Therapeutic HIV Vaccines and Broadly Neutralizing Antibodies

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe goals and challenges of therapeutic vaccine development
- Describe the status of clinical development of broadly neutralizing antibodies (bNAbs) for treatment
- Describe advances in bNAbs

Slide 3 of 40

Outline

- Why pursue ART-free approaches like therapeutic vaccines and antibodies to HIV-1 treatment?
- What are therapeutic vaccines
- What are broadly neutralizing antibodies - bNAbs
- Advances in bNAbs for treatment and potential for cure

Slide 4 of 40

Why Pursue ART-free Approaches to Treatment?

- Impossible to eradicate HIV from latent viral reservoirs with ART alone
- Important to have OPTIONS including agents with potential for less frequent dosing
- Gaps in ART delivery
- Long term side effects of ART
- Adherence and retention in care remain a challenge

Is it possible to achieve sustained HIV-1 remission/control without antiretrovirals?

Slide 5 of 40

Rationale for Therapeutic HIV-1 Vaccines

- Evidence from individuals whose immune system naturally control HIV-1 without ART (LTNP, elite controllers)
  - effective host mediated anti-HIV immunity is possible
- **Is it possible to augment the host immune response to kill infected CD4 T cells and neutralize circulating virions?**

Pantaleo &Levy, Curr Opin HIV AIDS 2013
Stephenson Curr Opin HIV AIDS 2018

Slide 6 of 40

Goals of a Therapeutic Vaccine

- **At minimum**
  - Make simplified ART regimens possible
  - Allow for periodic Analytic Treatment Interruption [ATI]
- **Optimally**
  - Eliminate need for ART either by eradicating the virus or inducing host immune response capable of controlling virus replication

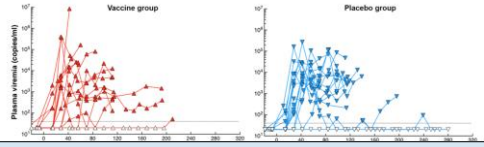
In placebo-controlled studies that included interruption of ART to measure efficacy, therapeutic vaccine not successful in achieving durable suppression of HIV viremia.

Slide 7 of 40

Science Translational Medicine

A randomized controlled safety/efficacy trial of therapeutic vaccination in HIV-infected individuals who initiated antiretroviral therapy early in infection

Michael C. Sneller,[1] J. Shawn Justement,[1] Kathleen R. Gittens,[2] Mary E. Petrone,[1] Katherine E. Clarridge,[2] Michael A. Proschan,[3] Richard Kwan,[2] Victoria Shi,[1] Jana Blazkova,[1] Eric W. Refsland,[1] Daryl E. Morris,[4] Kristen W. Cohen,[4] M. Juliana McElrath,[4,5] Rong Xu,[6] Michael A. Egan,[6] John H. Eldridge,[6] Erika Benko,[7] Colin Kovacs,[7,8] Susan Moir,[1] Tae-Wook Chun,[1,*] Anthony S. Fauci[1,*]



- No effect of DNA/rVSV therapeutic vaccination on control of HIV rebound following ART interruption
- 26% of placebos sustained suppression of viremia after treatment interruption

Slide 8 of 40

Selected Randomized Controlled Trials of Therapeutic Vaccines

Vaccine Name	Population	Latency Reversal Agent	Result
DC-HIV: Dendritic cells loaded w/heat inactivated autologous HIV	ATI	No	Significant/transient decr in VL during ATI, incr T cell responses
ALVAC-HIV, Lipo-6T, IL-2: Canarypox vector (Env, Gag, Pol, Nef), lipopeptide vaccine (Nef, Gag, Pol, IL-2)	ATI	No	Induced HIV-specific CD4 and CD8 T cell responses which predicted virologic control during ATI
HIVAX: mutated HIV strain expressing range HIV proteins	ATI: no placebo	No	Broad responses/Reduced VL vs. pre-ART
DNA/rVSV	ATI in pts who started ART in early infection	No	Vx did not prevent viral rebound; 26% placebos had sustained suppression viremia after ATI
MVA-B: clade B gp120, Gag, Pol, and Nef	ATI	Yes Disulfiram	Safe & immunogenic; no sig effect on VL rebound after ATI or viral reservoir with or without LRA

Garcia et al JID 2011, Levy et al. AIDS 2005; Levy et al AIDS 2006; Tung et al Vaccine 2016; Sneller et al Sci Trans Med 2017; Mothe et al J Antimicrob Chemother 2015

Towards a More Effective Therapeutic Vaccine: Improved Combination Approaches

nature

Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV–infected rhesus monkeys

Erica N. Borducchi[1], Crystal Cabral[1], Kathryn E. Stephenson[1], Jinyan Liu[1], Peter Abbink[1], David Ng'ang'a[1], Joseph P. Nkolola[1], Amanda L. Brinkman[1], Lauren Peter[1], Benjamin C. Lee[1], Jessica Jimenez[1], David Jetton[1], Jade Mondesir[1], Shanell Mojta[1], Abishek Chandrashekar[2], Katherine Molloy[3], Galit Alter[2], Jeffrey M. Gerold[1], Alison L. Hill[3], Mark G. Lewis[4], Maria G. Pau[5], Hanneke Schuitemaker[5], Joseph Hesselgesser[6], Romas Geleziunas[6], Jerome H. Kim[1†], Merlin L. Robb[1], Nelson L. Michael[1] & Dan H. Barouch[1,2]

Ad26/MVA alone	Ad26/MVA + TLR7 agonist
• Induced broad cellular immune responses • No clinically significant decrease in VL setpoint after ATI	• 1.75 log reduction in VL • 2.5-fold delay of viral rebound • 33% monkeys maintained undetectable VL after ATI

Borducchi et al, Nature 2016.

Slide 10 of 40

Therapeutic Vaccines: Take Home Points

- No randomized controlled trials of therapeutic vaccination that induced long-term remission after analytical treatment interruption
- Need vaccines that induce broad host immune responses to recognize diverse escape viral variants after viral rebound
- Therapeutic vaccine may need to be paired with potent latency reversal agent (eg vorinostat) or immune modulators (TLR7 agonist) to induce long-lasting remission

Stephenson, Curr Opin HIV AIDS 2018
Graziani & Angel, JIAS, 2015
Seddiki & Levy, Curr Opin HIV AIDS 2018

Slide 11 of 40

ARS Question 1: Would any of your HIV-infected patients be interested in bNAb based therapies as an alternative to ART?

1. None, my patients are happy taking daily ART
2. Yes but less than 25%
3. Yes, between 26-50%
4. Yes, between 51-75%
5. Yes, more than 76%

Slide 12 of 40

Potential use of Abs for HIV-1 Treatment

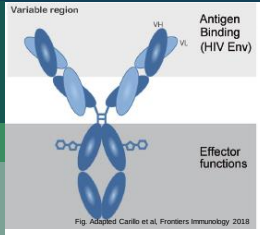


Fig. Adapted Carillo et al. Frontiers Immunology 2018

- Block HIV replication by inhibiting viral entry into cell (neutralizing activity)
- Capable of engaging the host immune system
  - Mediate killing of infected cells **(ADCC)**
- Potential to clear latently infected cells and enhance immune responses against HIV-1
  - Potentially target latent viral reservoir

Slide 13 of 40

ARS Question 2: Broadly neutralizing Antibodies (bNAbs) are being evaluated for treatment and prevention of HIV. Which statement is TRUE with respect to bNAbs

bNAbs can be engineered to extend their half-life by mutating the Fc portion of the Ab

Bispecific and trispecific bNAbs are being evaluated for treatment and prevention and have been shown in clinical studies to be well tolerated

Current formulations of bNAbs have to be administered approximately every 2 weeks to maintain constant serum levels

Both A and B

Both A and C

Both B and C

Start the presentation to see live content. Still no live content? Install the app or get help at PollEv.com/app

Slide 15 of 40

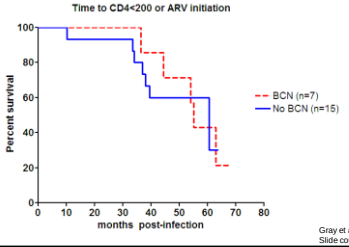
What are Broadly Neutralizing Antibodies against HIV-1

- Minority of HIV-1 infected individuals (5-10%) develop the ability to neutralize various heterologous viruses from different subtypes within 2-3 years after infection
- Very broad and potent neutralizing antibodies have been isolated from these individuals
- Bind to relatively conserved regions of Env
- Passive transfer of bNAbs investigated for treatment, eradication/cure, prevention, and to guide preventive vaccine design

Walker et al. Science 2009; Doria-Rose etal, Nature 2014; Liao et al. Nature 2013; Bonsignori et al. Cell 2016; Martin van Gils, AIDS Conference 2018

Slide 16 of 40

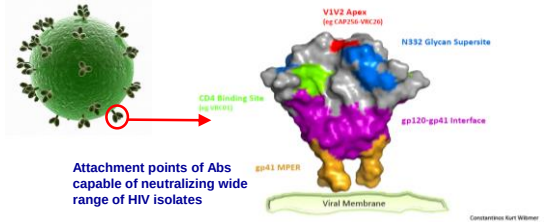
Broadly cross-neutralizing antibodies have NO impact on HIV disease progression: CAPRISA 002 Cohort



Gray et al J of Virology 2011
Slide courtesy L. Morris

Slide 17 of 40

Broadly Neutralizing Antibody Targets on the HIV-1 Envelope Trimer



Attachment points of Abs capable of neutralizing wide range of HIV isolates

Slide 18 of 40

Examples of Broadly Neutralizing Abs in Clinical Development

N332 Glycan Supersite:
PGT121, 10-1074

V1V2 Glycan:
PGT141-45, PGDM1400, CAP256-VRC26

CD4 Binding Site:
VRC01, 3BNC117, VRC07-523

Trimer (gp120/41)
8ANC195, PGT151

gp41 MPER:
10e8

Slide adapted from presentations the Subramaniam, Kwong, and Wilson groups.

Slide 19 of 40

Passive Infusion of Broadly Neutralizing Antibodies Delays the Rebound of Plasma HIV Viremia Following Interruption of ART

LETTER

doi:10.1038/nature18929

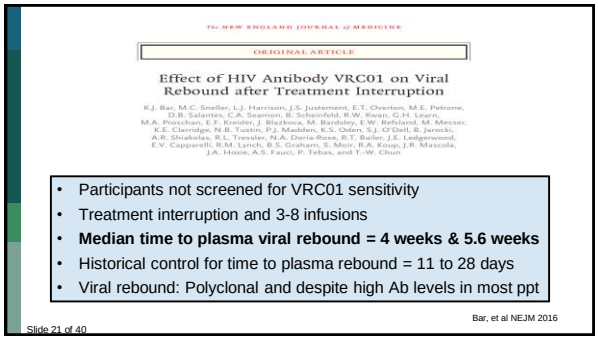
HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Johannes F. Scheid[1,2]*, Joshua A. Horwitz[3]*, Yoram Bar-On[1], Edward F. Kreider[2], Ching-Lan Lu[2], Julio C. C. Lorenzi[1], Anna Feldmann[4], Malte Braunschweig[4], Lilian Nogueira[1], Thiago Oliveira[1], Irina Shimeliovich[1], Roshni Patel[1], Leah Burke[1], Yehuda Z. Cohen[1], Sonya Hadrigan[1], Allison Settler[1], Maggi Witmer-Pack[1], Anthony P. West Jr[4], Boris Juelg[2], Tibor Keler[5], Thomas Hawthorne[5], Barry Zingman[6], Roy M. Gulick[6], Nico Pfeifer[4], Gerald H. Learn[3], Michael S. Seaman[2], Pamela J. Bjorkman[4], Florian Klein[1,2,7], Sarah J. Schlesinger[1], Bruce D. Walker[2,8], Beatrice H. Hahn[9], Mitchell C. Nussenzweig[1,2] & Marina Caskey[1]

- 13 ART-treated participants with 3BNC117-sensitive viruses
- Analytical treatment interruption (ATI) and 2 - 4 infusions
- **Infusions delayed viral rebound average of 8.4 weeks vs. historical controls**
- Rebound virus with low diversity and resistance to 3BNC117 in most ppt

Slide 20 of 40

Scheid et al Nature 2016



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption

K.J. Bar, M.C. Sneller, L.J. Harrison, J.S. Justement, E.T. Overton, M.E. Petrone, D.B. Salantes, C.A. Seamon, B. Scheinfeld, R.W. Kwan, G.H. Learn, M.A. Proschan, E.F. Kreider, J. Blazkova, M. Bardsley, E.W. Refsland, M. Messer, K.E. Clarridge, N.B. Tustin, P.J. Madden, K.S. Oden, S.J. O'Dell, B. Jarocki, A.R. Shiakolas, R.L. Tressler, N.A. Doria-Rose, R.T. Bailer, J.E. Ledgerwood, E.V. Capparelli, R.M. Lynch, B.S. Graham, S. Moir, R.A. Koup, J.R. Mascola, J.A. Hoxie, A.S. Fauci, P. Tebas, and T.-W. Chun

- Participants not screened for VRC01 sensitivity
- Treatment interruption and 3-8 infusions
- **Median time to plasma viral rebound = 4 weeks & 5.6 weeks**
- Historical control for time to plasma rebound = 11 to 28 days
- Viral rebound: Polyclonal and despite high Ab levels in most ppt

Bar, et al NEJM 2016

Slide 21 of 40

Selected Clinical Trials involving bNAbs in HIV-1 infected individuals

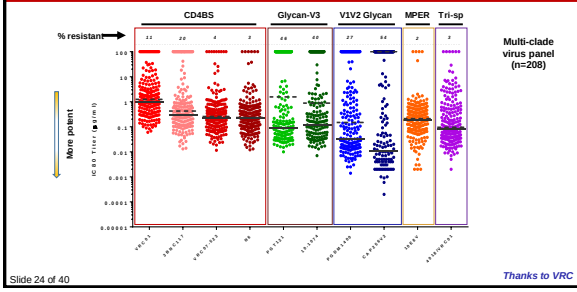
Antibody	Population	Target	Major Findings
VRC01	On ART and viremic	CD4-bs	• VL Decr 1.1–1.8 $\log_{10}$ after single infusion • ATI: viral strains not selected for VRC01 sensitivity Median delay in viral rebound of 4 and 5.6 wks after ART d/c • $t_{1/2}$ 12 days in HIV+
3BNC117	On ART & viremic	CD4-bs	• Average VL Decr of 1.48 $\log_{10}$ after single dose • ATI: Viral strains screened for 3BNC117 sensitivity: Average delay in viral rebound of up to 9.9 wks after ART d/c & multiple doses • $t_{1/2}$ 9.6 days in HIV+
10-1074	On ART and viremic	V3 loop	• VL Decr 1.52 $\log_{10}$ after single infusion • Emergence of resistant viral strains in few wks (sensitive to non-V3 loop Ab) • $t_{1/2}$ 12.8 days in HIV+
PGT121 *CROI 2019*	On ART and viremic	V3 loop	• High baseline VL: 1.7 $\log_{10}$ drop with rebound resistant virus (5/9 responders) • Low baseline VL: 2 pts suppressed >6 months
PGDM 1400	Viremic	V1/V2 loop	• Ongoing. Will evaluate PDGM1400 +/- PGT121

Optimizing bNAbs for the Treatment of HIV Infection

- More potent antibodies
- Extend half-life of antibodies
- Combinations of antibodies
- Next generation of antibodies

Slide 23 of 40

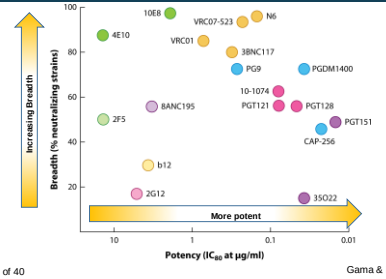
Potency & Breadth: In Vitro Neutralization Profiles



Slide 24 of 40

Thanks to VRC

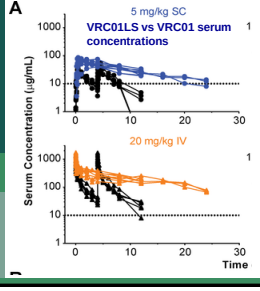
Potency & Breadth



Slide 25 of 40

Gama & Koup Annual Rev Med 2018

Antibody Modifications Extend Half-life: Intermittent Dosing



- **LS mutation:** Two amino acid mutation in Fc region of the Ab
- Increased affinity for neonatal Fc receptor (FcRn): extend **plasma half-lives**
- Potential for less frequent administration of mAb
- Increased Ab at mucosal surface in animal studies
- Studies with LS versions are ongoing

Julie Ledgerwood et al. J Virol. 2014
Gaudinski et al, PLOSMedicine 2018

Modifications of Fc region can also Increase Effector Functions

- Fc modifications to increase antibody dependent cell-mediated cytotoxicity (ADCC) or phagocytosis
  - Potentially reduce or target the HIV reservoir
- **CROI 2019:** Engineered variant of PGT121 with enhanced effector function (GS-9722)
  - Enhanced killing of HIV infected CD4+ T-cells by NK cells

Thomsen et al. Abstract 356. CROI 2019

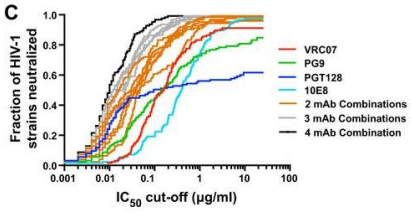
Slide 27 of 40

Potential of Combination bNAb Therapy for the Durable Control of HIV

- In studies to date, rebound viruses did not demonstrate increased resistance to other Ab that target different envelope epitopes
- Combinations of two or more bNAbs are likely to lead to more robust and sustained antiviral effects
  - Increase overall breadth and potency
  - Prevent emergence of resistance

Slide 28 of 40

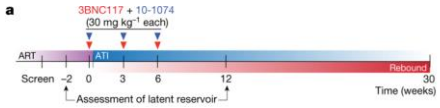
Combining Abs to Improve Potency and Breadth



Rui Kong et al. J. Virol. 2015;89:2659-2671

Slide 29 of 40

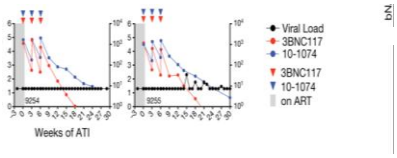
Combination bNAbs and Treatment Interruption



- Patients Virologically suppressed on ART >24 months
- Pre-screened for 3BNC117 and 10-1074 sensitivity
- 3 infusions of combination Abs during Treatment interruption (ATI)
- Median duration of suppression with **Ab-sensitive virus**: 21 weeks
- Median duration of suppression with **Ab-resistant virus**: 5 weeks

Mendoza et al Nature 2018

Combination bNAbs and Treatment Interruption



- 2 participants maintained virologic suppression long after Ab levels waned
  - 1 remains suppressed
- **Important to explore if bNAbs can be a component of cure strategies**

Mendoza et al Nature 2018

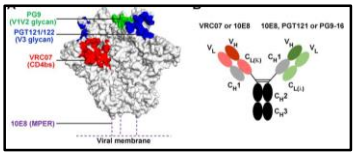
Combination bNAbs

- Combinations will be necessary to increase overall breadth and potency and to prevent the emergence of resistance
- Number of bNAbs required may differ based on the indication
  - **In active viremia:** combination of 3 or 4 current bNAbs may be required to cover the swarm of viruses present
- **Screening for bNAb sensitity pre-therapy to potentially reduce number of bNAbs required for Rx and amplify efficacy**
  - **CROI 2019:** Potential of PhenoSense HIV nAB Assay

Reeves et. Abstract 305. CROI 2019

Next Generation bNAb: Bispecific and Trispecific

- Engineered Ab (single protein) that targets multiple independent epitopes on virus
- Potentially lower likelihood of escape mutations compared to single Ab or combination of 2-3 Ab
- Enhanced potency and breadth

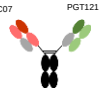


Monteiori et al. Cell, 2016; Huang et al, Cell 2016; Asokan et al, J Virol, 2015; Xu et al. Science 2017

Bispecific Antibodies Concept

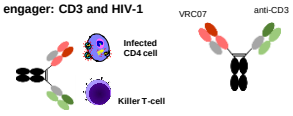
Two different antibody binding arms on one IgG

Broader, more potent, less viral escape



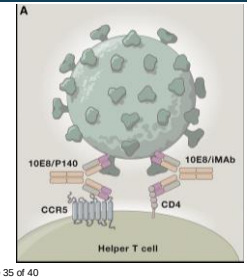
Bispecific T-cell engager: CD3 and HIV-1

Mediate cell killing



Slide courtesy John Mascola

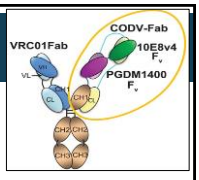
Example of Bispecific Ab: 10E8.4/iMab



- **One arm** of IgG binds an epitope in the membrane proximal external region (MPER) of gp41
- The **other arm** binds either the HIV-1 CD4, or, CCR5 co-receptor molecule on T-helper cell
- Phase 1, first in human, clinical study for treatment and prevention is starting 2019

Y. Huang et al. Cell 2016.

Trispecific Ab



- Combines specificities of 3 Abs binding to
  - CD4 binding site & V1V2 glycan site
  - membrane-proximal external region
- ***New data from CROI 2019***
  - Potent Fc effector functions in animal studies: promising for mediating ADCC and phagocytosis
  - Potent suppression of viral replication in viremic SHIV infected animals
- Phase 1 ascending dose study in HIV-infected infected starting 2019Q1

Ling Xu et al, Science 2017
Pegu A et al, Abstract 28, CROI 2019

Slide 36 of 40

Desirable Properties of bNAbs

- Every 6 month regimen of passive transfer of **combination** of bNAbs
- SC injection
  - easier to implement
- Replaces daily antiretroviral therapy
- Safe & well tolerated
- Scalable [Inexpensive]
- Manufacturing: public private partnerships

Slide 37 of 40

Broadly Neutralizing Antibodies: Next Steps

- A new generation of highly potent and broadly neutralizing HIV-1 antibodies has been identified
- HIV-1 exhibits genetic diversity and viral escape mechanisms.
  - Prudent to consider using a combination approach
  - Potential to screen for bNAb sensitity prior to therapy?
- Like ART, combinations of mAbs could reduce the likelihood of viral escape, and increase neutralization breadth
- Alternative delivery systems: gene delivery viral vectors Vector-based antibody production in vivo

Slide 38 of 40

Summary

- bNAbs are a promising approach towards durable control of HIV rebound in absence of ART
  - also actively pursued for prevention both as passive prevention and platform for design of vaccines
- No randomized controlled trials of therapeutic vaccination that induced long-term remission after analytical treatment interruption
- Combination strategies of bNAbs, therapeutic vaccines, immunomodulators (e.g. TLR7 agonist) may be needed to diminish the reservoir

Slide 39 of 40

Acknowledgements

- Scott Hammer
- John Mascola
- Larry Corey
- Shelly Karuna
- Lynn Morris
- David Montefiore

Slide 40 of 40

Question-and-Answer

Slide 40 of 40