Broadly Neutralizing Antibodies for HIV Treatment and Prevention

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Outline

- Basic facts about bNAbs
- Pre-clinical data
- Human clinical trials data
- 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
  - Vaccinal effect (?)

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

Wu X et al Science 2010
Binding sites for HIV-1 bNAbs

- **CD4-binding site**
  - b12, VRC01, VRC07, NIH45-46, 3BNC117, VRC-PG04

- **V1/V2**
  - PG9, PG16, CH01-04, PGT141-145, PGDM1400

- **V3/Asn332 glycan patch**
  - PGT121-123, PGT125-131, PGT135, 10-1074, 2G12

- **gp120/gp41 interface**
  - PGT151, 35O22, 8ANC195

- **MPER**
  - 2F5, 4E10, 10E8

Potential clinical uses of bNAbs

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

- Infrequent dosing
- No cross-resistance with standard antiretroviral drugs
- 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
Single-dose of bNAbs protects against repeated rectal SHIV$_{\text{AD8-EO}}$ challenge

Guatam R et al Nature 2016
bNAb combinations protect against mixed SHIV challenge in macaques

Juelg B et al Sci Transl Med 2017
Human Clinical Trials
Single-dose PK of VRC01

Lynch RM et al Science Transl Med 2015
Multi-dose PK of VRC01

Mayer K et al PLoS Med 2017
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

**Both studies fully enrolled**
- Next DSMB review scheduled for November 2019
Single dose PK of 3BNC117

Caskey M et al Nature 2015
Antiviral activity of VRC01

Lynch RM et al Science Transl Med 2015
Antiviral activity of 3BNC117

Caskey M et al. Nature 2015
Emergence of 3BNC117-resistant variants during ART interruption

LS modification prolongs VRC01 half-life

Gaudinski MR et al PLoS Medicine 2018
Comparison of VRC01LS and VRC07-523LS

Chen G et al IAS 2019, Mexico City
Neutralization activity of bNAb against clade C virus panel

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

Wagh K et al PLoS Pathogens 2016
Combination bNAbs in viremic participants 3BNC117 + 10-1074

Baro-On Y et al Nat Med 2018
Combination bNAbs—effect on viral rebound

Mendoza P et al. Nature 2018
Tri-specific bNAb (SAR 441236)

Xu L et al Science 2017
Breadth and potency of trispecific bNAbs
A Phase I, First-in-human, Ascending Dose Study of SAR441236, a Tri-specific Broadly Neutralizing Antibody in HIV-infected Participants

Athe Tsibris, Evelyn Zheng, Ed Acosta, Katy Bar, Lucio Gama, Raj Gandhi, Randy Tressler, Evelyn Hogg, Pablo Tebas, Dan Kuritzkes
A5377: Study design

- A5377 is a phase I, first-in-human, ascending dose study of SAR441236.
- It will include 2 parts with 4 cohorts in each (1, 3, 10 and 30 mg/kg).
- N=54 (6 each in Cohorts 1-3 and 5-8, and 12 in Cohort 4). The 10 placebos are all in the ART suppressed group.
  - Part 1: HIV suppressed with a CD4 count of ≥200 cells/mm³.
  - Part 2: HIV naïve with HIV-1 RNA >5,000 copies/mL and CD4 count of ≥350 cells/mm³.
Tatelo Study

- A Clinical Trial to Evaluate the Impact of Broadly Neutralizing Antibodies VRC01LS and 10-1074 on Maintenance of HIV Suppression in a Cohort of Early-Treated Children in Botswana

- Sample Size: Up to 35 children

- Study Population: HIV-infected children enrolled in the Early Infant Treatment (EIT) Study who are at least 96 weeks of life and meet entry criteria
# Study Design

## Cohort 1:

- **PK Step (8 weeks)**
  - ART + 10-1074 (4 participants)
  - ART + VRC01LS (4 participants)

- **Step 1 (8+ weeks)**
  - ART + 10-1074 + VRC01LS (all participants)

- **Step 2 (24 weeks)**
  - 10-1074 + VRC01LS (all participants)

- **Step 3 (28 Weeks)**
  - End bNAb, re-start ART

## Cohort 2:

- **Step 1 (8 weeks)**
  - ART + 10-1074 + VRC01LS (all participants)

- **Step 2 (24 weeks)**
  - 10-1074 + VRC01LS (all participants)

- **Step 3 (28 Weeks)**
  - End bNAb, re-start ART

**Study Duration:** 68-92 weeks
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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