HIV-1 bNAbs: Looking Ahead

Marina Caskey, MD
Professor of Clinical Investigation
The Rockefeller University, New York, NY

This activity is jointly provided by Physicians’ Research Network and the Medical Society of the State of New York.
Outline

• Potential roles of HIV-1 bNAbs

• HIV-1 bNAbs clinical data: *Prevention, Therapy, Cure*

• Advances: promising preclinical data, new technologies & delivery systems
Single B cell cloning methods allowed the identification of many bNAbs targeting different epitopes

**HIV bNAbs in Clinical Development**

- **V1/V2 Glycan**
  - PDGM1400, CAP256-VRC26LS,
  - rAAV1-PG9

- **CD4 binding site**
  - VRC01, VRC01LS, 3BCN117,
  - 3BNC117-LS, VRC07-523LS,
  - rAAV8-VRC07, N6-LS, 1-18

- **N332 Glycan Supersite (V3 Loop)**
  - 10-1074, 10-1074-LS,
  - PGT121, GS-9722

- **Clustered N-glycans**
  - gp120-gp41 Interface

- **MPER**
  - 2F5, 4E10, 10e8VLS

Adapted from Mouquet *et al.*, Trends Immunol 2014
Potential roles of bNAbss in HIV-1 infection

**Treatment or prevention:**
Long-acting alternative to ART

**Safety:** As a class, mAbs are considered safe

**Adherence:** mAbs have long half-lives, that can be prolonged to > 2 months

**Provide immediate protection**

**Treatment-free remission:**
Immune-mediated control of viral replication

mAbs might “boost” or “improve” existing immune responses

mAbs have potential to directly eliminate infected cells and therefore interfere with the HIV latent reservoir
Clinical Experience: Safety & Pharmacokinetics

• **Safety:** 15 “new generation” bNAbs tested in clinical studies to date (including bi- and tri-specific antibodies)
  
  • Well tolerated: AMP studies: repeated VRC01 >30,000 doses to >3,000 participant
  - Infrequent infusion related reactions (most mild).
    
    Pediatric studies: VRC01LS+10-1074 in Children on ART
    
    Capparelli *et al*, CROI 2021
  
  • 10e8.VLS - Grade 3 local reactogenicity, study suspended

• **PK:** Half-lives of naturally occurring bNAbs range between 2-3 weeks
  
  • Half-life can be extended by ~3-fold
HIV-1 bNAbs: Prevention

Antibody Mediated Prevention (AMP) Studies: VRC01 showed overall prevention efficacy of only 18.1%

Corey L, NEJM 2021
VRC01 achieved *prevention efficacy* against *neutralization sensitive* viruses

• Prevention can be achieved by bNAb administration
   *However, it is dependent on neutralization sensitivity of circulating strains* (*only 30% VRC01 sensitive*)

• *In vitro* neutralization assays can predict outcome
   *But predictions based on TZM/bl assays against pseudoviruses were about 1 log “off” from required in vivo sensitivity against “real viruses”.*

> Viruses from placebo arm tested for other bNAbs – triple combination can achieve coverage of 90%

Corey L, NEJM 2021
Antibody Mediated HIV Prevention: Looking Ahead

**Challenges:**
- Antibody resistance among circulating strains is a major challenge
- Combination of potent antibodies will be needed
  - Will 2 or 3 long-acting antibodies be sufficient?
- Manufacturing challenges / high cost - SARS CoV-2 has shown these may be addressed
- LA-cabotegravir has shown efficacy and others are moving into efficacy studies
  - Long-term safety? Risk of resistance emerging to standard therapy?

**Opportunities:**
- Antibodies may provide a safe/viable alternative for long-term prevention:
  - e.g. SC/IM delivery or yearly IV infusions (?)
- May have a niche in special settings: e.g. PMTCT
HIV-1 bNAbs: Therapy

Effects on Plasma Viremia

- Across studies: A subset of participants with baseline bNAb resistance
- Reduction in plasma viremia of \( \approx 1.5 \log_{10} \text{cp/ml} \).
- Viral suppression only achieved with low starting VLs
- Selection of resistant viral strains with monotherapy.
  - Prolonged viral suppression observed in PGT-121 in 2 participants with low VLs (< 1,000 cp/ml) (Stephenson, CROI 2019)

Also tested/planned: VRC01, VRC01LS, N6LS, 10-1074, PGT121, PDGM-1400, CAP256V2LS

Caskey, Klein et al., Nature 2015
Bar-On, Nat Med et al. 2018
HIV-1 bNAbs: Therapy

*Engineered antibodies: Increased Potency and/or Breadth*

**Mono-specific**

VRC07-523LS: CD4bs bNAb with superior breadth & potency

Chen, IAS 2019

**Bi-specific**

iMab/10e8v2.0

**Tri-specific**

VRC01/10E8v4-PGDM1400-LS (SAR441236)

Sobieszczyk, R4P 2021:

- Good safety profile
- Detected in serum – PK analysis ongoing
- No neutralizing ADA (except for 1 participant)
- VL decline of 1.5 log_{10} cp/ml

A5377:

- Enrollment ongoing
- No safety concerns to date

*Binding to different epitopes*
HIV-1 bNAb: Therapy

Engineered antibodies: Increased Bioavailability

LS mutations (M428L/N434S) enhance FcRn binding and prolong half-life

VRC01-L5

10-1074-L5

3BNC117-L5

VRC01-L5 $t_{1/2}$ 71 days
(vs. VRC01 $t_{1/2}$ of 15 d)

10-1074-L5 $t_{1/2}$ 73.5 days
(vs. 10-1074 $t_{1/2}$ of 24 d)

3BNC117-L5 $t_{1/2}$ 61.3 days
(vs. 3BNC117 $t_{1/2}$ of 17.6 d)

Gaudinski et al, PlosOne 2018

- Half-life of LS variants > 3 fold longer than parental mAbs
- Allows for quarterly SC or yearly IV administration
Combination of two bNAbs: maintains viral suppression in the absence of ART

~ 75% (13 out 17 participants) maintained viral suppression for > 20 wks post ATI
  ➢ 2 maintained suppression for at least 12 months
  ➢ Early rebounds associated with resistance to at least 1 of the bNAbs.

Scheid et al, Nature 2016
Mendoza et al, Nature 2018
During combination bNAb therapy
Gag-specific T cell responses were enhanced

During ART-mediated viral suppression

During bNAb-mediated viral suppression

Niessl et al, Nat Med 2020
HIV bNAbs: Clinical Findings to Date

• bNAbs are generally **safe** in humans and have **half-lives of 2 and 3 wks.**
  • LS mutations prolong half-lives by > 3-fold.

• Proof-of-principle that **antibody-mediated protection can be achieved** against sensitive viruses
  • *But also highlights need for improved breadth and potency*

• In viremic individuals, single bNAb infusions lead to **significant decline is plasma viremia** ( ~ 1.5 log copies/ml). Resistant strains are selected.

• A combination of two bNAbs lowers viremia and maintains viral suppression for **longer period** of time than monotherapy.
  • *De novo* resistance to both antibodies did not occur.

• Short-term bNAb studies so far did not show significant **changes in latent reservoir size**.

• Studies suggest that humoral & T cell responses can be enhanced during bNAb therapy.
HIV-1 bNAbs: Cure or Remission

By **direct antiviral activity** and **Fc-mediated mechanisms**, bNAbs have the potential to:

- **Limit the establishment**
  - Early ART

- **Reduce**
  - Resistance to infection
  - Block/lock viral replication
  - Induce viral replication

- **Control**
  - Depletion of infected cells
  - Enhance immunity

- *bNAb activity depends on binding to antigen*
  - Can CD8⁺ T cell modulation be achieved in the presence of ART?
  - Will control require additional immune modulation and antigen expression: vaccines, TLR agonists or cytokines, as in cancer therapies?
bNAb Studies in NHP Lead to Long-term Viral Control in a Subset of Animals

- **Early bNAb therapy** leads to CD8 mediated control of SHIV-AD8-E infection in NHP

  - **7/12 controllers**
    - Viral RNA copies/ml
    - DG34: 1.0E+08, 1.0E+06, 1.0E+04
    - DF7G: 1.0E+08, 1.0E+06, 1.0E+04

- **Accumulation of follicular CXCR5+ CD8+ T cells in LNs**

  - Nishimura et al, JEM 2020

- **Early therapy with Fc-engineered bNAbs** control viremia

  - SHIV-AD8-EO IR challenge
    - VRC07-523LS + PGT121
    - VRC07-523LS/DEL + PGT121/DEL
    - No tx

  - WT bNAb Tx: 1/6 aviremic
  - DEL bNAb Tx: 3/6 aviremic

- **Fc-modified bNAb-treated monkeys** developed a distinct LN transcriptomic profile

  - Dias J. et al CROI 2021
bNAbs in acute infection: clinical trials planned/underway

<table>
<thead>
<tr>
<th>Name</th>
<th>Intervention</th>
<th>Population</th>
<th>Status</th>
<th>ATI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV398 (MHRP - Ake)</td>
<td>- VRC01 &gt; ART</td>
<td>Acute infection</td>
<td>Enrolled / analysis ongoing</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>- VRC01 + ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5388 (ACTG – Crowell/Hsu)</td>
<td>- VRC07-523LS + PGT121BIJ414LS + ART</td>
<td>Acute infection</td>
<td>Planned 2021</td>
<td>yes</td>
</tr>
<tr>
<td>RHVIERA (Pasteur – Saez-Cirion)</td>
<td>- 3BNC117-LS + 10-1074-LS + ART</td>
<td>Acute infection</td>
<td>Planned 2021</td>
<td>yes</td>
</tr>
</tbody>
</table>
Combination Immunotherapy to increase antigen expression and modulate innate and adaptive responses

**bNAb + IL15 (N-803)**
SHIV-AD8 - ART at ~ 7 weeks

- NK and T cell activation
- CD8 depletion led to rebound

**bNAb + TLR7**
SHIV-162.P3 – ART at 1 wk

- NK and T cell activation
- No HIV-1 DNA and T cell responses in LNs

*Borducchi E et al, Nature 2018*  
(*Nkolola J et al, CROI 2020 (Chronic Infection)*

**Vaccine + bNAb + TLR7**
SHIV-162.P3 – ART at 1 wk

- CD4 activation and vaccine T and B cell responses
- VL setpoint and Gag+ responses correlated with control

**Vehicle control**

6/8 controllers

**Log SHIV RNA cp/ml**

3BNC117+10-1074

5/11 controllers

**Figure 7**

SHIV-162.P3 – ART at 2 wks

- Immune effects (NK cells, T cells) were observed
- **Long-term control achieved in a subset of animals**
  - Mechanisms of control not fully elucidated
  - But evidence of CD8 involvement in control
- Related to reservoir size/composition?

**Hsu D, Plos Pathogens in press**
## Combination immunotherapy: clinical trials planned/underway

<table>
<thead>
<tr>
<th>Name</th>
<th>Intervention</th>
<th>Population</th>
<th>Status</th>
<th>ATI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROADMAP (Sogaard/Caskey/Fatkenheuer)</td>
<td>3BNC117 Romidepsin</td>
<td>Chronic</td>
<td>CROI2020</td>
<td>yes</td>
</tr>
<tr>
<td>eCLEAR (Sogaard/Fidler)</td>
<td>3BNC117 Romidepsin</td>
<td>Early infection (viremic)</td>
<td>Late follow up</td>
<td>yes</td>
</tr>
<tr>
<td>A5386 (ACTG – Wilkin/Caskey/Jones)</td>
<td>VRC07-523LS 10-1074 N-803</td>
<td>Chronic</td>
<td>Planned 2021</td>
<td>yes</td>
</tr>
<tr>
<td>U01 – RU/Penn/Cornell (Caskey/Wilkin/Tebas)</td>
<td>3BNC117-LS 10-1074-LS N-803</td>
<td>Chronic</td>
<td>Planned 2021</td>
<td>yes</td>
</tr>
<tr>
<td>BEAT HIV2 (Monaner/Tebas)</td>
<td>3BNC117 Type I IFN</td>
<td>Chronic</td>
<td>Ongoing</td>
<td>yes</td>
</tr>
<tr>
<td>TITAN (Sogaard/Lewin)</td>
<td>3BNC117 10-1074 TLR9</td>
<td>Chronic</td>
<td>Ongoing</td>
<td>yes</td>
</tr>
<tr>
<td>amfAR/UCSF (Deeks)</td>
<td>VRC07-523LS 10-1074 DNA/MVA TLR9</td>
<td>Treated during acute infection</td>
<td>Ongoing</td>
<td>yes</td>
</tr>
<tr>
<td>A5374 (ACTG – Riddler/Gay/Mellors)</td>
<td>3BNC117-LS* 10-1074-LS* ChAd/MVA TLR7</td>
<td>Treated during acute infection</td>
<td>Planned 2021</td>
<td>yes</td>
</tr>
</tbody>
</table>
HIV-1 bNAbs Advances

• New naturally occurring and engineered antibodies with greater breadth and potency:
  • 1-18: a new CD4bs bNAb (Schommers et al., Cell 2020)
  • BISC-1A: V2-V3 Loop bi-specific (Davis-Gardner et al., mBio 2020)

• Delivery systems – long-term (in vivo) secretion of bNAbss
  • AAV Vectors
  • DNA Gene Transfer
  • B Cell Engineering
Sustained production of bNAbs by your own cells

AAV Vectors

Neonatal Delivery of AAV/bNAb Vectors in NHP

- AAV8- eCD4-Ig or AAV8-3BNC117

Results in persistent bNAb serum concentrations for >89 wks

Protection infant rhesus macaques against repeated oral SHIV infection

Martins M, CROI 2021

AAV/bNAb Delivery in Humans

- AAV8-VRC07

- VRC 603: 8 people received AAV8-VRC07 (three doses)
- 2/3 at high dose had sustained production of VRC07.
- ADA responses detected Casazza et al., CROI 2020 (LB 41)

Casazza et al. CROI 2021
Sustained production of bNAbs by your own cells
DNA Gene Transfer

Delivery of multiple dmAb in immunodeficient mice

- Successful expression of multiple mAbs
- Maintain binding and neutralizing activity
- In NHP, achieved serum levels of 5 and up to 30 mcg/mL

Wise et al., JCI 2020
Reprogramming B cells to produce bNAbs

Engineered B cells by CRISPR/Cas9 secrete functional bNAb following immunization in mice

Targeting strategy

Antibody secretion in mice

Engineered B cells by CRISPR/Cas9 enable immunological memory and undergo clonal expansion in vivo

Engineered B Cells Expand in Vivo

B cell clones after immunization

Nahmed et al Nat Commun 2020
State of bNAbs – Future Directions

**Prevention**

- Proof-of-concept for antibody-mediated prevention
- Emerging evidence that bNAbs can maintain viral suppression
- Potential advantages: safety & no selection for ARV resistance
- Challenges: pre-existing resistance & cost
- Future: promising new molecules and delivery systems

**Therapy**

- Early promising data with long-term delivery
- An aspirational goal - likely to require combinations
- Promising results in non-human primates
- Multiple ongoing/planned studies over next 2 yrs
- Early promising data with long-term delivery

**Long-Term Control**

Immune-mediated (Treatment-free)

- Gene editing
- Latency reversal
- Block-and-lock

- NK cells
- Antibodies
- CTLs

Reduce: on ART
Control: off ART

Ndungu McCune, Deeks, Nature 2019
Acknowledgements

Study participants

Rockefeller University
Michel Nussenzweig
Julio Lorenzi
Pilar Mendoza
Christian Gaebler
Jill Horowitz
Katrina Millard
Irina Shimeliovich

Duke University
Georgia Tomaras
David Montefiori

BIDMC Harvard
Michael Seaman
James Whitney

Dartmouth
Margie Ackerman

University of Montreal
Daniel Kaufmann

Caltech
Pamela Bjorkman

Weill Cornell Medicine
Trip Gulick
Brad Jones
Tim Wilkin

Albert Einstein
Harris Goldstein
Barry Zingman
Kathy Anastos

Univ. of Pennsylvania
Beatrice Hahn
Pablo Tebas
Katie Bar

Wistar
Luis Montaner

Cologne University
Florian Klein
Gerd Fatkenheuer

Fred-Hutch
Julie McElrath
Allan deCamp

Univ. of Washington
Connie Celum

Aarhus University
Ole Soogard

IAVI
Pat Fast

MGH
Raj Gandhi
Bruce Walker
Johannes Scheid

Brigham & Women’s
Lindsey Baden

Special Thanks!!

Peter Hunt
Sarah Fidler
Ole Soogard
Katie Bar
Pablo Tebas

Elaine Abrams
Steve Deeks
Sandy Vasan
Mauricio Martins
Lucio Gama
Thank You for Your Attendance!

Please visit us at:

www.prn.org