Broadly Neutralizing Antibodies for HIV Eradication

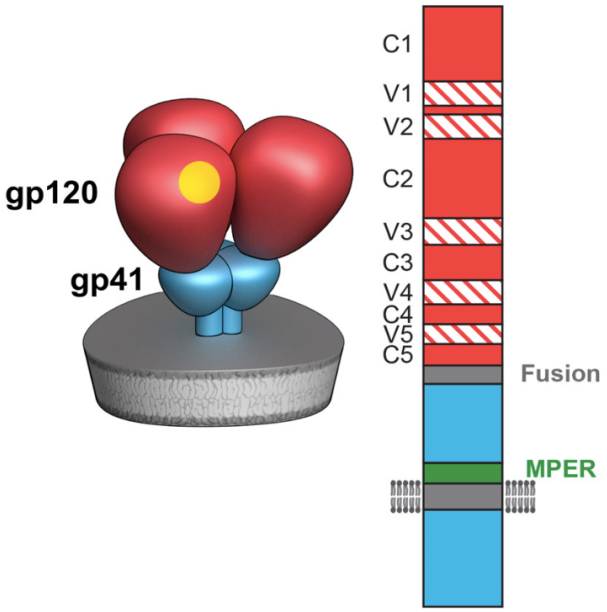
Kathryn Stephenson, MD, MPH

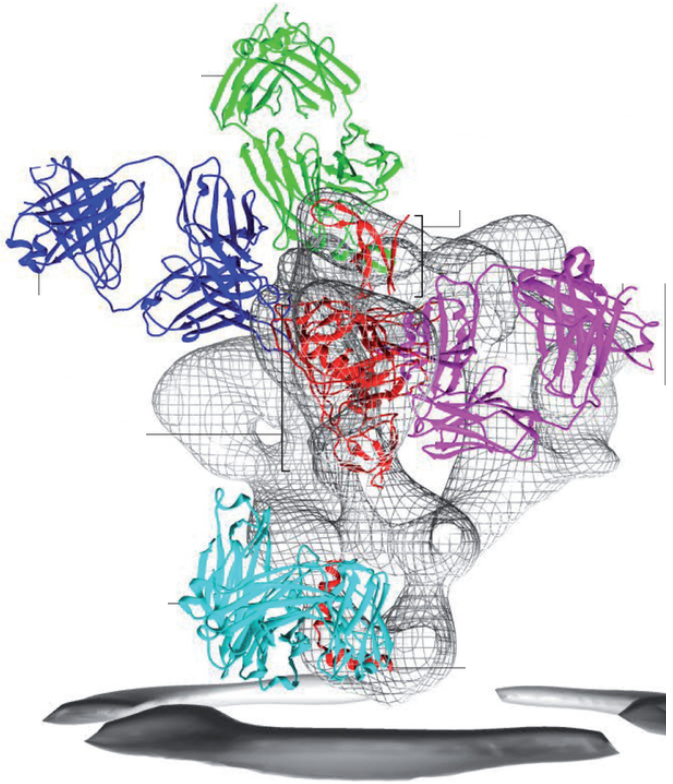
Assistant Professor of Medicine
Center for Virology and Vaccine Research
Beth Israel Deaconess Medical Center
Harvard Medical School

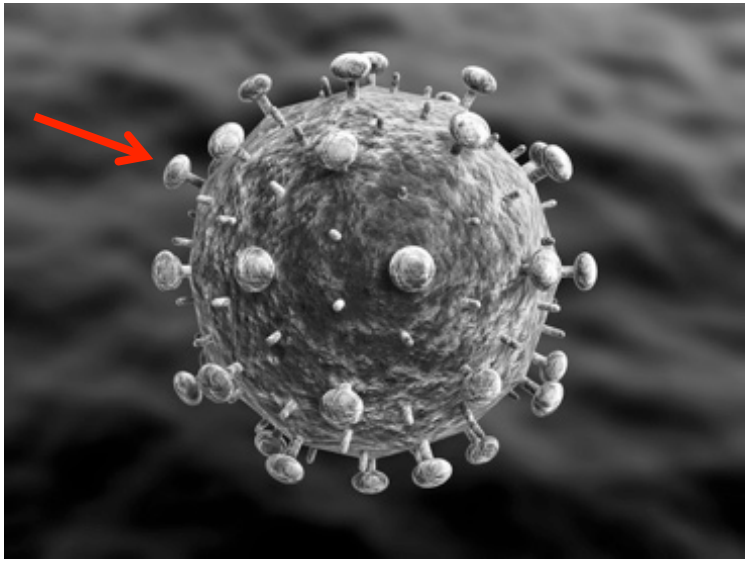
Outline: Broadly Neutralizing Antibodies for HIV Eradication

- 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)







Julien Science 2013: 1477
Lyumkis Science 2013: 1484
Harris JVI 2013: 7191

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?

Kwong Nature 1998: 393
Wyatt Nature 1998: 705

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

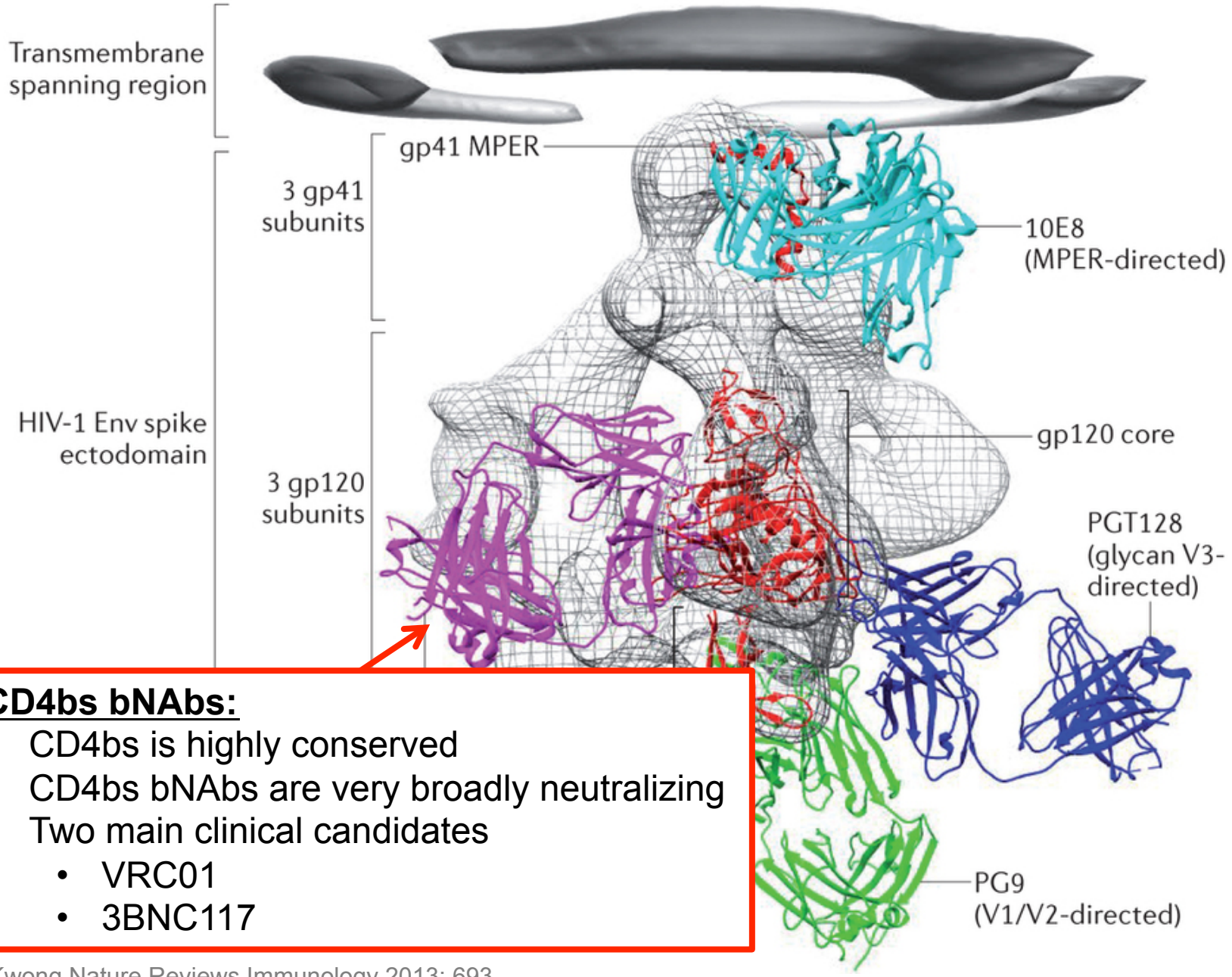
- 1995-2014: first bNAbs against HIV were discovered and tested in humans
- Several clinical trials focused on three monoclonal antibodies
  - 2G12 / 2F5 / 4E10
  - *In vitro* assays showed these Abs had breadth and potency
- Safe and well-tolerated in HIV-infected subjects on ART
- mAb combination therapy did not prevent viral rebound following treatment interruption
  - Viral escape mutations developed in nearly everyone

Armbruster JAC 2004: 915
Stiegler AIDS 2002: 2019
Trkola Nat Med 2005: 615
Joos AAC 2006: 1773
Morris PLoS ONE 2014: e116153
Gunthard JID 1994: 1384
Mehandru JVI 2007: 11016

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

Stephenson Current HIV/AIDS Reports 2016: [Epub ahead of print]



CD4bs bNAbs:

- CD4bs is highly conserved
- CD4bs bNAbs are very broadly neutralizing
- Two main clinical candidates
  - VRC01
  - 3BNC117

Kwong Nature Reviews Immunology 2013: 693

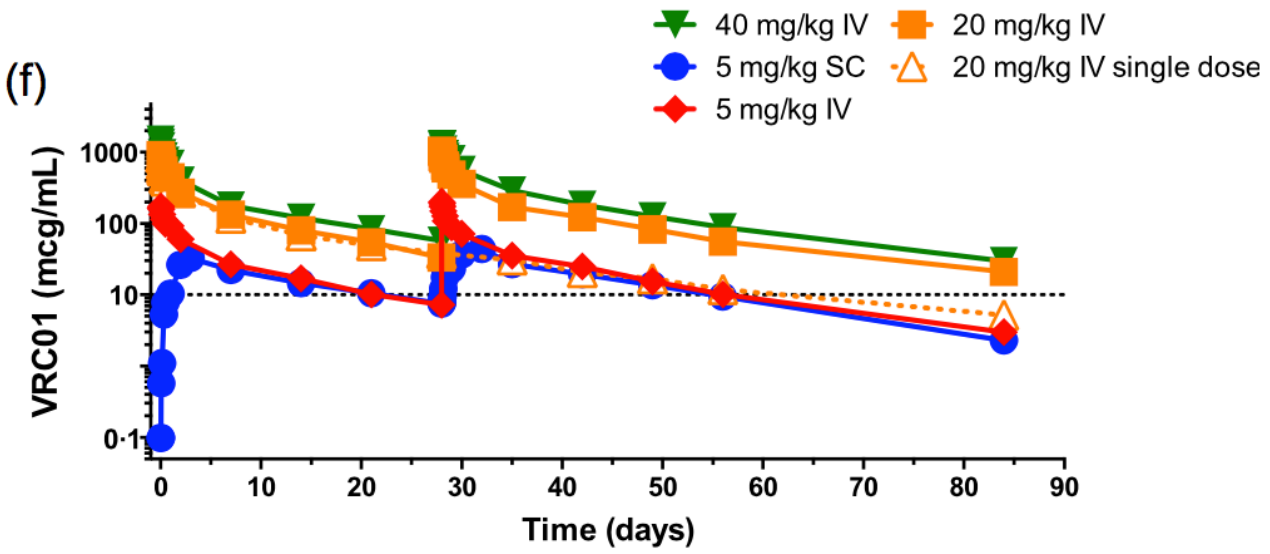
CD4bs Antibodies: VRC01

- 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)

Scheid Science 2011: 1633
Zhou Immunity 2013: 245
Wu JVI 2012: 5844
Wu Science 2010: 856
Wu Cell 2015: 470
Pegu Sci Transl Med 2014: 243ra88
Voronin PLoS MED 2014: e1001616
Ledgerwood Clin Exp Immunol 2015: 289

VRC01: Safety and Pharmacokinetics

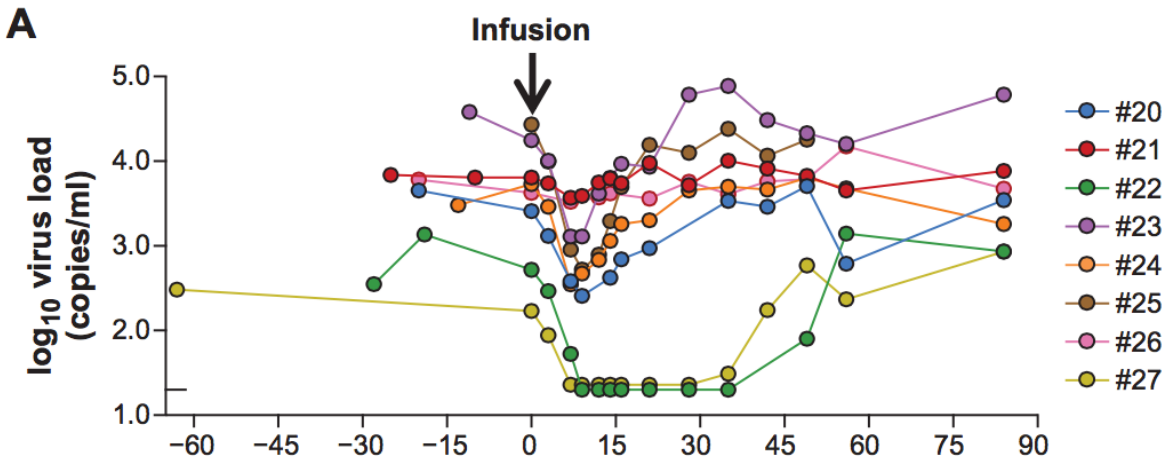
- Safe and well-tolerated following 43 administrations
- No development of anti-VRC01 antibodies
- Therapeutic levels up to 8 weeks



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



Lynch Sci Transl Med 2015: 319ra206

VRC01: Ongoing/Future Studies in HIV-infected Adults

- Safety and virologic effect of VRC01 during early acute HIV infection *[NCT02591420, not yet open]*
- Safety and effect of VRC01 on markers of HIV persistence in ART-treated HIV-infected adults *[NCT02411539, currently recruiting]*
- Safety, PK, and antiviral activity of VRC01 in HIV-infected adults undergoing treatment interruption
  - *[NCT02463227, ongoing but not recruiting]*
  - *[NCT02664415, not yet open]*
  - *[NCT02471326, currently recruiting]*

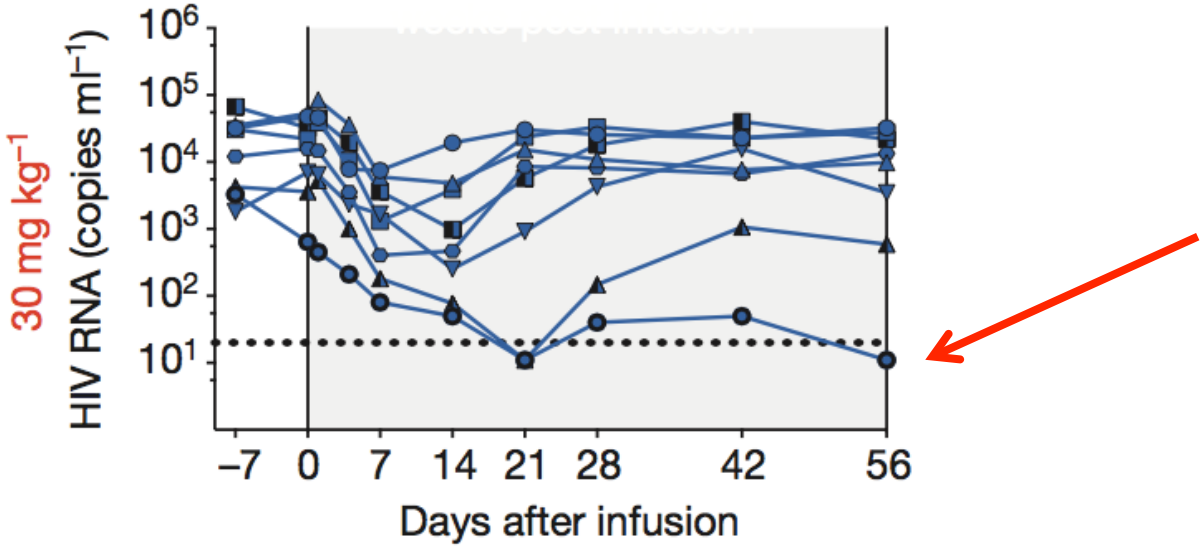
CD4bs Antibodies: 3BNC117

- 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)

Scheid Science 2011: 1633
Shingai Nature 2013: 277
Caskey Nature 2015: 487

3BNC117: Safety, Pharmacokinetics, and Antiviral Effect

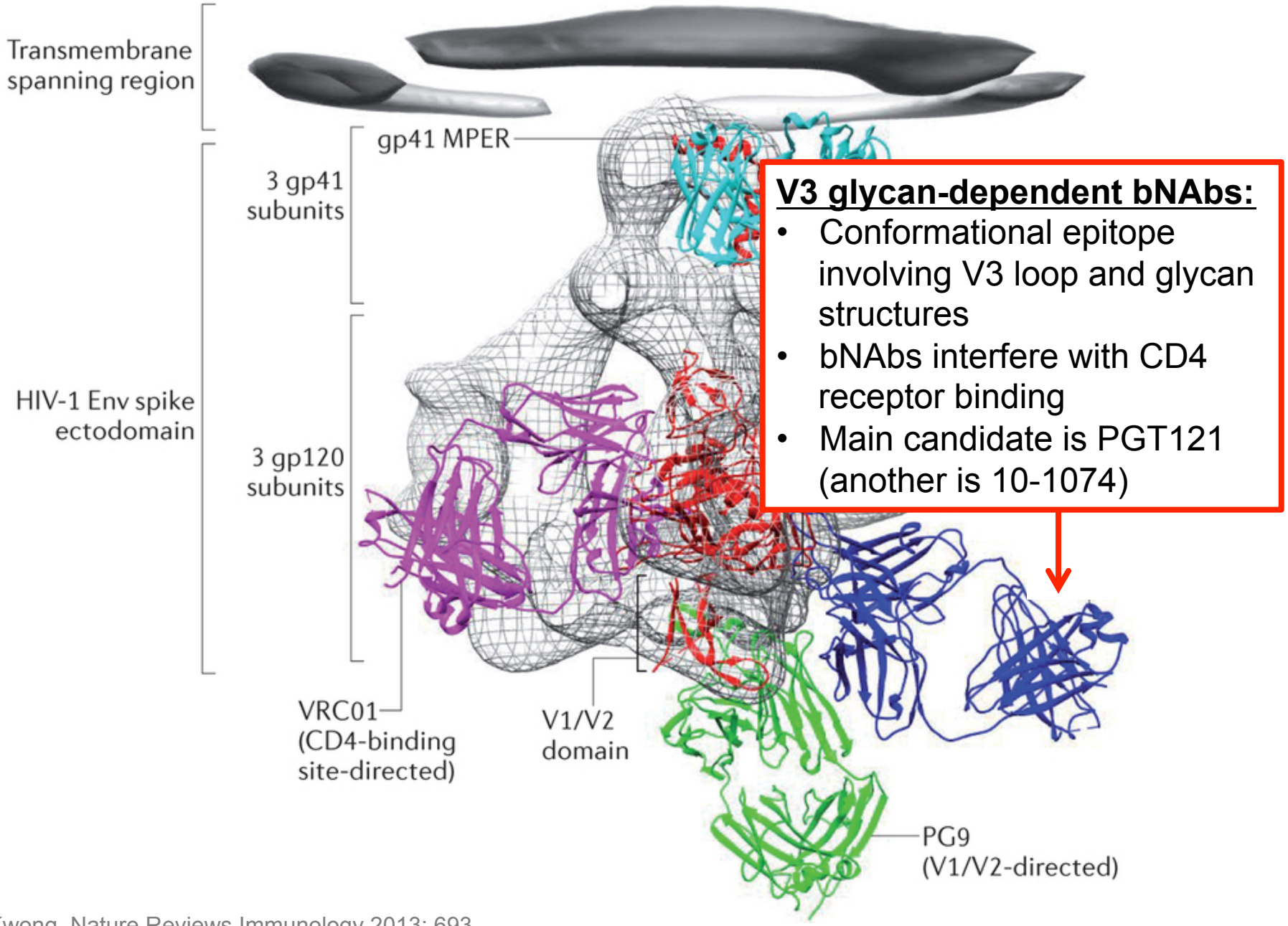
- Safe and well-tolerated in 29 subjects
- Half-life of 3BNC117 was shorter in viremic subjects
- Antiviral effect was dose dependent
- Signal of long-term suppression in subjects with low VL at baseline



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)

Kwong Nature Reviews Immunology 2013: 693

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

a

	Median IC_{50}
PGT121	0.03
PG9	0.23
VRC01	0.32
PGV04	0.20
b12	2.82
2G12	2.38
4E10	3.41

Key:
- < 0.2 (μg ml^{-1})
- 0.2–2 (μg ml^{-1})
- 2–20 (μg ml^{-1})

b

	Viruses neutralized		
	IC_{50} < 50 μg ml^{-1}	IC_{50} < 1 μg ml^{-1}	IC_{50} < 0.1 μg ml^{-1}
PGT121	70	57	44
PG9	77	54	29
VRC01	93	74	20
PGV04	88	65	25
b12	34	10	2
2G12	32	11	1
4E10	96	13	1

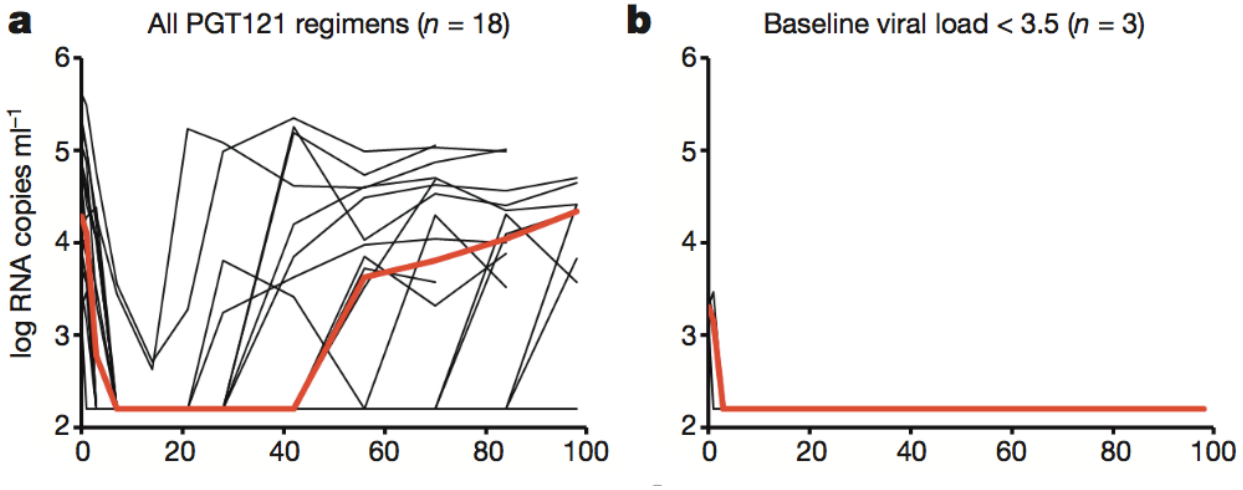
Key:
- > 90 %
- 60 - 90 %
- 30 - 60 %
- 1 - 30 %

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

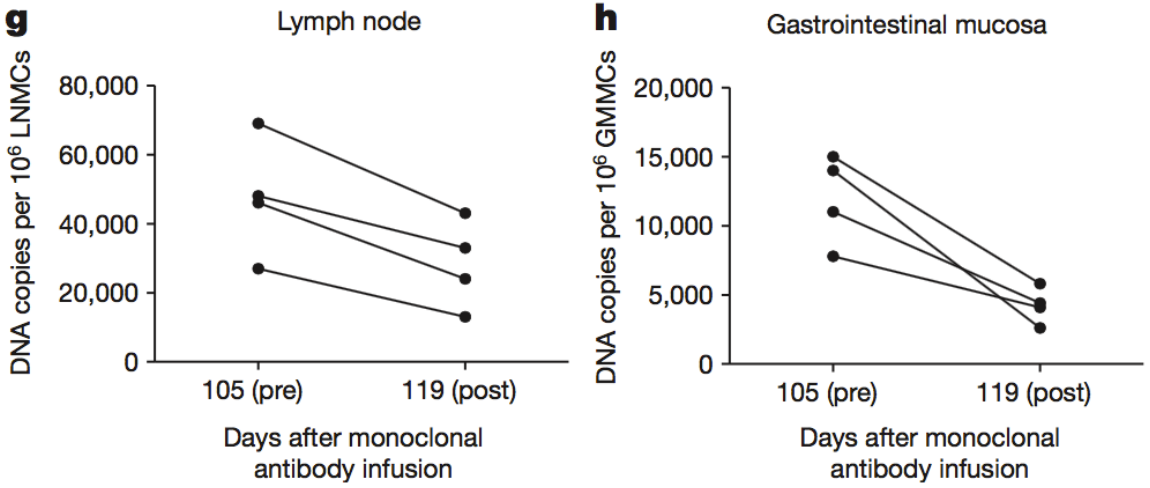
- PGT121 infusion resulted in rapid virologic control by day 7
- Viral rebound occurred only when PGT121 cleared from body; no viral escape observed
- Animals with lowest VL at baseline had long-term virologic control



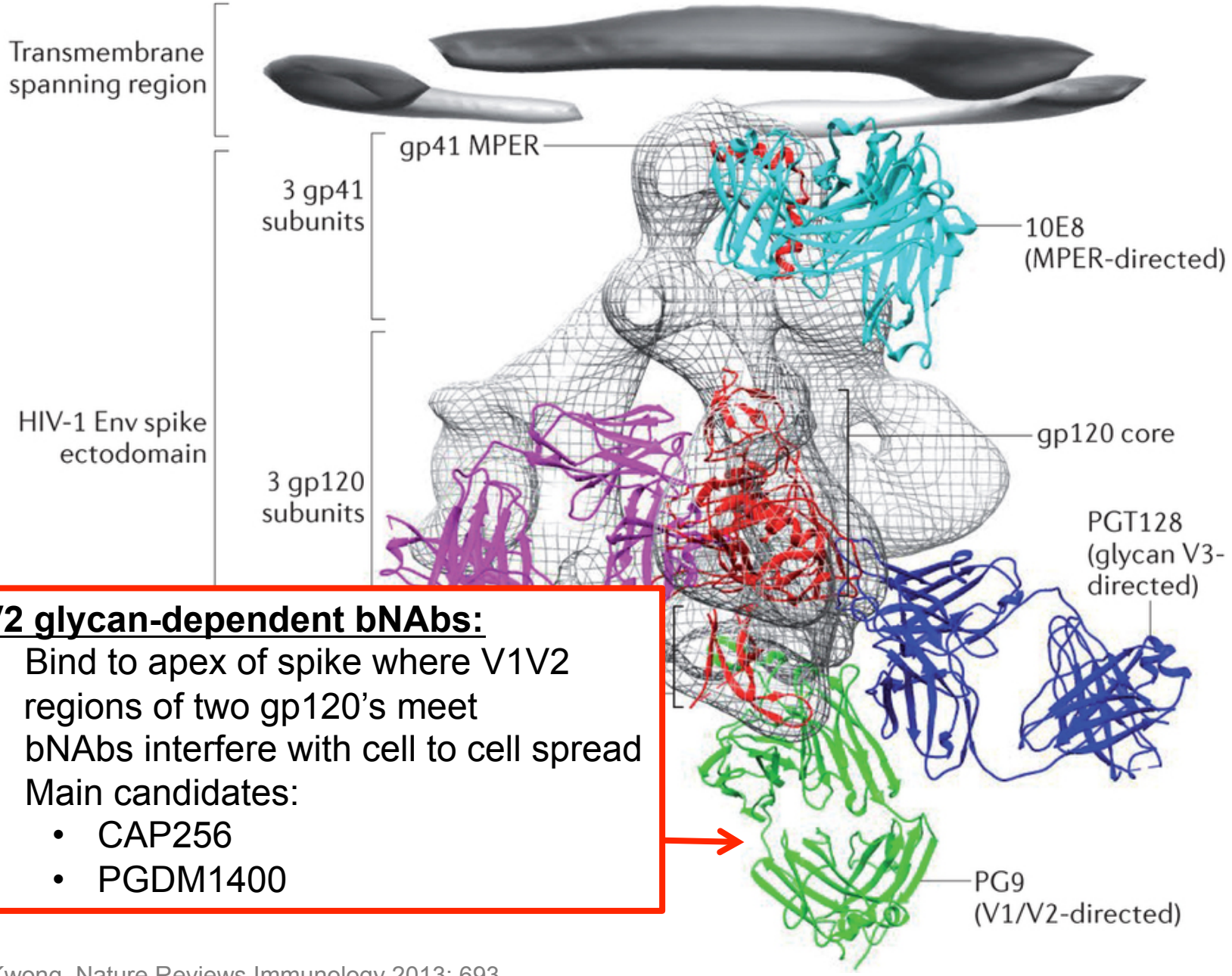
Barouch Nature 2013: 224

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



Barouch Nature 2013: 224



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

Kwong Nature Reviews Immunology 2013: 693

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

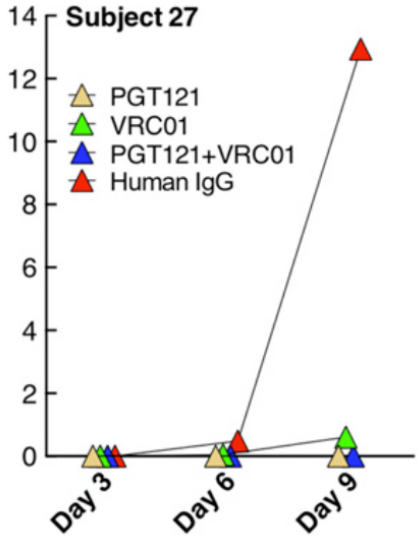
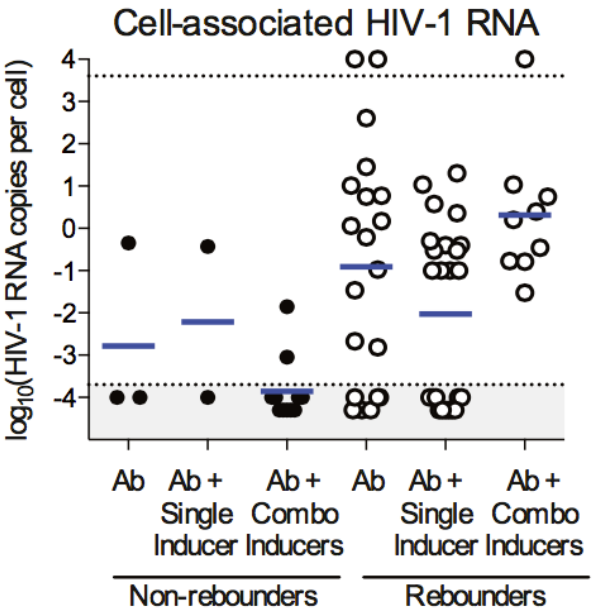


Figure: Chun PNAS 2014: 13151
Bournazos Cell 2014: 1243
Barouch Nature 2013: 224
Barouch Science 2014: 169
Stephenson Current HIV/AIDS Reports 2016: [Epub ahead of print]

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
Klein J Exp Med 2014: 2361

Stephenson Current HIV/AIDS Reports 2016: [Epub ahead of print]

Acknowledgements:

- Therapeutic Antibody Program at BIDMC/Harvard
  - BIDMC/Harvard: Dan Barouch (PI), Boris Juelg, Lori Maxfield, Faye Stephens, Peter Abbink
  - Gates Foundation/IAVI: Fran Priddy, Huub Gelderblom, Lisa Sunner, Chris Gast
- Funding
  - NIH K23 AI060354
  - Ragon Institute of MGH, MIT, and Harvard
  - amFAR, the Foundation for AIDS Research