Pipeline of HIV Monoclonal Antibodies for Prevention of HIV

Session on Antibody-Mediated Prevention
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Vaccine Research Center

2017 VRC Principal Investigators and Program Directors
VRC Research & Development: From AIDS to Zika

August 2000

- AIDS/HIV
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- MERS-CoV, SARS
- RSV
- Smallpox
- Tuberculosis
- W/E/V equine encephalitis viruses
- West Nile virus, Zika

Functional Activity of Anti-Viral Antibodies

- Neutralization
  - Aggregation
  - Attachment blocking
  - Cleavage inhibition
  - Fusion inhibition
  - Preventing particle release
- Fc-mediated functions
  - Antibody dependent cell-mediated cytotoxicity (NK, Macrophage, Neutrophil)
  - Complement binding and activation
- Opsinization and clearance by non-susceptible cells
- Blocking pathogenic immunomodulatory molecules
Long History of Using Antibodies to Treat Infectious Diseases (Serum Therapy)

1890: Emil von Behring and Shibasaburo Kitasato worked on “antitoxins” for tetanus and diphtheria that led to the concept for serum therapy.

1901: Emil von Behring - 1901 Nobel Prize in Physiology or Medicine

“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”.

Also worked with Paul Ehrlich on serum therapy for streptococcal infections in pre-antibiotic era.

Application and Regulation of Serum Therapy

Collection of blood for production of antitoxin horse serum. Jin was the horse associated with the deaths of 13 children treated with immune serum collected near the time of his death from tetanus in 1901. The 1902 Biologics Control Act established standards for the processing and labeling of biological products for human use.

Clinical Use of Antibodies
Prevention and Treatment are Different

**Prevention**
- Prevent acquisition of infection
- Block Transmission event

**Treatment**
- Different mechanism of action
- Eliminate infected cells; reduce viral reservoir
- Maintain viral suppression induced by ARV

Passive Antibody Prevention of HIV/SHIV in NHP for > 25 years

- 1990 - polyclonal IgG protects Chimps from HIV
- 1998 - polyclonal IgG protects against SHIV
- 2000 - first use of use of mAbs (2F5, 2G12, F105) and protection against mucosal challenge
- 2009 - Low-dose mucosal SHIV challenge
- 2012 - Protection with newer generation mAbs (PGT121, 3BNC117, 10-1074, VRC01, VRC07)
- 2016 – Clearance of SHIV infection in neonatal macaques when treated with mAbs post-challenge
**Key Sites of Neutralization-Sensitivity on HIV-1 gp160**

V1V2 Glycan

CD4 Supersite

N332 Glycan-V3 Supersite

Membrane-proximal external region (MPER)

**Broadly Neutralizing mAbs in Development**

PG9, PG16
PGT141-145
CAP256-VRC26
PGDM1400
CH01-04

VRC01, VRC01-LS, PG04, CH31, 3BNC117, CH103, 12A12, VRC13, VRC07
VRC07-523-LS
Z258-N6, DH270, BANC131, CH235

PGT121
PGT128
10-1074
DH270

Anti-CD4-BS/10e8 bi-specific
Anti-CD4-BS/ anti-V2/ anti-MPER tri-specific

2F5
4E10
10e8v5R
Broadly Neutralizing mAbs in Development

- V1V2 Glycan
- CD4 Supersite
- N332 Glycan-V3 Supersite
- Membrane-proximal external region (MPER)

- PG9, PG16
- PGT143-145
- CAP256-170
- PGDM1400
- CH01-04
- VRC01, VRC01-LS, PG04, CH01, BANC117, 1H93, 12A12, VRC05, VRC07
- 225-6-N0, DH270, BANC131, CH235
- PGT121
- PGT128
- 10-1074
- DH270
- Anti-CD4-BS/10e8 bi-specific
- Anti-CD4-BS/ anti-V2/ anti-MPER tri-specific
- 2F5
- 4E10
- 10e8v5R

Target Product Profile for mAb Prevention

- Product: Two (possibly 3) IgG mAbs (or one bi-/tri-specific)
- Indication: Prevention of HIV infection
- Efficacy Profile: Prevents infection by >98% strains
- Target Population: Adolescents/adults: high-risk of HIV infection
- Dosage Administration: Adolescents/adults: 5 mg/kg SQ q3-6 months
- Target Population: Infants of HIV+ mothers: at birth; during breastfeeding
- Dosage Administration: Infants: one birth dose ~20 mg/kg SQ
- Safety/Tolerability: Adverse event frequency – rare
- Cost of Goods: <$50 per person, per year
- Hinges on human efficacy data, commercial interest in producing mAbs for broad use
AMP = Antibody Mediated Prevention Studies

VRC01 administered at 30 mg/kg, or 10 mg/kg, vs placebo

Administered once every 8 weeks by IV infusion

- High risk men in North and South America
- High risk women in South and East Africa

What serum level of mAb is associated with protection?
Powered to define an overall 60% efficacy

VRC01 Concentrations Over Time

- Follow monthly
- Associate serum level with breakthrough infection

Weeks post infusion
- 30 mg/kg
- 10 mg/kg
- 16 ug/ml
- 4 ug/ml

Weeks since infusion
- 30 mg/kg group
- 10 mg/kg group
AMP Approaches to Learning About Correlates of Prevention Efficacy (PE)

1. Compare VRC01 dose groups
   • Compare PE of the 10 vs. 30 mg/kg VRC01 dose groups

2. Case-control VRC01 marker analysis
   • Assess how HIV-1 risk and PE varies over subgroups defined by VRC01 markers

3. Sieve analysis (VRC01 vs. placebo)
   • Assess how PE varies with AA sequence and phenotypic characteristics of breakthrough founder HIV-1s

- HIV-1 Dx tests included between peaks and troughs

Improving HIV mAbs for Prevention

- **Longer half-life** = VRC01 is I.V. every 2 months  
  Goal: SQ injection once every 3 - 6 months

- **More potent (10x)** = protect at lower concentration  
  Goal: Use less mAb - SQ injection

- **Broader coverage** = VRC01 breadth 80-90%  
  Goal: 98% circulating viruses in all regions of world
LS Modification Prolongs Half-Life of VRC01

Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults

Dose/Route VRC01LS
- 5 mg/kg SC
- 5 mg/kg IV
- 20 mg/kg IV
- 40 mg/kg IV

Breadth/Panel of 206 Env-pseudoviruses:
Doria-Rose, Louder, Bailer et al.

Improve Potency and Breadth of CD4-BS mAbs

- VRC 07-523 is 5-fold more potent than VRC01
- Coverage improves to >96%
- VRC07-523-LS phase 1 fully enrolled/ HVTN 127 written
- N6 phase I in spring 2018

Panel of 206 Env-pseudoviruses:
Doria-Rose, Louder, Bailer et al.
Other Antibodies with Improved Potency/Breadth

<table>
<thead>
<tr>
<th>Antibody</th>
<th>% resistant</th>
<th>More potent</th>
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<tbody>
<tr>
<td>VRC01</td>
<td>13</td>
<td>10</td>
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<tr>
<td>3BNC17</td>
<td>20</td>
<td>10</td>
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<tr>
<td>3C19-5G25</td>
<td>4</td>
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<td>N6</td>
<td>3</td>
<td>10</td>
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<tr>
<td>PGT121</td>
<td>46</td>
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<td>10-074</td>
<td>41</td>
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<td>PGDM 400</td>
<td>27</td>
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<td>CAP26-VPD26-25</td>
<td>54</td>
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<td>10E8</td>
<td>2</td>
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<td>10E8-A-VPD10G4F</td>
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Doria-Rose, Louder, Bailer et al.
Panel of 208 Env-pseudoviruses

Other considerations: How transmission occurs

How transmission occurs may impact antibody efficacy

How does antibody block HIV-1 transmission event?

Human mAb against HIV
Sensitive virus
Resistant virus
Mucosal Surface
Other considerations: How transmission occurs

How transmission occurs may impact antibody efficacy

How does antibody block HIV-1 transmission event?

May differ by route and target population

Advanced Development and Implementation

- Development of a preventive mAb combination product would be greatly facilitated by big Pharma interest/investment
- Big Pharma mostly interested if there is a therapeutic indication
- Therapeutic product could then be used as a preventive agent
- TPP for therapeutic agent will be different from that of preventive agent
- Alternatively, need government of NPO to establish manufacturing and distribution capacity

Will likely require coverage of viruses by at least two mAbs to avoid escape
Achieving dual coverage in combination mAb Rx

Theoretical Combinations of VRC07-523-LS+10E8v4-V5R-100cF+PGDM1400

Multiclad Virus Panel (n=208)

% of viruses neutralized

IC80 µg/mL

Achieving dual coverage in combination mAb Rx

Theoretical Combinations of VRC07-523-LS+10E8v4-V5R-100cF+PGT121

Multiclad Virus Panel (n=208)

% of viruses neutralized

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Achieving dual coverage in combination mAb Rx

Theoretical Combinations of VRC07-523-LS+10E8v4-V5R-100cF+ either PGDM1400 or PGT121

VRC07 HIV-1 mAb Portfolio and Timelines

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<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
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<tr>
<td>VRC01</td>
<td>Phase II: AMP Study (Proof-of-concept)</td>
<td>Serum mAb level</td>
<td>Serum neutralization level (bridge to other mAbs)</td>
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<td>VRC07-523-LS</td>
<td>Phase I: VRC07-523-LS</td>
<td>Expanded Phase I: HVTN 127 / HPTN 087</td>
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<td>Z258-N6-LS</td>
<td>Dev and Manufacturing</td>
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<td>CAP256-LS</td>
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<td>Tri-specific-LS</td>
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<td>Combo</td>
<td>Two mAb combinations (efficacy)</td>
<td>Down-select Optimal Mabs 99% coverage 10x more potent</td>
<td>Phase IIb: Proof of Product (Two mAbs, or Tri-specific)</td>
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**Summary**

- Passive immunization with immunoglobulins for prevention and treatment of viral diseases has a long successful history
- mAbs can prevent SIV/SHIV infections in NHP
- Using mAbs for HIV prevention is becoming a practical option
  - engineering potency, breadth, and extended half-life
  - manufacturing advances
- Proof-of-concept for prevention of HIV infection with neutralizing mAb will be available in ~2 years
- Planning for success should include developing new business plans for large scale manufacturing and product deployment

**Acknowledgements**

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- Sarah Read
- Sheryl Zwerski
- Diana Finzi

Mark Connors NIAID Lab
- Leo Laub
- Jinghe Huang

CAVD, VIMC
- Michael Seaman
- David Montefiori
HVTN 703/HPTN 081 Protocol Team

- Chairs: Larry Corey & Mike Cohen
- Co-Chairs: Nyaradzo Mgodi & Sri Edupuganti
- Protocol Team Leader & Core Medical Monitor: Shelly Karuna
- DAIDS Medical Officers: Marga Gomez & David Burns
- Statisticians: Allan DeCamp, Deborah Donnell, Peter Gilbert, Michal Juraska, Nidhi Kochar
- Laboratory Representatives: John Hural, Sue Eshleman, On Ho, David Montefiori, Vanessa Cummings, Estelle Piwowar-Manning
- VRC Representatives: Julie Ledgerwood, Barney Graham, John Mascola
- Investigator Representatives: Ken Mayer, LaRon Nelson, Manuel Villaran, Sinead Delaney-Moretwe
- Social & Behavioral Scientist: Michele Andrasik
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- Community Engagement Representatives: Gail Broder, Jonathan Lucas, Jontraye Davis
- Clinic Coordinators: Christie Heiberg, Deb Dunbar, Ana Ramachi
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