Towards and HIV Cure Symposium
July 18, 2015

Neutralizing Antibodies: Potential role in HIV-1 treatment approaches

John R. Mascola, M.D.
Vaccine Research Center
NIAID, NIH
Background on HIV-1 neutralizing antibodies

Opportunities and limitations of clinical use of monoclonal antibodies (mAbs)

Phase I clinical data: VRC01 in HIV-1 infected viremic subjects

Disclaimer: VRC01 was isolated in my laboratory at VRC, NIAID, NIH
Listed as inventor on an NIH patent for VRC01
Neutralization Epitopes on Env Trimer

Peter Kwong, Jonathan Stuckey
Two HIV-1 Antibodies: Improved Potency and Breadth

Fraction viruses neutralized

VRC07
PGT128

Experimental Mix
Theoretical Mix

ug/ml

0.001 0.01 0.1 1 10 100
VRC01 mAb: Healthy volunteers

Single infusion of 20 mg/kg I.V. into 3 subjects

VRC01 median potency
IC80 = 1.0 ug/ml

VRC, NIAID: Ledgerwood et al. (In press)
Clinical Use of HIV-1 mAbs

**Pros**

- Likely very safe, don’t interfere with DNA replication
- Long *in vivo* effect – potentially months
- > 50 licensed mAbs – growing industry
- Different mechanism than ARV – block entry
- Potential to kill infected cells, ADCC or other Fc-mediated effector functions

**Cons**

- Each single mAb has gap in coverage (5% to 50%)
- Use a combinations of 2 mAbs, some viruses are only sensitive to one of the two mAbs
- Expensive and time consuming to manufacture
- Parenteral route: perhaps mitigated by SQ
Clinical Use of HIV Antibodies

Prevention
- High risk young adults
- High risk MSM
- Discordant couples
- Breastfeeding infants

Maximize Coverage (breadth)
Potent enough to work

Treatment
- Acute affect on viremia
- Treatment interruption/sparing
- Impact on viral reservoir
- Combined with ARV (functional cure)

Maximize potency
Avoid escape
Cell killing
Antibody-mediated Prevention Trial (HVTN 703/HPTN 081)

Phase IIB study

- Can VRC01 mAb, given every 2 months, prevent acquisition of HIV-1 infection in high risk adults (currently no human data)

- Cohorts: High risk women in S. Africa, and high risk men in Americas (n = 3900 total)

- Importantly: What antibody plasma level is associated with protection;
  - e.g. do we need 100 ug/ml, 10 ug/ml or 1 ug/ml
Viraemia suppressed in HIV-1‐infected humans by broadly neutralizing antibody 3BNC117

Marina Caskey1,*, Florian Klein1,*, Julio C. C. Lorenzi1, Michael S. Seaman2, Anthony P. West Jr3, Noreen Buckley4, Gisela Kremer4,5, Lilian Nogueira1, Malte Braunschweig1,6, Johannes F. Scheid1, Joshua A. Horwitz1, Irina Shimeliovich1, Sivan Ben‐Avraham1, Maggi Witmer‐Pack1, Martin Platten4,7, Clara Lehmann4,7, Leah A. Burke1,8, Thomas Hawthorne9, Robert J. Gorelick10, Bruce D. Walker11, Tibor Keler9, Roy M. Gullick8, Gerd Fätkenheuer4,7, Sarah J. Schlesinger1 & Michel C. Nussenzweig1,12
Long View (optimistic) for use of HIV-1 mAbs

- Continue to find (and design) better neutralizing mAbs
- More potent (10-100 fold)
- Longer half-life – lasting 6 months
- Improved ADCC, cell killing
- Bispecific mAbs in various formats
• The Fc region binds to FcRn at an acidic pH (<6.5) in endosome
• **Protects antibody from endosomal degradation**
• IgG released back into circulation at physiological pH (7.4)
• **Increased FcRn binding results in prolonged circulating half life.**

Means (± standard deviations) of mota-YTE and motavizumab serum concentrations after a single dose (days).

Robbie G J et al.
Bispecific antibodies

Two different antibody binding arms on one IgG

Bispecific T-cell engager: CD3 and HIV-1

VRC07  PGT121

VRC07

CD3

Infected CD4 cell

CD8 killer cell
Clinical Use of HIV-1 mAbs (idealized product & clinical profile)

- **Potency:** > 10-fold than current, thus allowing SQ administration of lower dose (1 mg/kg)
- Improve manufacturing and cost by > 10-fold
- **Optimal breadth:** Two mAbs together that are each >90% broad; both highly potent
- Extend half life and thus, dosing interval to every 3-6 months
- **Potential for giving mAbs SQ, every 3-6 months for prevention of infection; to maintain viral suppression, part of arsenal to attack latent reservoir**
Acknowledgements

Virology Studies
Rebecca Lynch
Eli Boritz
Gideon Wolf
Patrick Madden
Danny Douek
Krisha McKee
Mark Louder
Sijy O’Dell
Rui Kong
Steve Schmidt
Nicole Doria-Rose
Evan Cale
Marissa Jarosinski
Nathan Radakovich

Clinical Trials Program
Julie Ledgerwood
Emily Coates
Adam DeZure
Mary Enama
Pamela Costner
Ingelise Gordon
Sarah Plummer
Lasonji Holman
Cynthia Hendel
Sandra Sitar
Brenda Larkin
Galina Yamshchikov
Olga Vasilenko
Iris Pittman
Nina Berkowitz

Vaccine Production Prog.
Richard Schwartz
Leidos Pilot Plant staff

Regulatory Affairs and Product development
Judy Stein
Jason Gall
Gretchen Schieber
Hillery Harvey
Abe Mittelman
Florence Kaltovich
Hope Wilson
Zonghui Hu

NVITAL
Bob Bailor

Frederick NCI Lab
Brandon Keele

Rick Koup
Barney Graham