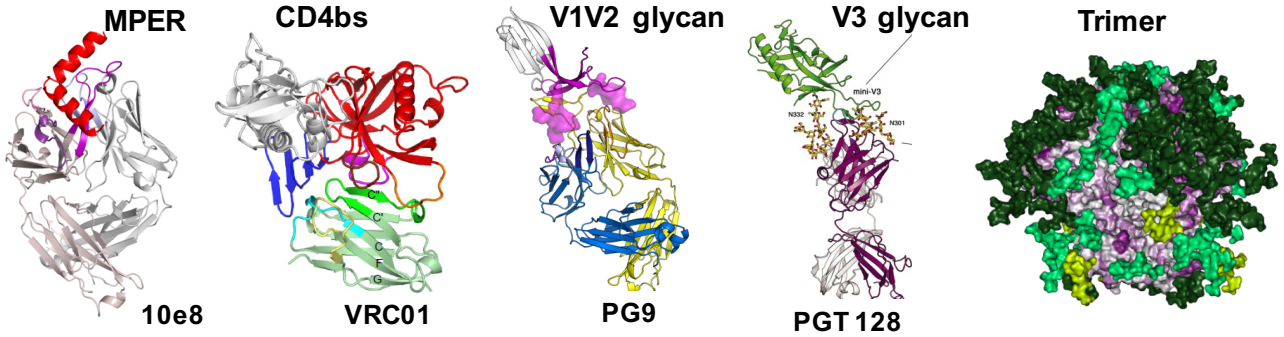
HIV-1 mAb Potency and Breadth

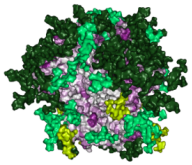


New antibodies up to 500-fold more potent than first generation mAbs

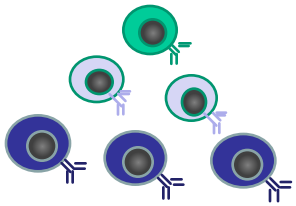
CAVD, VRC collaboration: Montefiori, Seaman, Bailer, Louder et al.

Antibodies Teach us About HIV Vaccine Development

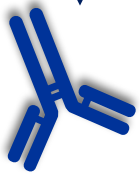




Active Vaccination



Immune pathways of antibody evolution (B cell biology)



Passive Immunization
- Systemic IgG
- Gene-based Ab (AAV)

Talk Outline

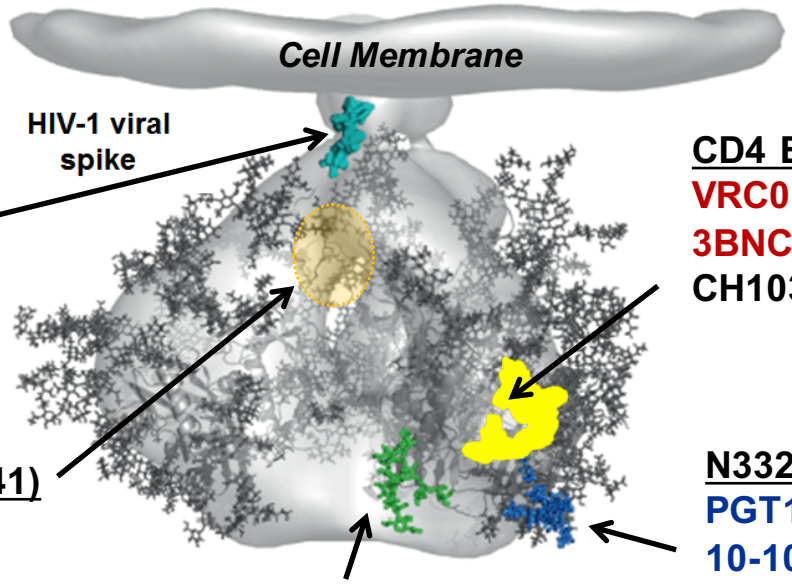
- Background on HIV-1 Antibodies: Why are we currently focusing on using antibodies clinically?
- **Can antibodies be used to prevent HIV-1 infections; i.e., as a means of PreP?**
- **Do antibodies have a role in treatment of HIV-1 infection?**

Passive Antibody Prevention of HIV/SHIV in NHP for > 20 years

- 1990 - 1992: polyclonal IgG protects Chimps from HIV infection
- 1998 - 1999: polyclonal IgG protects against SHIV challenge
- 2000 - present: first use of use of mAbs (2F5, 2G12, F105) and protection against mucosal challenge
- 2009-present: Low dose mucosal SHIV challenge
- 2012: Protection with newer generation mAbs (PGT121, 3BNC117, 10-1074, VRC01, VRC07)

But there are no human data regarding passive protection by HIV-1 monoclonal antibodies

Neutralizing Monoclonal Antibodies plans for clinical trials



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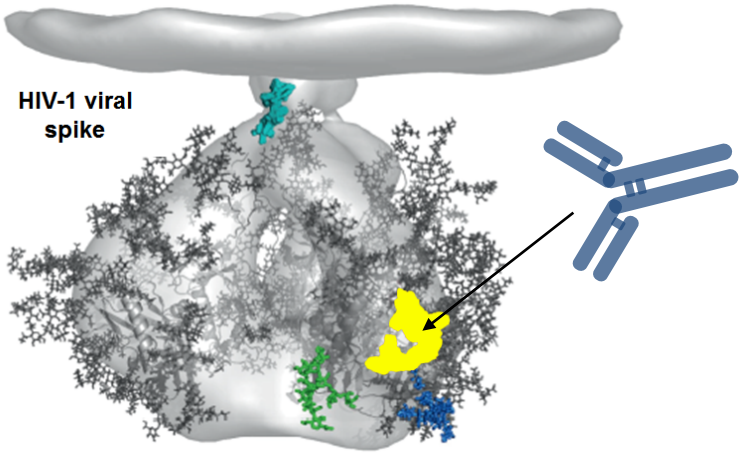
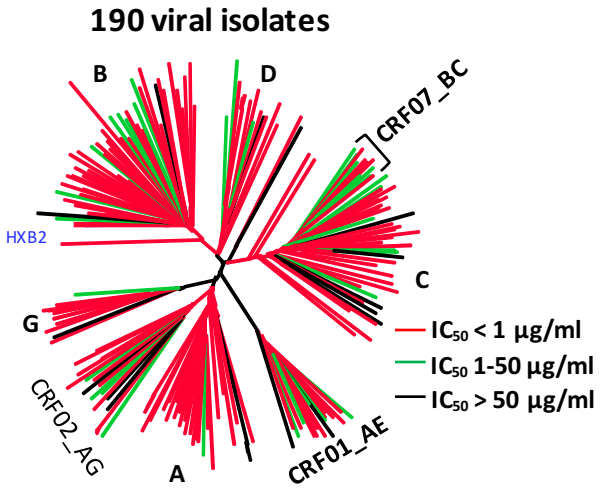
PGT141-45, PGDM1400
CAP256-VRC26

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups

CD4 Binding Site Antibody: VRC01





Wu et al. Science (2010)
Zhou et al. Science (2010)

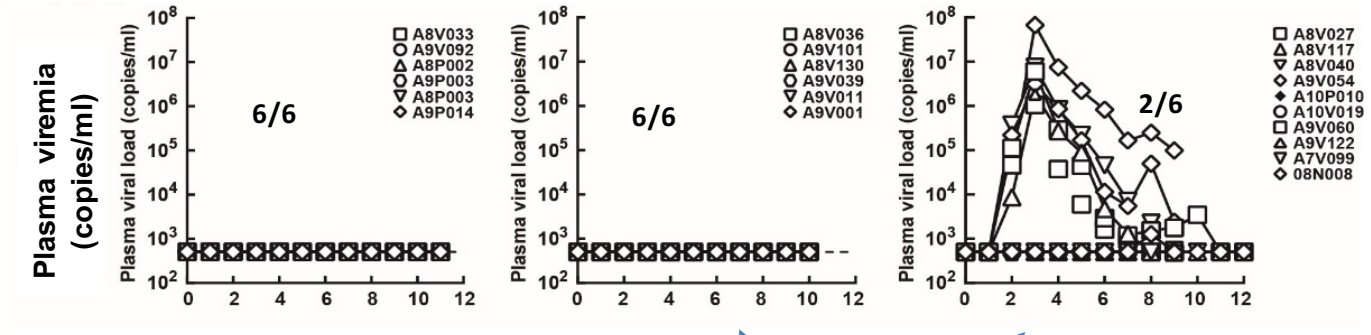
Human monoclonal antibody VRC01

- CD4bs is functionally conserved:
- Neutralizes 80 - 90% of diverse viruses, all clades
- Mean IC80 = 1.0 ug/ml: should work at physiologically attainable levels

Protective Efficacy of VRC01 in SHIV challenge model

- **Infuse VRC01 (SC or IV) and wait 2-5 days**
- **Rectal challenge with virus: SHIV-BaLP4**

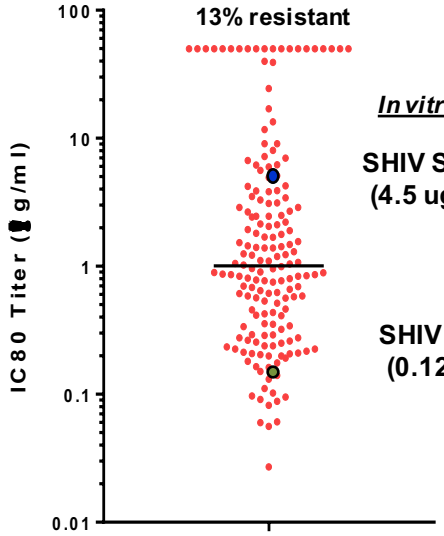
VRC01 Dose: 20 mg/kg 5 mg/kg 0.3 mg/kg



What is the serum level of VRC01 at time of SHIV challenge?

Pegu et al. Science Tranl Med (2014)

VRC01 Serum Level needed to Protect Against SHIV Infection



VRC01 neutralization panel of 190 viral strains

In vitro IC80

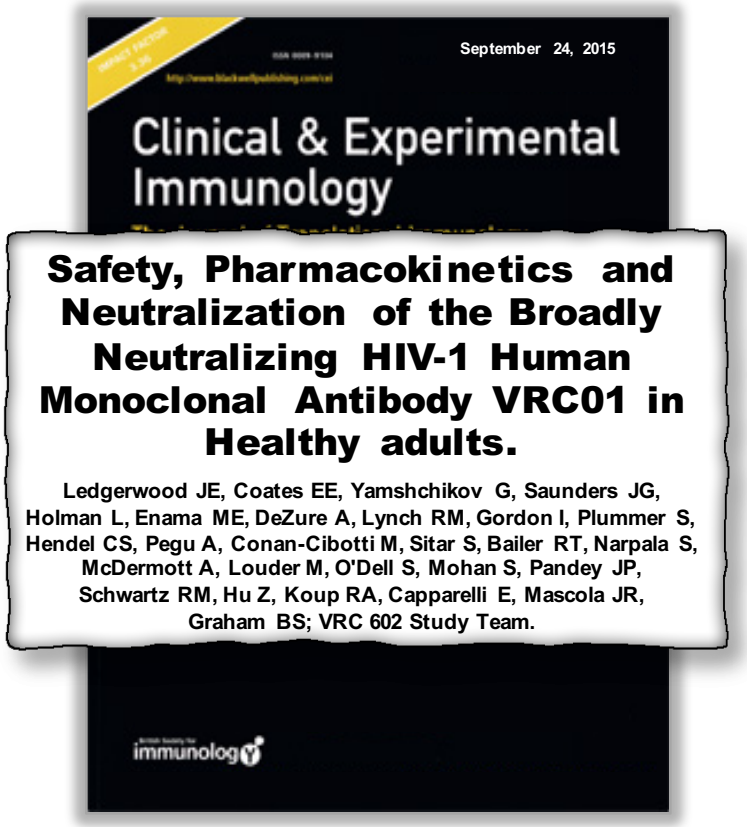
SHIV SF162P3 (4.5 ug/ml) → 20 ug/ml

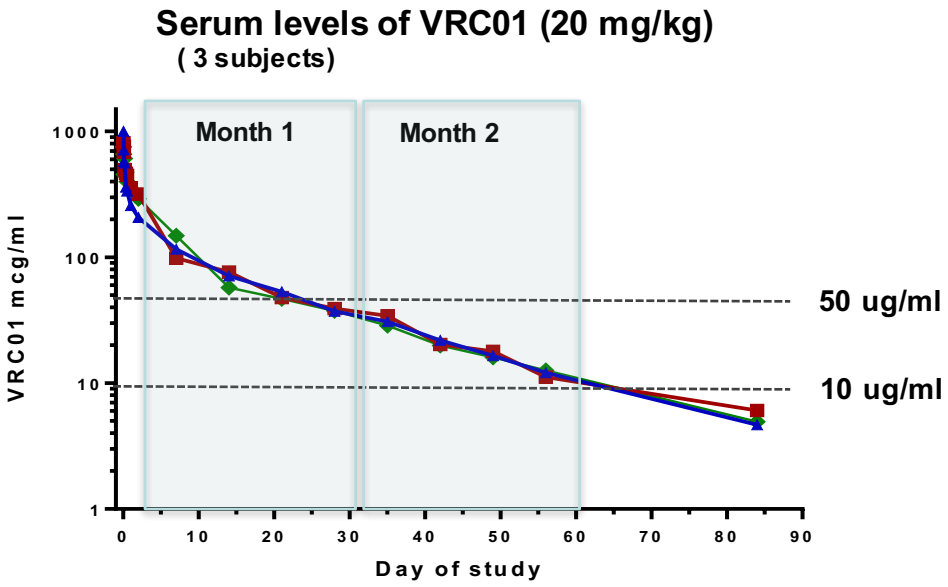
SHIV BaLP4 (0.12 ug/ml) → 1.5 ug/ml

Plasma Concentration for *in vivo* protection of NHP (EC50)

Pegu et al. Science Transl Med (2014)
Ko et al. Nature (2014)
Rudicell et al. J Virol (2014)

VRC01 Phase I Study (Safety and PK)





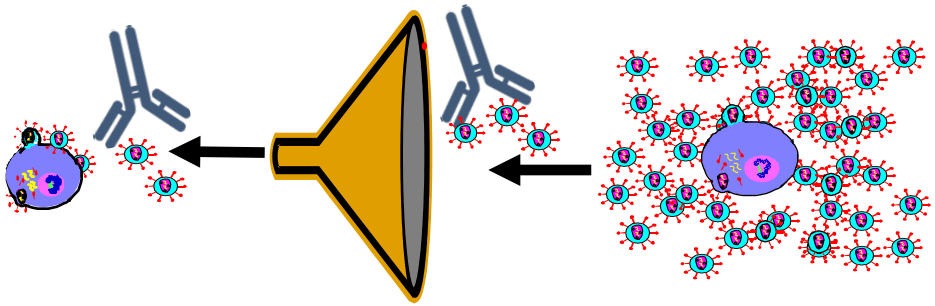
Potential for q2 month regimen

Antibodies to Prevent HIV-1 Infection

Unanswered Questions

- Can antibodies prevent HIV-infection in humans?
- What level of mAb is needed to protect?
- Where and how does the mAb work: lumen, epithelial surface, mucosal or lymphoid tissue
- Are Fc-mediated effector functions (ADCC) needed for protection

Can antibody block HIV-1 transmission event



Passive Antibody Prevention
Phase IIB Efficacy

AMP = Antibody Mediated Prevention

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults

(Conducted by HPTN and HVTN)

The AMP Study: Highlights

- Placebo controlled trial of VRC01 mAb (IV), given on q2 month schedule
- Two cohorts
  - 2400 MSM + TG in North & South America
  - 1500 Women in sub-Saharan Africa
- Powered to detect 60% efficacy; and to associate VRC01 plasma level with protection
- Anticipated to open in: Q2 2016

What Happens With Success:

i.e. VRC01 mAb decreases risk of infection?

- We define the level of plasma mAb needed to protect against infection (e.g., 5 - 10 ug/ml)
- Translate that into:
  - SQ administration of mAbs to achieve this level
  - Incentive to develop next generation mAb (more potent, longer half life)
  - Options for genetic immunization (AAV, DNA, mRNA) to provide medium to long-term protective antibody levels
  - Knowledge that neutralizing mAb can protect will guide vaccine field: i.e. immunogen that achieves this level of neutralization

HIV Prevention – Why should we test antibodies?

Px Option		Current Status at a Site Near Us
	Vaginal gel	❑ Grappling with results of FACTS 001 from Q1 2015
	Rectal gel	❑ First phase II just finishing and results Q1 2016
	Vaginal ring	❑ Two phase IIIs reporting in Q1 & Q4 2016
	Oral PrEP	❑ WHO recommends for all at substantial risk as of Sept 2015
	Long-acting Injectable ARV	❑ Two phase IIs; will there be a phase III in 2017
	Preventive vaccines	❑ P5 – licensure: Research trials launch in 2016 ❑ Janssen Ad26/mosaic, early stages
	Antibodies	❑ HVTN/HPTN with VRC01; launch in Q2 2016

Modified from: HIV Prevention – the State of the Field: AVAC

HIV Prevention – Why should we test antibodies?

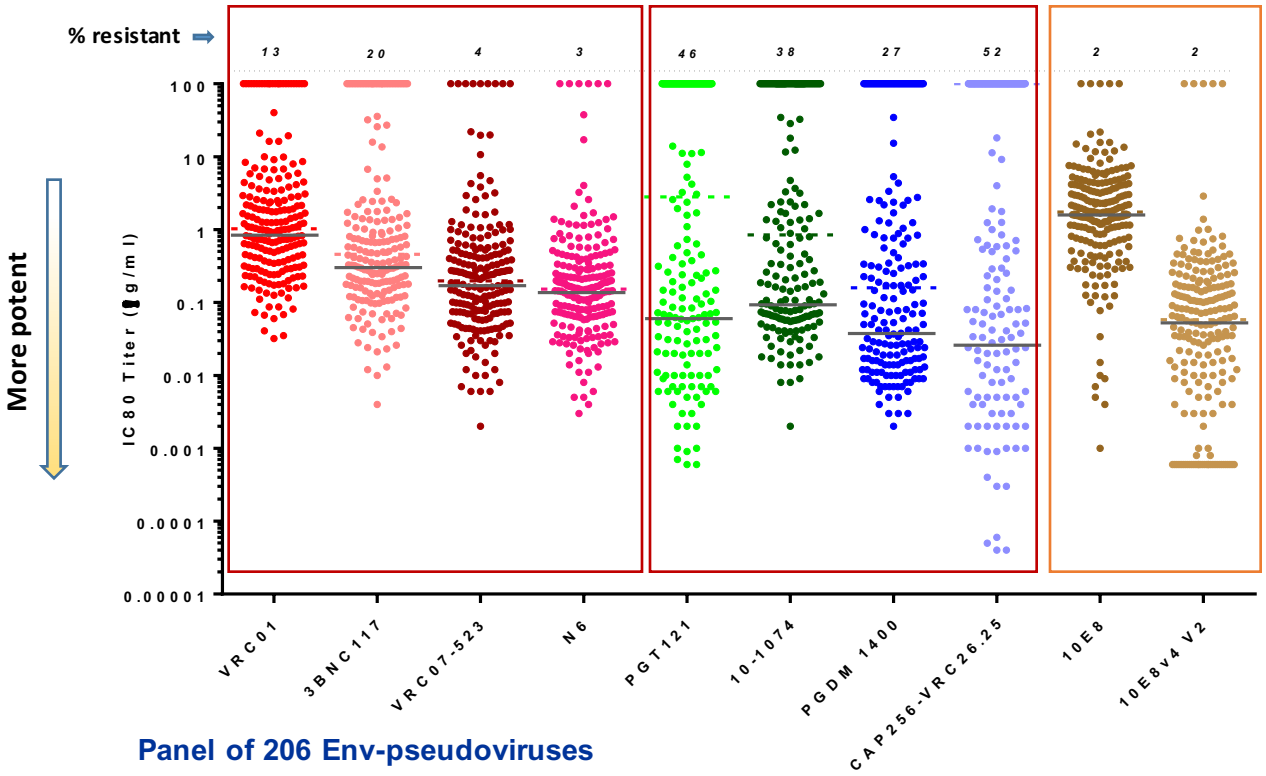
- Reasonable likelihood that antibodies will work
- Likely to be safe and well tolerated (human mAbs)
- Potential that Single shot – confer long lasting protection
- If we achieve clinical efficacy, mAbs could be developed for larger scale use

Goal: A SQ injectable antibody product given one every 3 - 4 months, that safety and effectively protects high risk individuals from HIV-1 infection

Profile of a second generation mAb product: to effectively prevent HIV-1 infections

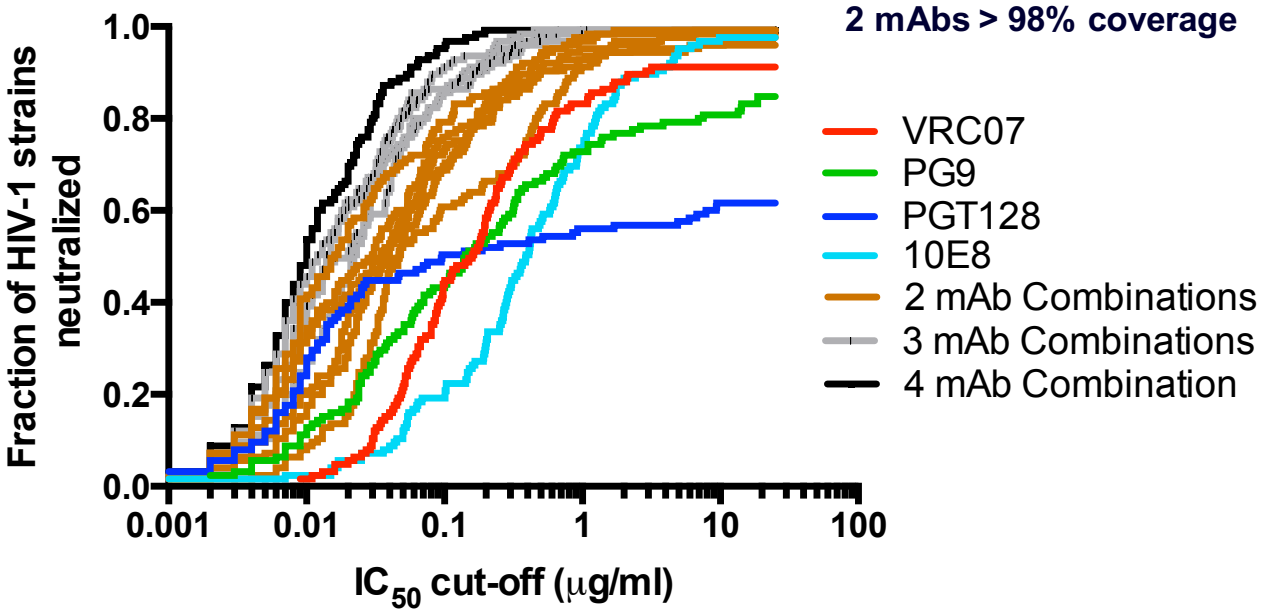
- Cover 98-99% of viral diversity (2 mAb or bispecific)
- Ideally: 10-fold more potent than current mAbs (cost effective and manufacturable)
- Given by SQ injection once every 3-4 months (vs IV infusion every 2 months)
- Cost comparable to ARV drugs or other PreP modalities

Antibodies with Improved Potency/Breadth



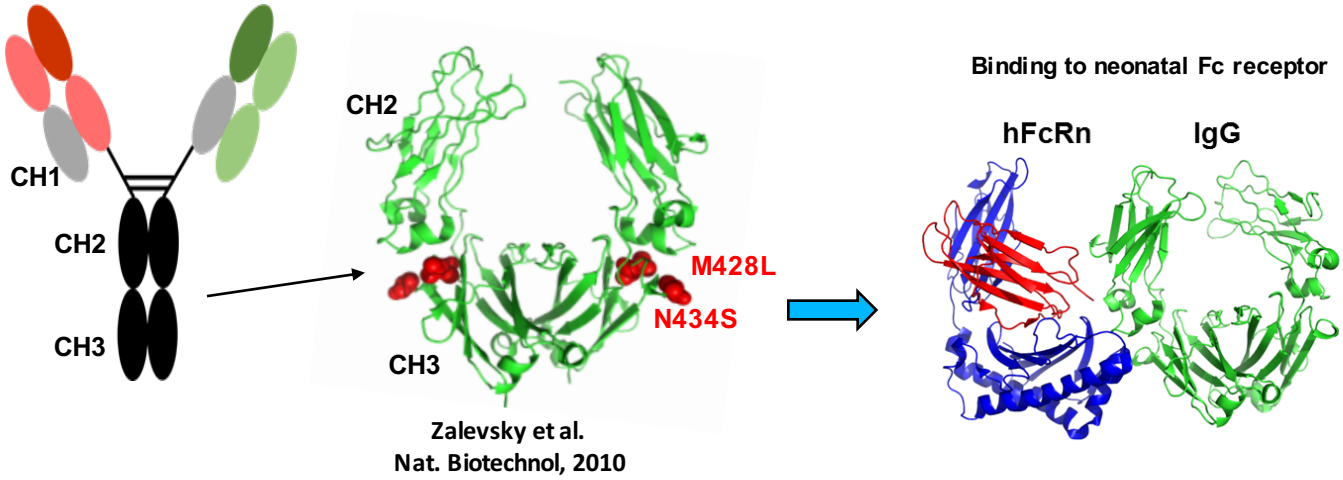
Panel of 206 Env-pseudoviruses

Combined Antibodies:
Improved Potency and Breadth



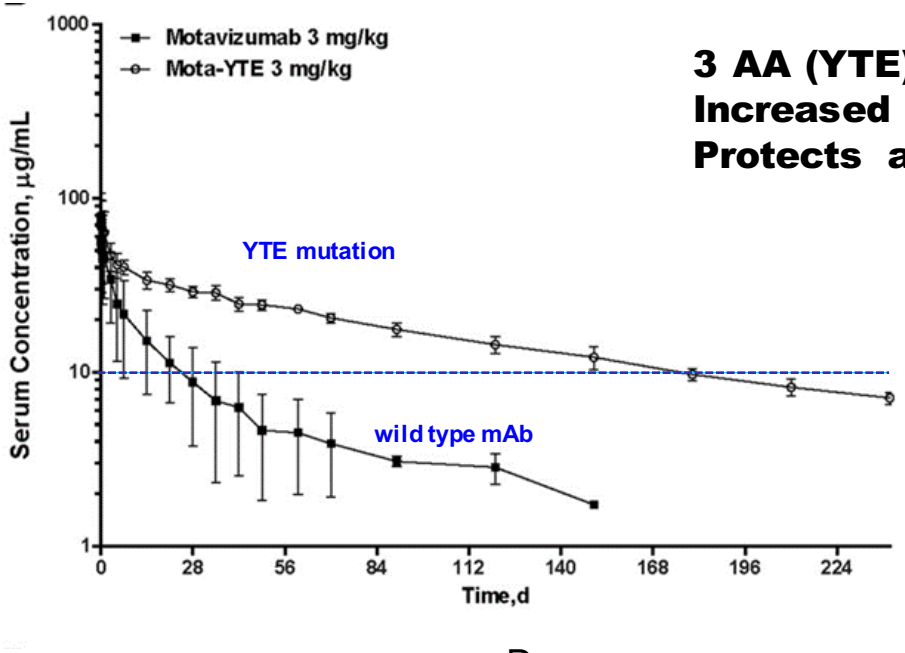
Kong, Montefiori Korber et al.
J. Virol (2015)

Extending mAb half-life in humans



- 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)
- Results in prolonged circulating half life

Extending half-life in humans



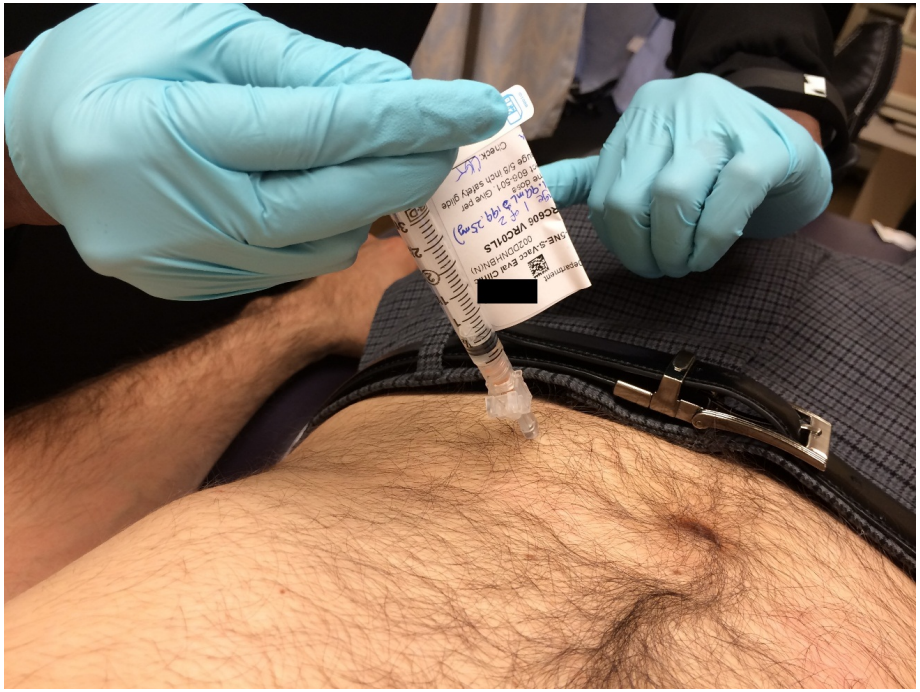
Days

3 AA (YTE) mutation in Fc region
Increased affinity for FcRn
Protects antibody from catabolic pathway

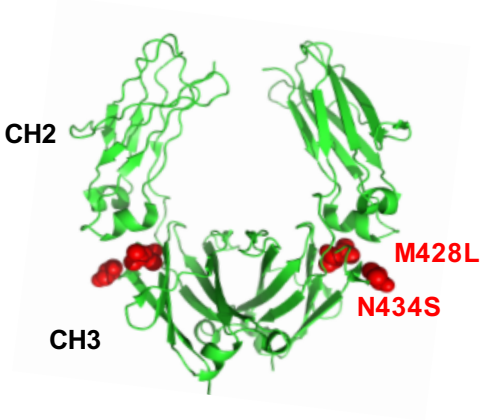
➡ **Maintain > 10 ug/ml for ~ 6 months**

Robbie G J et al.
Antimicrob. Agents Chemother. 2013;57:6147-6153
Antimicrobial Agents and Chemotherapy

Extending half-life in humans
(VRC01-LS phase I trial)



2 AA (LS) mutation in Fc region
Increased affinity for FcRn



Potential for a single administration of mAb to have therapeutic effect for several months

Potential Role in interruption of Maternal-to-Child-Transmission

Examples: HBIG for Hep B virus; Synagis mAb for RSV

Could HIV-1 mAb:

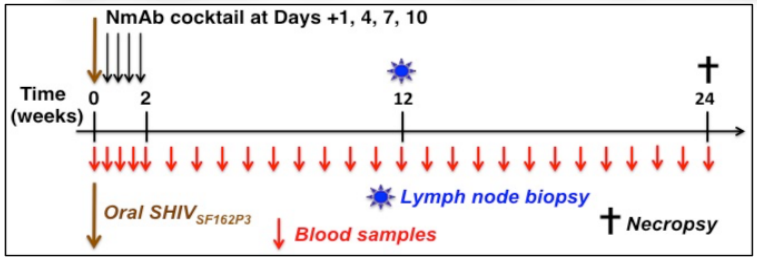
- **Protect against infection resulting from intrapartum exposure to HIV**
  - **i.e., early post-exposure treatment after childbirth**
- **Protect infants of HIV-1 infected mothers during the course of breastfeeding (months)**
  - **e.g., S.Q infusion at birth and every 6 months**

HIV mAb Protection in neonatal macaques

Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in newborn macaques

Ann J. Hessell, Nancy L. Haigwood et al.

Nature Medicine (in press)



Two HIV-1 mAbs, administered starting one day after oral challenge, were able to completely prevent infection of neonatal macaques

- Infant macaque model of intra-partum MTCT.
- One-month-old macaques are inoculated orally with SHIV SF162P3
- mAbs given SC, on day 1, 4, 7, 10 (5 mg/kg each of PGT121 and VRC07-523)

These animal models results suggest that mAbs could interrupt intra-partum HIV-1 transmission and also suggest a role in preventing infant infection during breastfeeding.

Passive Antibody Prevention Summary

- Animal models tell us that HIV mAbs can provide complete protection against infection
- Proof-of-concept in humans would provide key data and knowledge to advance the field, and such a phase IIB study is planned
- With foreseeable engineering; e.g., potency and half-life; - mAbs could play an important role in the prevention of HIV-1 infection in high risk populations

Talk Outline

- Background on HIV-1 Antibodies: Why are we currently focusing on using antibodies clinically?
- Can antibodies be used to prevent HIV-1 infections; i.e., as a means of PreP?
- **Do antibodies have a role in treatment of HIV-1 infection?**

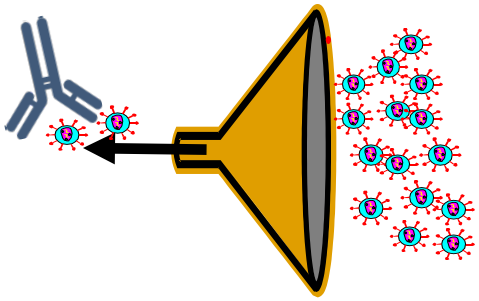
Clinical Use of Antibodies

Prevention and Treatment are Different

Prevention

- Prevent acquisition of infection

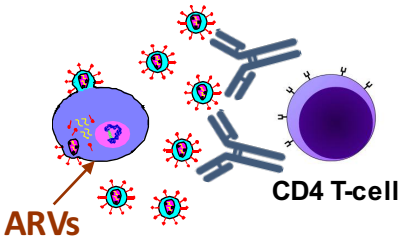
Block
Transmission event



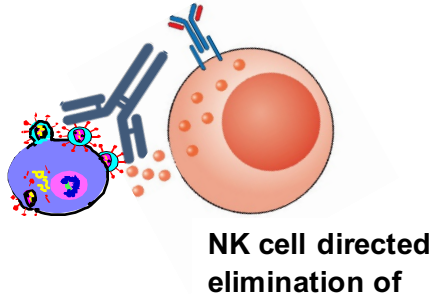
Treatment

- mAbs complementary to ARV drugs
- Different mechanism of action
- Potential to eliminate infected cells
- Impact the cell-associated viral reservoir

Block viral entry



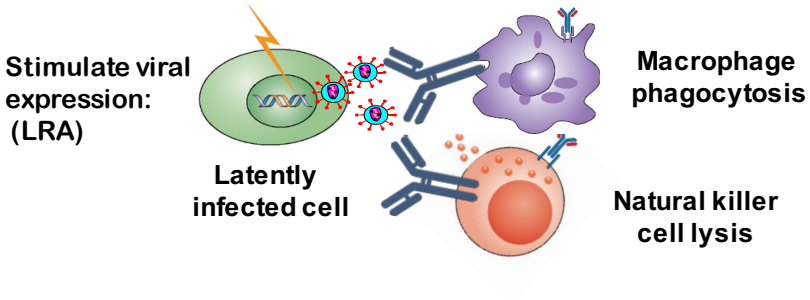
Cell killing



NK cell directed elimination of infected cells

Antibodies for Treatment
How might mAbs be used?

- During acute HIV-infection, with ARV, to rapidly reduce viremia and limit seeding viral reservoir
- To maintain long-term viral suppression induced by ARV – take advantage of long half-life and safety of antibodies (mAbs)
  e.g., LA-ARV + mAb given once every 2-3 months
- Reduce cell-associated viral reservoir: Fc-mediated effector functions (ADCC, ADP) – functions distinct from ARV drugs



Clinical Use of mAbs For HIV-1 Treatment

Opportunities

- Distinct mechanism of action from ARV (NRTI, PIs): Block entry
- Marshal immune mediated effectors (NK cells, Phagocytic)
- Potential to eliminate HIV-1 infected cells
- Safe, well tolerated
- Potential for long therapeutic effect (months)

Limitations

- Unlicensed biologics – lack of immediate availability
- Intrinsic resistance, not effective vs 100% viruses
- Need for mAb combinations
- SQ injection (not oral)
- Limited clinical data, and limited industry development

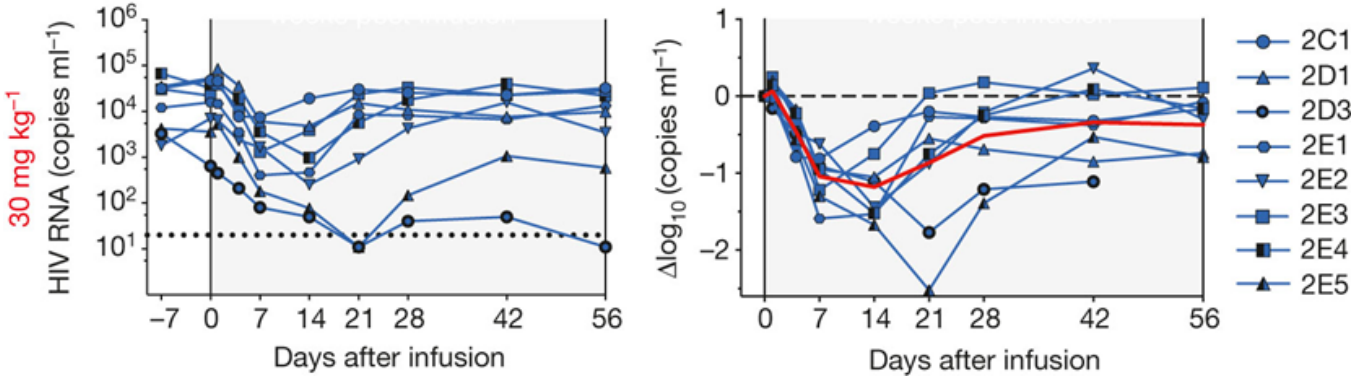
mAb 3BNC117 (CD4bs): phase I

LETTER Nature 522, 487–491 (25 June 2015)

doi:10.1038/nature14411

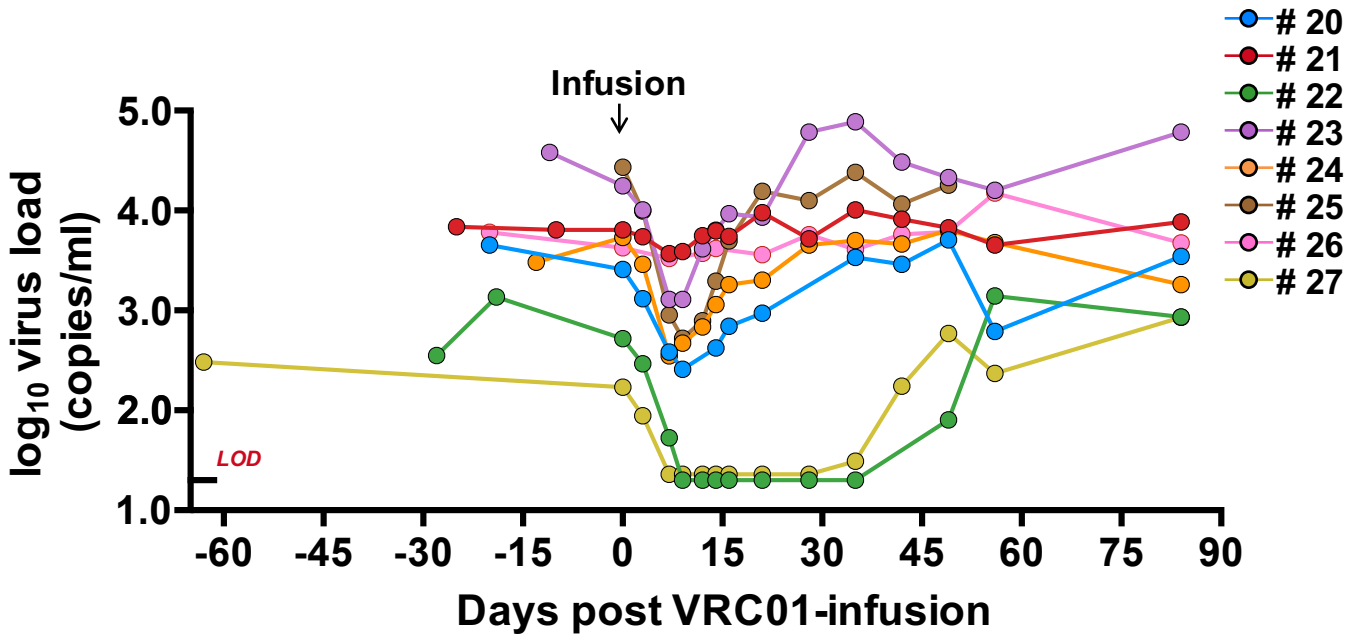
Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117

Marina Caskey[1]*, Florian Klein[1]*, Julio C. C. Lorenzi[1], Michael S. Seaman[2], Anthony P. West Jr[3], Noreen Buckley[1], Gisela Kremer[4,5], Lilian Nogueira[1], Malte Braunschweig[1,6], Johannes F. Scheid[1], Joshua A. Horwitz[1], Irina Shimeliovich[1], Sivan Ben-Avraham[1], Maggi Witmer-Pack[1], Martin Platten[4,7], Clara Lehmann[4,7], Leah A. Burke[1,8], Thomas Hawthorne[9], Robert J. Gorelick[10], Bruce D. Walker[11], Tibor Keler[9], Roy M. Gulick[8], Gerd Fätkenheuer[4,7], Sarah J. Schlesinger[1] & Michel C. Nussenzweig[1,12]



VRC01 Phase I Trial

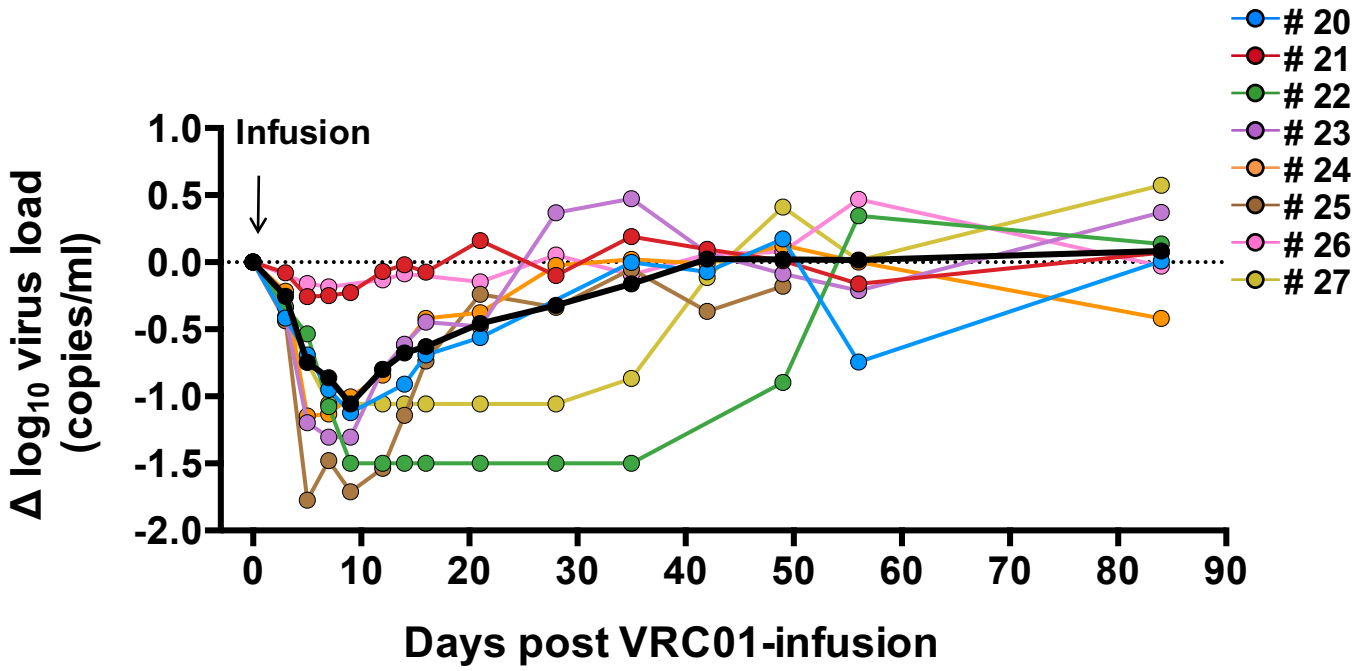
8 HIV-1 infected subjects



3 Patterns

Lynch, Ledgerwood et al. Science Transl Med (2015)

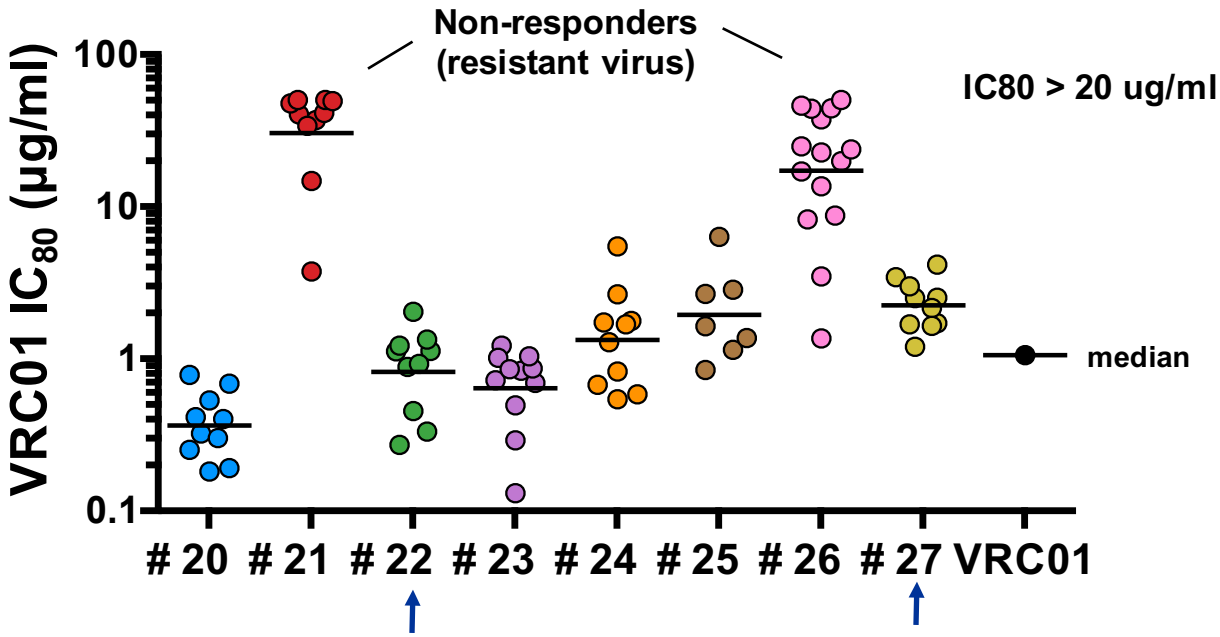
VRC01 Phase I Trial



3 Patterns

Lynch, Ledgerwood et al. Science Transl Med (2015)

Pre-infusion resistance to VRC01

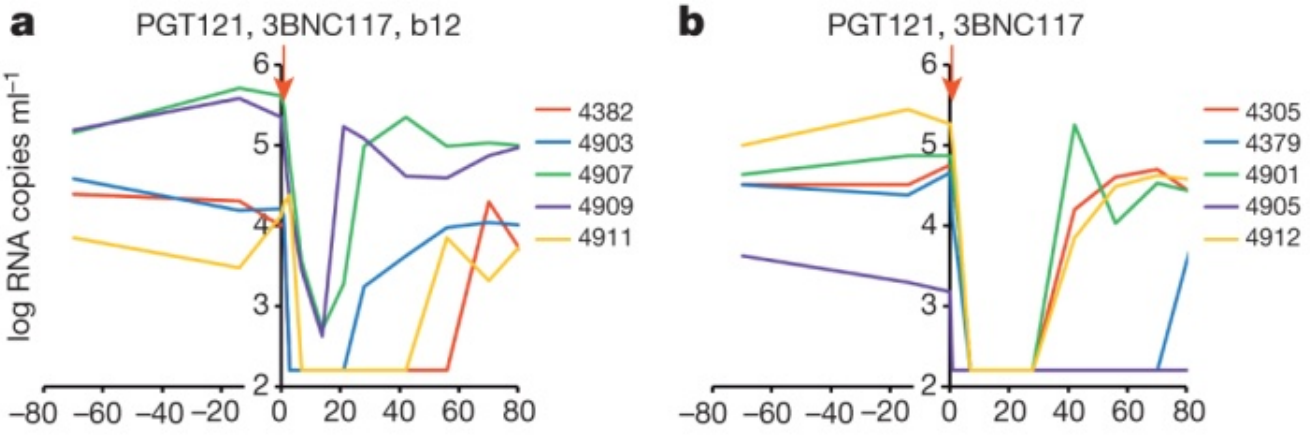


Two low responder had most resistant viral quasi-species

Subjects 22 and 27 had low initial VL and went to undetectable

Lynch, Ledgerwood et al. Science Transl Med (2015)

mAb Combination therapeutic effect in NHP SHIV model



Therapeutic Efficacy of Potent Neutralizing HIV-1-Specific Monoclonal Antibodies in SHIV-Infected Rhesus Monkeys

DH Barouch, MC Nussenzweig, DR Burton, et al.

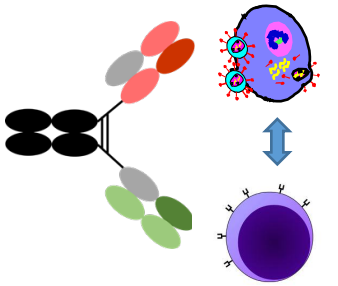
Antibody-Mediated Immunotherapy of Macaques Chronically Infected with SHIV Suppresses Viraemia

M Shingai, MC Nussenzweig, MA Martin, et al.

Nature (2013)

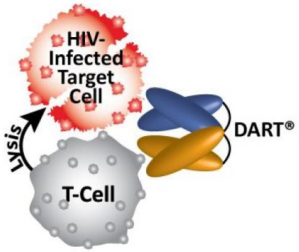
Bi-functional antibodies
(e.g. bind HIV and CD3/CD8)

Bispecific
T-cell engager
(BITE)



Infected
CD4 cell

CD3+CD8+
Killer T-cell

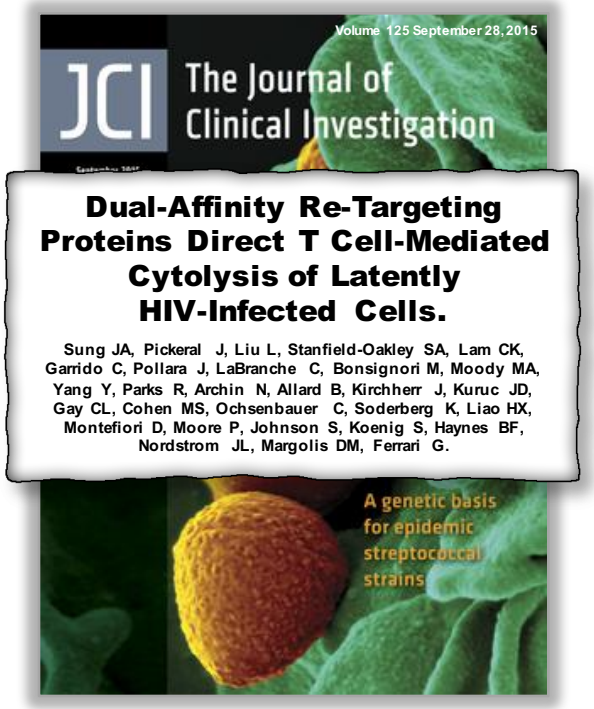


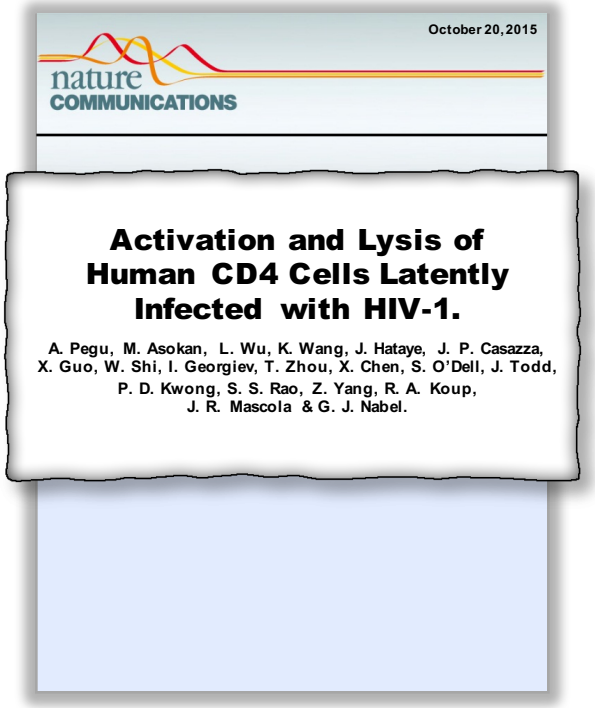
Dual-affinity
re-targeting
protein
(DARTs)

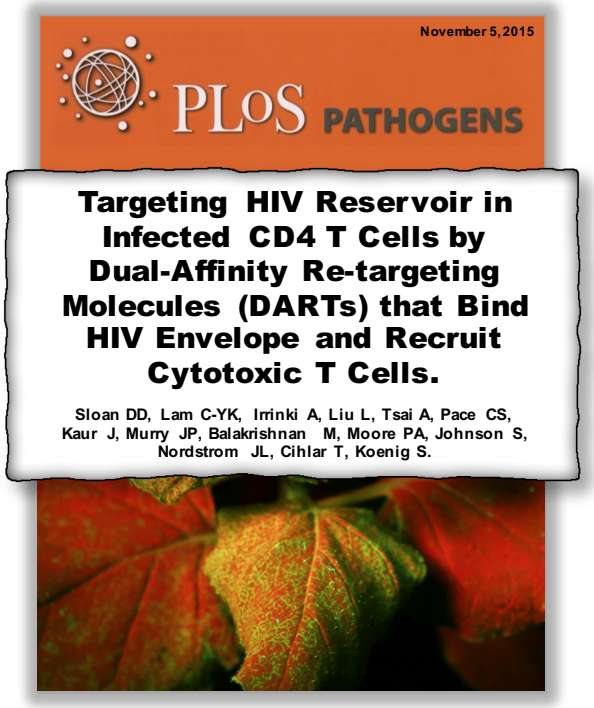
Potential to mediate cell killing

- Antibody platforms exist and entered clinical trials (Cancer Rx)
- For HIV-1: *In vitro* proof-of-concept of cell killing

Bifunctional: DARTs and BITEs
(in vitro proof-of-concept)







Little or no in vivo data yet , even in animal models – emerge in next years

Lessons Phase I and animal model studies

- **HIV-1 mAbs are biologically active – single mAb can reduce plasma virema 1-2 log10**
- **Selection for resistant strains can occur rapidly in setting of incomplete viral suppression**
- **Combinations of mAbs (or mAbs + ARV drugs) are likely required for effective viral suppression**
- **Impact on viral reservoir will likely require longer-term administration, potentially with LRAs, and will require prospective clinical studies**

Antibodies for Prevention and Treatment of HIV-1 (Summary)

- Rapid advancement of potent HIV-1 mAbs into clinical trials (since first discovery in 2009)
- Antibodies classically used to prevent infection: Phase IIb study for HIV-1 prevention (PrEP) will begin in next few months
- Treatment: mAb could contribute to long term viral suppression; target and kill infected cells; Require careful clinical studies
- Improved mAbs continue to be discovered or engineered
- Clinical data needed to stimulate future development of antibodies for prevention or treatment of HIV-1 infection

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