Clinical Development of Long-Acting Broadly Neutralizing Monoclonal Antibodies: Lessons Learned Thus Far

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Rapid identification of human mAbs has created new options for discovery and engineering

Cesar Milstein and Georges Köhler developed technique for making murine monoclonal antibodies leading to 1982 Nobel prize:

1975

2008

Human mAbs: RSV HIV Ebola Influenza Malaria
Antibodies for HIV-1 Prevention and Treatment

- Overview of existing HIV MAbs
- Antibody engineering for better potency and breadth
- Fc mutations and how they affect antibody PK
- Lessons from protection and treatment trials
Key Sites of Neutralization-Sensitivity on HIV-1 gp160

V1V2 Glycan
N332 Glycan-V3 Supersite
CD4 Supersite
gp120-gp41 Interface
Membrane-proximal external region (MPER)

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014
Broadly Neutralizing mAbs in Development

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Broadly Neutralizing mAbs in Development

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Antibodies with Improved Potency/Breadth

Multi-clade virus panel (n=208)
Potency and Breadth

Potency (IC$_{80}$ at ug/ml)

Breadth
Antibodies for HIV-1
Prevention and Treatment

• Overview of existing HIV MAbs
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Antibodies with Improved Potency/Breadth

Multi-clade virus panel (n=208)

More potent IC50 Titer (μg/ml)

Resistant (%)
Potency and Breadth

Potency (IC\textsubscript{80} at ug/ml)

Breadth

- 10E8V4
- 10E8
- VRC01
- VRC07
- 3BNC17
- PG9
- PGDM1400
- 10-1074
- PGT121
- PGT128
- PGT151
- CAP256.25
- 35O22

- 4E10
- 2F5
- b12
- 2G12

- 10E8V4_V6R
- 100cF
- 10E8V4_100cW
Combined Antibodies: Improved Potency and Breadth

Engineered Bispecific Antibodies with Exquisite HIV-1-Neutralizing Activity.

Huang Y, Yu J, Lanzi A, Yao X, Andrews CD, Tsai L, Gajjar MR, Sun M, Seaman MS, Padte NN, Ho DD.

Antibodies with Improved Potency/Breadth

Cross-MAb Technology
Antibodies with Improved Potency/Breadth
Trispecific Broadly Neutralizing HIV Antibodies Mediate Potent SHIV Protection in Macaques.

Trispecific Broadly Neutralizing HIV Antibodies Mediate Potent SHIV Protection in Macaques.

Broad and Potent Coverage of Trispecific Antibodies
Potency and Breadth

![Graph showing the relationship between potency (IC₈₀ at ug/ml) and breadth. The graph includes markers for different samples, such as 10E8V4, VRC01, 3BN17, PGD1400, and others. The x-axis represents potency, and the y-axis represents breadth.](image-url)
Antibodies for HIV-1
Prevention and Treatment

• Overview of existing HIV MAbs
• Antibody engineering for better potency and breadth
• Fc mutations and how they affect antibody PK
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Extending mAb half-life in humans

- Fc region binds with high affinity to FcRn at acidic pH (<6.5) in endosome
- Protects antibody from endosomal degradation
- IgG released back into circulation at physiological pH (7.4)
- Results in prolonged circulating half life
Safety and Pharmacokinetics of the Fc-modified HIV-1 Human Monoclonal Antibody VRC01LS: A Phase 1 Open-label Clinical Trial in Healthy Adults.

Antibodies for HIV-1
Prevention and Treatment

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Passive Antibody Prevention of HIV/SHIV in NHP for > 20 years

- 1990 - 1992: polyclonal IgG protects Chimps from HIV infection
- 1998 - 1999: polyclonal IgG protects against SHIV challenge
- 2000 - present: first use of use of mAbs (2F5, 2G12, F105) and protection against mucosal challenge
- 2009-present: Low dose mucosal SHIV challenge
- 2012: Protection with newer generation mAbs (PGT121, 3BNC117, 10-1074, VRC01, VRC07)

But there are no human data regarding passive protection by HIV-1 monoclonal antibodies
Passive Antibody Prevention
Phase IIB Efficacy

AMP = Antibody Mediated Prevention

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?

(Conducted by HPTN and HVTN)
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

Two harmonized studies

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

4600 subjects
3725 enrolled as of March 19, 2018
What Happens With Success: i.e. VRC01 mAb decreases risk of infection?

• We define the level of plasma mAb needed to protect against infection (e.g., 5 - 10 ug/ml)
• Translate that into:
  • SQ administration of mAbs to achieve this level (Q6 months with LS antibodies?)
  • Incentive to develop next generation mAb (more potent, longer half life)
  • Options for genetic immunization (AAV, DNA, mRNA) to provide medium to long-term protective antibody levels
  • Knowledge that neutralizing mAb can protect will guide vaccine field: i.e. immunogen that achieves this level of neutralization
### Target Product Profile for mAb Prevention

<table>
<thead>
<tr>
<th>Product</th>
<th>Two IgG mAbs (or one bi-tri-specific)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Prevention of HIV infection</td>
</tr>
<tr>
<td>Efficacy Profile</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 and commercial interest in producing mAbs for broad use
Pharma Partnership

- 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
  - Truvada PREP scenario
- TPP for a therapeutic agent will be different from that of a preventive agent
  
  Will likely require coverage of viruses by at least two mAbs to avoid escape
Antibodies for Treatment
How might mAbs be used?

- During acute HIV-infection, with ARV, to rapidly reduce viremia and limit seeding viral reservoir

- To maintain long-term viral suppression induced by ARV – take advantage of long half-life and safety of antibodies (mAbs) e.g., LA-ARV + mAb given once every 2-3 months

- Reduce cell-associated viral reservoir: Fc-mediated effector functions (ADCC, ADP) – functions distinct from ARV drugs
Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117

Virologic Effects of Broadly Neutralizing Antibody VRC01 Administration During Chronic HIV-1 Infection.


December 23, 2015
Pre-infusion resistance to VRC01

Two low responder had most resistant viral quasi-species

Non-responders (resistant virus)

IC80 > 20 ug/ml

Two low responder had most resistant viral quasi-species
mAb 10-1074 (Glycan V3): phase I

Antibody 10-1074 Suppresses Viremia in HIV-1-infected Individuals.

HIV-1 Antibody 3BNC117 Suppresses Viral Rebound in Humans During Treatment Interruption.

Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption

Rapid advancement of potent HIV-1 mAbs into clinical trials (since first discovery in 2009)

Antibodies classically used to prevent infection: Phase IIb study for HIV-1 prevention (PrEP) has begun

Multiple phase I treatment studies completed with single mAbs

It is unlikely that single mAbs will be able to maintain long term viral suppression (resistance)

- Combinations, engineered potency and breadth, multispecific antibodies
- Combination with ARVs
- Regimens in which virtually every virus is covered by 2 antibodies (+/- a long acting ARV) will probably be needed
Dual Antibody Coverage in mAb Combinations
Dual Antibody Coverage in mAb Combinations

IC80 (µg/ml)

>50
10.0-<50
1.00-10.0
0.100-1.00
0.01-0.100
0.001-0.01
<0.001

PGT121  PGDM1400  Both active  Either active

PT121  VRC07-523  Both active  Either active

VRC07-523  10E8V5  Both active  Either active
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