Antibodies for Prevention and Treatment of HIV-1 Infection

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Talk Outline

- Background on HIV-1 neutralizing antibodies
- Antibodies to prevent HIV-1 infection
- Potential role in treatment of infection

Disclosure: VRC01 was isolated in my laboratory at VRC, NIAID, NIH. I am listed as inventor on an NIH patent for VRC01
Cryo-EM Structure of a Fully Glycosylated Soluble Cleaved HIV-1 Envelope Trimer

Crystal Structure of a Soluble Cleaved HIV-1 Envelope Trimer.
Science. 2013 Dec 20;342(6165):1477-83

BG505 SOSIP
Sanders, Moore et al.
Epitopes on Env Trimer

CD4-binding site

V2 apex (glycan)

High-mannose Patch (V3-glycan)

gp120-gp41 interface

gp41 MPER

PG9

PGT128

VRC01

8ANC195

Peter Kwong, Jonathan Stuckey
In Vitro Neutralization Profiles
(190 Diverse strains of HIV-1)

% viruses resistant

More potent

IC80 Titer (μg/ml)

Variation in breadth of coverage

Mark Louder, Bob Bailer et al.
Two HIV-1 Antibodies: Improved Potency and Breadth

Fraction viruses neutralized

0.001 0.01 0.1 1 10 100
0.0
0.2
0.4
0.6
0.8
1.0
ug/ml

VRC07
PGT128

Experimental Mix
Theoretical Mix

Two HIV-1 Antibodies: Improved Potency and Breadth
Talk Outline

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Long History of Antibodies to Prevent Viral Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Product Description</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Measles</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Polio</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus Immune Globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Immune serum globulin (ISG)</td>
<td>Prevention (travel)</td>
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<tr>
<td>Hepatitis B</td>
<td>Hepatitis B Immune Globulin</td>
<td>Post Exposure</td>
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<tr>
<td>Rabies</td>
<td>Rabies Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>RSV</td>
<td>mAb (palivizumab) for prophylaxis of high risk infants</td>
<td>Prevention in High Risk Infants</td>
</tr>
<tr>
<td>VZIG</td>
<td>Varicella Zoster Immune Globulin</td>
<td>Post Exposure</td>
</tr>
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Most effective vaccines induce antibodies that neutralize the pathogen
What do we know about antibodies to prevent HIV-infection?

- SHIV monkey model: 15 years of data showing that potent mAbs can completely block infection
- Many of the new generation mAbs have been tested in this model: VRC01, 3BNC117, PGT121
- The level of plasma antibody needed to protect is not too high – can be achieved by infusing physiological dose of antibody (passive transfer)
HIV Antibodies for HIV-1 Prevention
What we Don’t Know

- No direct evidence that neutralizing antibodies can prevent HIV-1 infection in humans
- No data on the level of antibody need to protect
- If we passively infuse mAb – don’t know how much or how long the antibody would protect
- Does a vaccine have to elicit a neutralization titer of 1:10, 100, or 1:000 to protect?
Vaccine Induced Antibodies

The underlying premise for our work on HIV vaccines is that we are aiming to induce broadly reactive neutralizing antibodies (bNAbs): Type of response likely needed for high level protective immunity.

Neutralizing antibodies that recognize the majority HIV-1 strains
Antibody-mediated Prevention Trial (HVTN 703/HPTN 081)

**Phase IIB efficacy study**

- Can infusion of VRC01 mAb, given every 2 months, prevent acquisition of HIV-1 infection in high risk adults
- Cohorts: High risk women in S. Africa, and high risk men in Americas
- Importantly: Designed to assess the plasma level of antibody associated with protection
VRC01 mAb: Healthy volunteers

Single infusion of 20 mg/kg I.V. into 3 subjects

Plasma levels

VRC, NIAID: Ledgerwood et al, (In press)
VRC01 mAb: Healthy volunteers

Single infusion of 20 mg/kg I.V.

Month 1

Month 2

Phase IIB prevention study: q 8 week dosing
What would clinical study teach us?

- Demonstrate that antibodies can protect humans from acquisition of HIV-1 infection
- Establish the level of antibody needed to protect
- This sets that stage for our vaccine efforts
- Test new vaccines in phase I studies: know what kind of antibody response to look for
- Allow faster iterative vaccine studies – pathway to an effective vaccine
Talk Outline

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Potential use of antibodies for HIV-1 infection

- ARV drugs remain cornerstone of treatment
- Antibody could augment viral suppression by ARV, e.g., used early after infection
- To maintain viral suppression – withdrawal if ARV
- To kill cells expressing virus (e.g., ADCC); part of functional cure approaches

Infected CD4 cell
mAb 3BNC117 (CD4bs): clinical trial


doi:10.1038/nature14411

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

Marina Caskey1*, Florian Klein1*, Julio C. C. Lorenzi1, Michael S. Seaman2, Anthony P. West Jr3, Noreen Buckley4, Gisela Kremer4,5, Lilian Nogueira1, Malte Braunschweig1,6, Johannes F. Scheid1, Joshua A. Horwitz1, Irina Shimeliovich1, Sivan Ben-Avraham1, Maggi Witmer-Pack3, Martin Platten3,7, Clara Lehmann4,7, Leah A. Burke1,8, Thomas Hawthorne9, Robert J. Gorelick10, Bruce D. Walker11, Tibor Keler9, Roy M. Gulick8, Gerd Färkenheuer4,7, Sarah J. Schlesinger1 & Michel C. Nussenzweig1,12

![Graph showing HIV RNA levels over days after infusion.](image-url)
HIV-1 infected viremic subjects (off ARV)
Plasma viral load after VRC01 infusion

Single infusion of VRC01 (40 mg/kg)

Days post VRC01-infusion

Log_{10} plasma virus (RNA copies/ml)

Lynch, Boritz, Ledgerwood et al.
VRC, NIAID: Unpublished Data
Plasma virus load over time

6/8 subjects have >10 fold decrease in virus load post-infusion with peak nadir ~ day 9

VRC, NIAID: Unpublished Data
Antibodies are biologically active – can decrease plasma viral load

Additional studies needed to address whether antibodies can help maintain viral suppression

Key question: Can antibodies impact the viral reservoir?
Future Directions

- More antibodies into clinic (n = 2 mAbs)
- Antibodies that are both highly potent and broadly reactive
- Longer acting antibodies – triple half life; active for up to 6 months
- New antibody formats: bi-specific antibodies
Means (± standard deviations) of mota-YTE and motavizumab serum concentrations after a single dose (days).

Bispecific antibodies

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

VRC07

PGT121

anti-CD3

Infected CD4 cell

Killer T-cell
Many new HIV-1 antibodies (mAbs) – highly potent and broadly reactive

Potential to prevent HIV-1 infection – studies planned

Potential to complement ARV as part of HIV-1 treatment, especially regarding latent reservoir
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