Broadly Neutralizing Antibodies for Treatment and Prevention of HIV-1

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Outline

- Basic facts about bNAbs
- Pre-clinical data
- Human clinical trials data
- Translating bNAbs into practice
- Challenges and conclusions
Basic Facts about bNAbs
Broadly neutralizing antibodies

- Human monoclonal antibodies able to neutralize a wide range of HIV-1 isolates

- Target HIV-1 envelope

- Enhance various effector functions
  - Complement-mediated lysis
  - ADCC, ADCP
  - Increase HIV-1 specific immune responses

- Can be genetically engineered to combine multiple specificities or extend half-life
Broad neutralization by VRC01 mAb

<table>
<thead>
<tr>
<th>Titer</th>
<th>VRC01</th>
<th>b12</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC₅₀ &lt; 50 µg/ml</td>
<td>91%</td>
<td>41%</td>
</tr>
<tr>
<td>IC₅₀ &lt; 1 µg/ml</td>
<td>72%</td>
<td>17%</td>
</tr>
<tr>
<td>Geometric mean IC₅₀ (µg/ml)</td>
<td>0.33</td>
<td>1.79</td>
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</tbody>
</table>
Binding sites for HIV-1 bNAb

Potential clinical uses of bNAbs

A. HIV-1 Treatment Intensification
   - ART
   - bNAbs
   - Improvement of HIV-1 Therapy by concomitant treatment with classical ART and bNAbs

B. Maintaining HIV-1 suppression
   - ART
   - bNAbs
   - In viral-controlled HIV-1* individuals: Preventing viral rebound by bNAb administration

C. HIV-1 Immunotherapy
   - bNAbs
   - Possible HIV-1 treatment alternative (e.g. in the case of multi-drug resistance, ART intolerance, etc.)

D. HIV-1 Prevention
   - bNAbs
   - Pre- and Post-exposure prophylaxis; pMTCT (for late presenters)

Adapted from Klein F et al Science 2014
Potential advantages of bNAbs for PrEP or ART

- Infrequent dosing
- No cross-resistance with standard ARVs
- Established paradigms for therapeutic use of mAbs in other disease areas
- Potential for overcoming adherence challenges
- Potential for less stigma
- Potential to enhance HIV-specific immunity
bNAbs: Pre-clinical data
Antiviral activity of 3BNC117 and 10-1074 against SHIV in chronically infected NHP model

Shingai M et al Nature 2013
Martin M CROI 2018 Abstr 49
Effect of single or dual bNAb treatment in acute SHIV model
Single-dose of bNAbs protects against repeated rectal SHIV\textsubscript{AD8-EO} challenge

Guatam R et al Nature 2016
Human Clinical Trials
Single-dose PK of VRC01

Lynch RM et al Science Transl Med 2015
Efficacy trials of VRC01 as PrEP

- **AMP (HVTN 703/HPTN 081)**
  - Phase 2b study of q8 wk VRC01 (2 dose groups) vs placebo
  - 1500 women in sub-Saharan Africa
  - PrEP permitted but not study provided

- **AMP (HVTN 704/HPTN 085)**
  - Phase 2b study of q8 wk VRC01 (2 dose groups) vs placebo
  - 2700 MSM and transgender women
  - North and South America
  - PrEP permitted but not study provided
Single dose PK of 3BNC117

Caskey M et al Nature 2015
Cohen Y et al CROI 2018 Abstr 1062
Pharmacokinetics of the V3 Glycan-Dependent Broadly Neutralizing Antibody PGT121 in Humans

Mean Elimination Half-Life: 20 days

Dan Barouch, Katy Stephenson, Boris Julg, unpublished data
LS modification prolongs VRC01 half-life

Gaudinski MR et al PLoS Medicine 2018
Gaudinski MR et al CROI 2018 Abstr 1061
Antiviral activity of VRC01
Enhancement of autologous virus neutralization after bNAb administration

Schoofs T et al Science 2016
Failure of VRC01 monotherapy to maintain viral suppression

A A5340 Trial

B NIH Trial

Emergence of VRC01-resistant variants during ART interruption

Treatment interruption post BCN117

Neutralization activity of bNAbs against clade C virus panel

Wagh K et al PLoS Pathogens 2016
Extent of neutralization by multiple active bnAbs from best-in-category combinations

A. Best 2 bnAb combinations
B. Best 3 bnAb combinations
C. Best 4 bnAb combinations

bnAbs: CD4bs
  a. VRCC07-523
  b. CAP256-VRCC26.25
  c. 10-1974

  V2q:
  a. 3BNC117
  b. PGDM1400
  c. PGT128

  V3q:
  a. MPER
  b. 10E8
bNAb combinations protect against mixed SHIV challenge in macaques
# Tri-specific bNAb (SAR 441236)

![Diagram of Tri-specific bNAb](image)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>SHIV BaLP4</th>
<th>SHIV 325c</th>
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</thead>
<tbody>
<tr>
<td>VRC01</td>
<td>0.067</td>
<td>&gt;50</td>
</tr>
<tr>
<td>PGDM1400</td>
<td>&gt;50</td>
<td>0.015</td>
</tr>
<tr>
<td>VRC01/PGDM1400-10E8v4</td>
<td>0.055</td>
<td>0.168</td>
</tr>
</tbody>
</table>

Pegu A et al CROI 2018 Abstract 113LB.
Tri-specific bNAb protects against mixed SHIV challenge

Xu L et al Science 2017
Translating bNAbs into Practice
# Draft Target Product Profile for mAb Prevention

<table>
<thead>
<tr>
<th><strong>Product</strong></th>
<th>Two IgG mAbs (or one bi-tri-specific)</th>
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</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Prevention of HIV infection</td>
</tr>
<tr>
<td><strong>Efficacy Profile</strong></td>
<td>Prevents infection by &gt; 98% strains</td>
</tr>
</tbody>
</table>
| **Target Population** | Adolescents/adults: high-risk of HIV infection  
Infants of HIV* mothers: at birth; during breastfeeding |
| **Dosage Administration** | Adolescents/adults: 5 mg/kg SC q3-6 months  
Infants: one dose (20 mg/kg SQ) at delivery |
| **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

Courtesy of DAIDS and VRC, NIAID
Draft Target Product Profile of bNAbs for HIV Treatment

- **Easy, convenient dosing**
  - Q 4wk or less frequent (target q 6 mo) – similar $T_{1/2}$ if more than one bNAb
  - Home (SC) or infusion center (IV) administration
  - Single needle stick if possible (coformulation > coadministration > sequential IV administration)

- **Potent and durably suppresses HIV replication**
  - Drug/regimen covers all viruses (95-98%) at target plasma concentration (min 2 bNAbs/virus)
  - <30 mg/kg, ideally <1 mg/kg
  - No need for susceptibility testing
  - Achieves/maintains max viral suppression >48 wk
  - Infrequent emergence of escape/resistant virus

- **Safe**
  - Low risk of anaphylaxis or immune complex disease (low frequency/concentration of ADAs)
  - Rare SAEs with no increase in markers of chronic inflammation or immune activation

- **Affordable**
  - No more expensive than current first line therapy

Courtesy of DAIDS and VRC, NIAID
Challenges and Conclusions
Challenges in clinical development

- Choosing optimum bNAb combinations for human trials
- Dose-finding
  - How much?
  - How often?
  - Can dose-finding studies in macaques be translated to humans?
- Potential for ADA with non-natural bNAbs
- Emergence of bNAb-resistant virus
  - Need for susceptibility testing?
- Improving formulations
  - s.c. vs i.v.
- Sample size for prevention studies
Challenges in clinical use of bNAbs

- **Acceptability of infusion or injectable ART/PrEP**
  - IV or SC administration
- **Dosing frequency**
- **Cost**
- **Capacity**
- **Global access**
  - (see also Cost and Capacity, above)
Conclusions

- bNABs show promise as long-acting agents for treatment and prevention of HIV-1 infection
- Most likely will require combinations or bi-/tri-specific bNABs
- Efficacy and long-term safety remain to be determined
- Effects on the HIV-1 reservoir remain to be demonstrated
- Cost may be a significant barrier to wide adoption
- Advances in formulation and delivery are needed to simplify administration and maximize uptake
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