Broadly Neutralizing Antibodies for HIV Eradication

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Outline: Broadly Neutralizing Antibodies for HIV Eradication

- Structure of the HIV envelope (Env) protein
- Antibody responses in HIV infection
- Early efforts to use antibodies to treat HIV
- Current efforts to use broadly neutralizing antibodies to treat (and prevent) HIV
- Future of broadly neutralizing antibodies for HIV eradication
Background: Structure of the HIV Envelope (Env)
Background: Antibody Responses in HIV Infection

• Potent binding antibodies develop in nearly everyone
• Antibodies put immune pressure on viral replication, but the virus always escapes
• 10-20% develop broadly neutralizing antibodies after 2-3 years of infection
• These bNAbs are still outrun by viral escape and not useful for the individual patient
• Question remains: can these antibodies be useful for other patients who may have more sensitive viruses?
Early Efforts: Passive Immunotherapy with Pooled Plasma

- 1985-1995: infusions of pooled plasma from HIV-infected donors was explored as a treatment for HIV
- Three randomized, placebo-controlled trials (~350 subjects)
  - No statistically significant decrease in mortality
  - Little impact on CD4 count
  - Trend towards longer survival and OI’s
  - Evidence of transient drops in plasma HIV RNA
- Important early data that infusion of HIV-specific antibodies might lead to clinical benefits

Jackson Lancet 1988: 647
Jacobson JID 1993: 298
Levy Blood 1994: 2130
Vittecoq JID 1992: 364
Vittecoq PNAS 1995: 1195
Karpas PNAS 1990: 7613
Morand-Joubert Vox Sang 1997: 149
Early Efforts: First Generation ‘Broadly’ Neutralizing Antibodies

- 1995-2014: first bNAbs against HIV were discovered and tested in humans

- Several clinical trials focused on three monoclonal antibodies
  - 2G12 / 2F5 / 4E10
  - *In vitro* assays showed these Abs had breadth and potency

- Safe and well-tolerated in HIV-infected subjects on ART

- mAb combination therapy did not prevent viral rebound following treatment interruption
  - Viral escape mutations developed in nearly everyone

Current Efforts: Discovery of Broader and More Potent bNAbs

• Last 5 years: explosion in the number of bNAbs discovered
  – Advances in high throughput single-cell B cell amplification
  – New soluble trimeric Envs to select bNAbs

• Several classes of bNAbs are in clinical development
  – CD4 binding site antibodies
  – V3 glycan-dependent antibodies
  – V2 glycan-dependent antibodies
CD4bs bNAbs:
- CD4bs is highly conserved
- CD4bs bNAbs are very broadly neutralizing
- Two main clinical candidates
  - VRC01
  - 3BNC117
CD4bs Antibodies: VRC01

- Originally isolated from an HIV-infected individual who had untreated infection for >15 years
- Highly somatically mutated, evolved in response to viral escape
- Neutralizes 91% of tested viruses at <50 ug/ml
- Preclinical data showed protective activity in vivo
- Now in clinical development through the Vaccine Research Center at the NIH
  - Safety and pharmacokinetics (Ledgerwood et al. 2015)
  - Antiviral efficacy (Lynch et al. 2015)
VRC01: Safety and Pharmacokinetics

- Safe and well-tolerated following 43 administrations
- No development of anti-VRC01 antibodies
- Therapeutic levels up to 8 weeks

Ledgerwood Clin Exp Immunol 2015: 289
VRC01: Antiviral Efficacy

- Among 6 ART-treated subjects, VRC01 had no effect on measured virus reservoir
- Among 8 ART-untreated subjects, VRC01 led to ~1-2 log drop in plasma viremia in 6 subjects
  - 2 subjects with low VL at baseline had undetectable virus >20 days
  - 4 subjects were partially suppressed with signs of viral escape
VRC01: Ongoing/Future Studies in HIV-infected Adults

- Safety and virologic effect of VRC01 during early acute HIV infection \[NCT02591420, \text{not yet open}\]

- Safety and effect of VRC01 on markers of HIV persistence in ART-treated HIV-infected adults \[NCT02411539, \text{currently recruiting}\]

- Safety, PK, and antiviral activity of VRC01 in HIV-infected adults undergoing treatment interruption
  - \[NCT02463227, \text{ongoing but not recruiting}\]
  - \[NCT02664415, \text{not yet open}\]
  - \[NCT02471326, \text{currently recruiting}\]
CD4bs Antibodies: 3BNC117

- Originally isolated from an HIV-infected viremic controller
- Neutralized 195 out of 237 HIV-1 strains, very potent
- Preclinical data showed induction of rapid decline of plasma viremia that persisted for 20 days
- Now in clinical development through Rockefeller University and Gates Foundation
  - Safety, PK, and antiviral effect (Caskey et al. 2015)
3BNC117: Safety, Pharmacokinetics, and Antiviral Effect

- Safe and well-tolerated in 29 subjects
- Half-life of 3BNC117 was shorter in viremic subjects
- Antiviral effect was dose dependent
- Signal of long-term suppression in subjects with low VL at baseline

Caskey Nature 2015: 487
3BNC117: Ongoing/Future Studies in HIV-infected Adults

- Safety and antiretroviral activity of 3BNC117 in HIV-infected adults undergoing treatment interruption [NCT02446847, currently recruiting]

- Safety and antiretroviral activity of 3BNC117 in HIV-infected adults on combination ART [NCT02588586, currently recruiting]
V3 glycan-dependent bNAbs:
- Conformational epitope involving V3 loop and glycan structures
- bNAbs interfere with CD4 receptor binding
- Main candidate is PGT121 (another is 10-1074)
V3 Glycan-Dependent Antibodies: PGT121

- Isolated from an African donor in 2011
- Broadly neutralizing, but also extremely potent
- Therapeutic efficacy tested in non-human primates by Beth Israel Deaconess Medical Center/Harvard

![Table and diagram showing the IC50 values and viruses neutralized by PGT121 and other antibodies.]

- Walker Nature 2011: 466
- Julien PLoS Pathogen 2013: e1003342
- Sok Sci Transl Med 2014: 236ra63
- Barouch Nature 2013: 224
PGT121: Therapeutic Efficacy in Non-Human Primates

- PGT121 infusion resulted in rapid virologic control by day 7
- Viral rebound occurred only when PGT121 cleared from body; no viral escape observed
- Animals with lowest VL at baseline had long-term virologic control
PGT121: Therapeutic Efficacy in Non-Human Primates

- Host immune responses were improved
- Anti-reservoir activity observed with reductions in proviral DNA in lymph node and GI tract
- Now in clinical development through BIDMC/Harvard and Gates Foundation
**V2 glycan-dependent bNAbs:**

- Bind to apex of spike where V1V2 regions of two gp120’s meet
- bNAbs interfere with cell to cell spread
- Main candidates:
  - CAP256
  - PGDM1400
V2 Glycan-Dependent Antibodies: CAP256 and PGDM1400

- **CAP256**
  - Isolated from an HIV-infected adult in South Africa
  - Bias towards neutralizing subtype C and A viruses; remarkably potent
  - In clinical development by Centre for the AIDS Programme of Research in South Africa (CAPRISA) and Vaccine Research Center/NIH

- **PGDM1400**
  - Identified by using trimeric HIV-1 envelope as bait to select B cells
  - Also remarkably potent
  - Combination of PGDM1400 + PGT121 neutralizes 98% of viruses
  - In clinical development by BIDMC/Harvard and Gates Foundation

Moore JVI 2011: 3128
Doria-Rose Nature 2014: 55
McLellan Nature 2011: 336
Reh PLoS Pathog 2015: e1004966
Sok PNAS 2014: 17624
Future: Broadly Neutralizing Antibodies for HIV Eradication

- Preclinical data: bNAbs can target the latent viral reservoir
  - PGT121 study in non-human primates
  - VRC01, PGT121 inhibit viral replication in reactivated reservoir
  - 3BNC117 shown to have potential to kill infected cells in mice

Figure: Chun PNAS 2014: 13151
Bournazos Cell 2014: 1243
Barouch Nature 2013: 224
Barouch Science 2014: 169
Stephenson Current HIV/AIDS Reports 2016: [Epub ahead of print]
Future: Broadly Neutralizing Antibodies for HIV Eradication

- bNAbs will likely work best in combination, and with LRAs
  - bNAb cocktail plus LRAs led to undetectable cell-associated viral RNA in humanized mice

Combining bNAbs with LRAs will be tested in humans in next few years

Figure: Halper-Stromberg Cell 2014: 989
Barouch Science 2014: 169
Stephenson Current HIV/AIDS Reports 2016: [Epub ahead of print]
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