IAS 2019

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New prevention products in the pipeline: Advances in the field of broadly neutralising antibodies

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Mexico City, 22 July 2019
Conflict of interest declaration

I have no conflicts of interest to declare
Presentation outline

• The biology of HIV infection
  – transmission, eclipse, peak viraemia, viral set point
• Immune response to HIV infection
• Broadly neutralising antibodies
• The AMP studies
• Next generation bnAbs
  – Combination/tri-specific antibodies
• Summary
Biology of HIV infection

- HIV-1 encounters a genetic bottleneck during transmission
- Results in genetically homogenous population of initial plasma viremia

Josephs et al, *Nature Micro* (invited)
Acute HIV infection - immune response

Acute Phase Reactants Days -5 to -7

Onset cytokines apoptosis, Day 7

Immune Complexes Day 9

Free Antibody, Day 13

Autologous Neutralizing Antibody

Reservoir

CD8 T Cell Responses

CTL Escape

Autologous Neutralizing Antibody Escape

Virus Concentration in Extracellular Fluid or Plasma (Copies/ml)

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70

Time Post Exposure (days)

Transmission

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Development of broadly neutralising antibodies

The transmitted-Founder virus

Escape virus

HIV-1

Antibody

The initial neutralizing antibody response to HIV “autologous nAb”

Continuum with 10^-20% Broadly neutralizing antibodies
Broadly neutralising mAb to 5 major regions of Env

- V1V2-Glycan – binds to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

Antibodies (VRC01, 3BNC117) and others in early phase clinical trials

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014
Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?

Two harmonized protocols:
The AMP Studies:

HVTN 704/HPTN 085
(2700 MSM and TG in the Americas, Europe)

HVTN 703/HPTN 081
(1900 Women in sub-Saharan Africa)

Chairs – L Corey, M Cohen
Co-Chairs – S Edupuganti, N M Mgodi
# AMP Study design

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
<th>Notes</th>
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<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>634</td>
<td>1534</td>
<td>10 infusions total &amp; Infusions every 8 weeks</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>634</td>
<td>1534</td>
<td>Study duration: ~22 months</td>
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<tr>
<td>Control</td>
<td>900</td>
<td>634</td>
<td>1534</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1900</td>
<td>4600</td>
<td></td>
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</tbody>
</table>

- Two different infusion doses: important to know if lower dose of 10 mg/kg can protect
- Powered to associate mAb serum level with protection
- All subjects provided an HIV prevention package

VRC01 10 mg/kg

- 900 subjects
- 634 women in sub-Saharan Africa
- Total 1534 subjects
- 10 infusions total
- Infusions every 8 weeks
- Study duration: ~22 months

VRC01 30 mg/kg

- 900 subjects
- 634 women in sub-Saharan Africa
- Total 1534 subjects
- 10 infusions total
- Infusions every 8 weeks
- Study duration: ~22 months

Control

- 900 subjects
- 634 women in sub-Saharan Africa
- Total 1534 subjects
- 10 infusions total
- Infusions every 8 weeks
- Study duration: ~22 months

Total

- 2700 subjects
- 1900 women in sub-Saharan Africa
- Total 4600 subjects
- Study duration: ~22 months
AMP Study: Objectives and endpoints

- Safety & Tolerability of VRC01 infusion
  - Reactogenicity, AEs, SAEs, discontinuation rates
- Efficacy to prevent HIV infection
  - HIV infection by week 80 in those HIV-negative at enrollment

- Develop a marker(s) of VRC01 that correlates with the level and antigenic specificity of efficacy
  - Serum VRC01 concentration
  - Serum mAb effector functions
  - Breakthrough HIV viral sequences in infected people
  - VRC01 neutralization sensitivity of, & effector functions against, HIV strains from infected trial participants
Enrolment: 1924 (complete)

Retention: 96% - 34104/35591 visits

Adherence: 98% - 15673/16002 infusions

Data as of 20 July 2019
AMP MSM/TG summary

Enrolment: 2701 (complete)

Retention: 95% - 48937/51564 visits

Adherence: 100% - 22792/22844 infusions

Data as of 20 July 2019
Acceptability of bNAbs

AMP Behavioral Project
Six US Sites (HVTN 704/HPTN 085)
Mixed Methods - Exit Survey/Interview Focus
  Demographics, BnAbs, PrEP
  Perceptions of AMP community engagement efforts
  Perceptions of AMP participation
  Factors motivating participation in AMP
  Infusion Experience
  Recommendations to improve participant experience

AMP Success Story:
Strength of Relationships
Altruism-Being Part of the solution
Community support – Andrasik TUAD0104
Responding to concerns

Michele Andrasik, PhD
Director Social and Behavioral Sciences and Community Engagement
HIV Vaccine Trials Network (HVTN)
NEXT GENERATION MONOCLONAL ANTIBODIES
Knowledge of the structure of VRC01 was used to engineer a next-generation antibody with 5- to 8-fold increased potency *in vitro*.

A clonal relative of VRC01 has increased neutralization potency

07 denotes sequential numbering when discovered

VRC07-523 (“523” denotes sequential numbering when engineered variant generated)

VRC07-523LS (“LS” denotes 2 amino acid mutations)

*Optimized VRC07 protects against infection at lower plasma concentrations and has minimal autoreactivity*
Lessons learnt from HIV treatment

- HIV-1 exhibits genetic diversity and viral escape mechanisms
- Prudent to consider using a combination approach
- Like antiretroviral therapy, combinations of mAbs may reduce the likelihood of viral escape, and increase neutralization breadth
- Combining multiple bnAbs with specificities against different epitopes into a single molecule has the potential to:
  - improve efficacy
  - simplify prevention and treatment regimens
  - streamline the regulatory pathway to a licensed drug
- Trispecific mAbs derived from bnAbs with CD4bs, MPER, and V1V2 glycan specificities demonstrate remarkable breadth and potency in vitro and in vivo

Xu, Science; 2017
Theoretical combinations of mAbs

Adapted from M Cohen and T Gamble
BROADLY NEUTRALIZING ANTIBODY COMBINATIONS

As with antiretroviral combinations used in treatment to control the virus, passive immunization of broadly neutralizing antibodies to protect against HIV will likely require two or more bNAbs that target different parts of the virus. There are many factors to consider when selecting bNAb combinations, including how many bNAbs and which ones work best together. Here we outline the bNAb combinations being explored in early clinical studies.

### bNAb Cocktails: Two or more antibodies in a regimen

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<td>Phase I, Planned</td>
<td>NIAID</td>
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<td>Columbia University</td>
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### Combining bNAbs to broaden neutralization*

![Graph showing the percentage of virus neutralized with different numbers of bNAbs](image)

- **1 bNAbs**: 79%
- **2 bNAbs**: 89%
- **3 bNAbs**: 98%
- **4 bNAbs**: 98%

Different antibodies have different neutralizing activities. Modeling and preclinical studies suggest that combining bNAbs may lead to broader neutralization compared to giving bNAbs alone, and multispecific antibodies might perform better than combinations. Clinical trials will validate whether these differences are seen in humans, and guide selection of best antibodies and combinations types.

*Data: Koenig 

### Multispecific: Parts of two or more antibodies on a single antibody

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<td>Sanofi, NIAID</td>
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<td>+</td>
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<td>Aaron Diamond AIDS Research Center (ADARC)</td>
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**KEY**

- 10-104
- 10F8
- 3BNC117
- CAP256-S
- VRC01
- VRC01-324
- PGDM4A10
- 10F9

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Joint HVTN/HPTN mAb portfolio

AMP (VRC01)

VRC07-523LS (>VRC01)

Iterative combinations of 2-3 antibodies (multiple mAbs/targets)

Trispecific (1 mAb, 3 targets)

Adapted from T Gamble
Next generation mAbs - Summary

• If virus is targeted by multiple or trispecific bNAbs, then escape is difficult.
• Studies are using/ will use trispecific bNAbs or combinations of mAbs to improve efficacy through both better coverage and higher potency.
• The goal of these studies is to identify the best regimens for moving to a licensure trial.
Acknowledgements

- Mike Cohen
- Wafaa el Sadr
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- S Edupuganti
- Nirupama Sista
- Mike Chirenje
- Theresa Gamble
- Lisa Donohue

And the many participants, research communities and researchers who have helped develop studies that will end the HIV epidemic!
obrigado  Dank U  mahalo  Köszü
chacubo  Grazie  Thank you  maaururu
Gracias  Dziekuję  Dékuju  danke
Kiitos