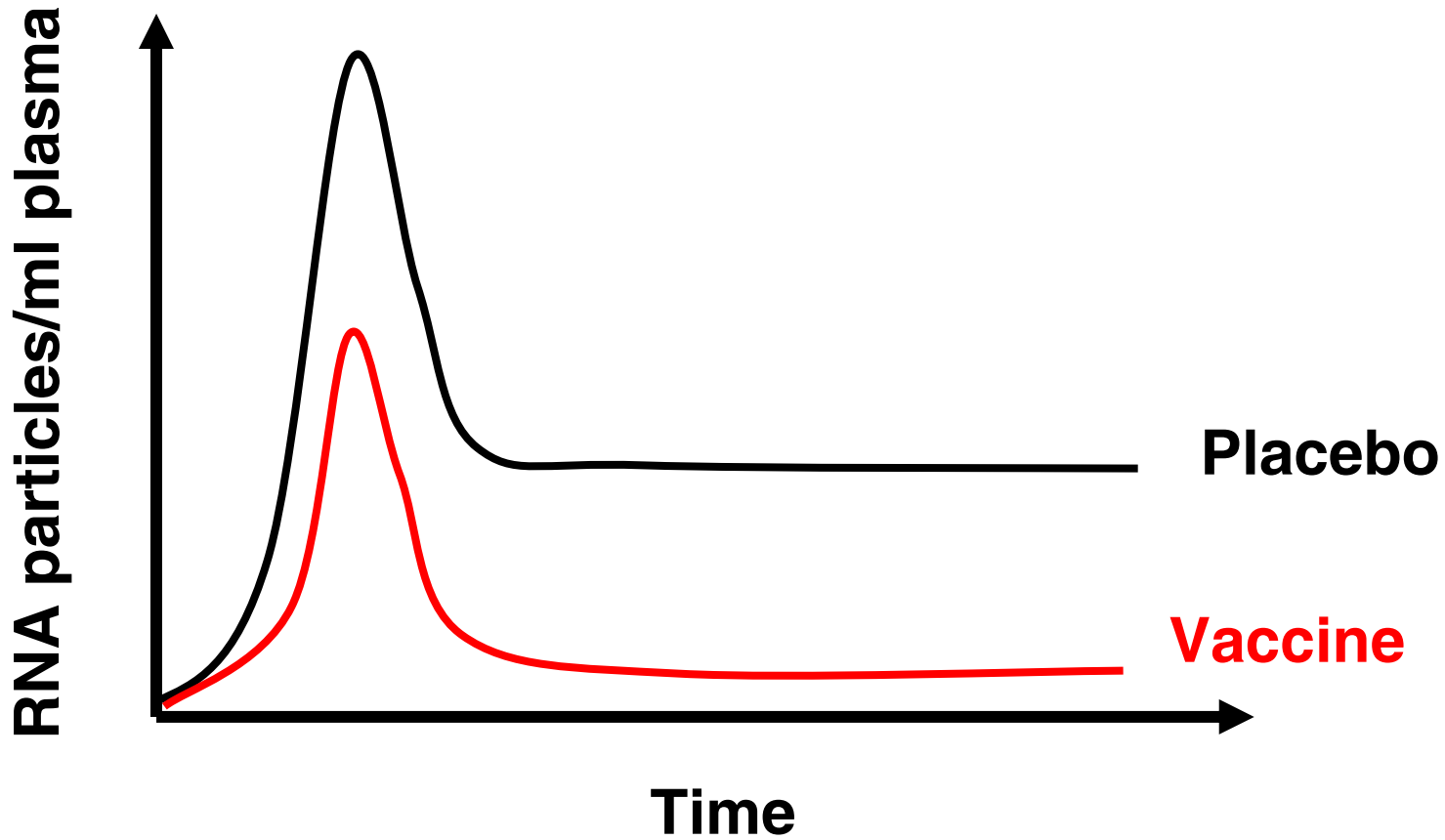


Correlates of vaccine induced T cell immunity

Bruce D Walker, MD

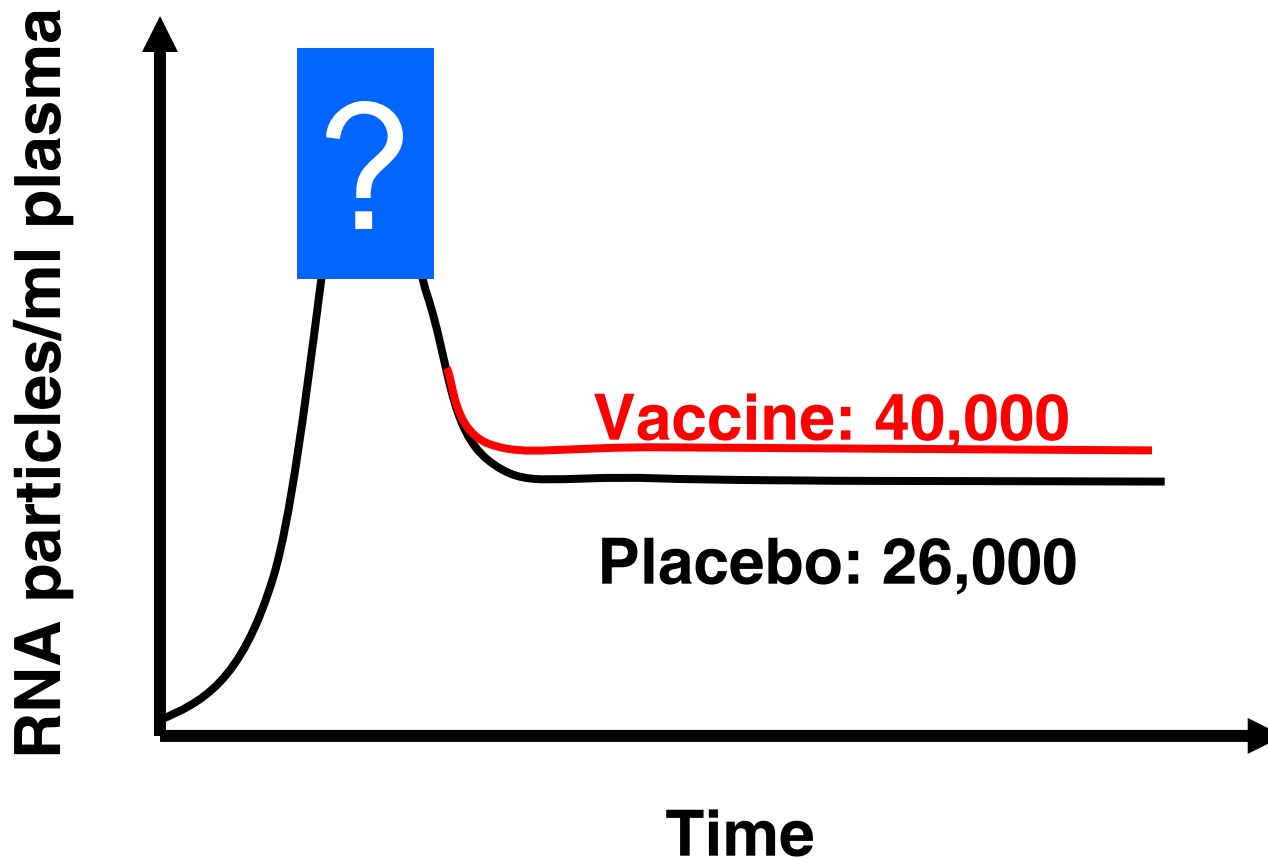
Partners AIDS Research Center
(Ragon Institute)

T cell vaccination?

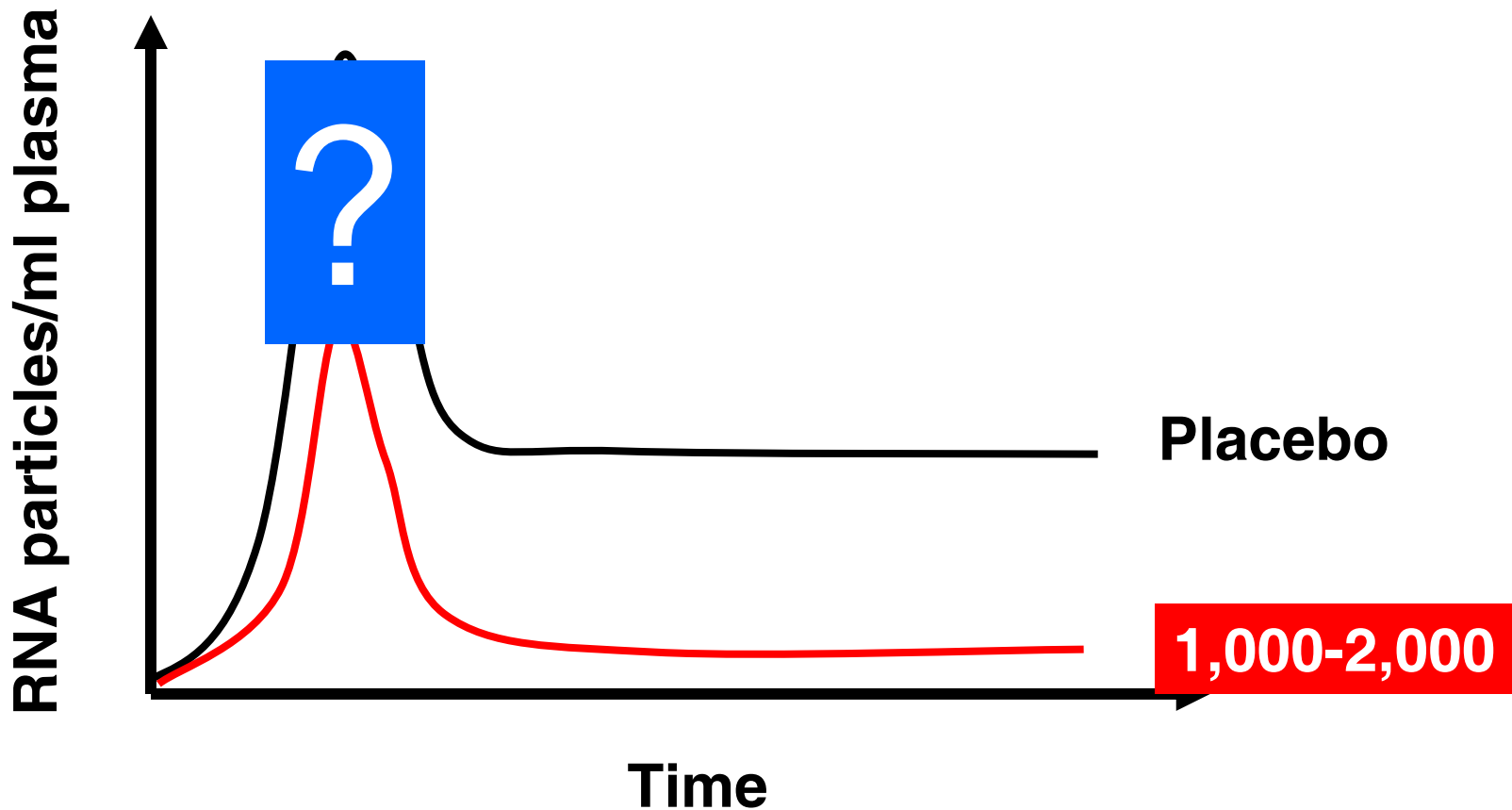


STEP Trial Results

Impact on set-point viral load



HIV Controllers: A human model for successful T cell vaccination?

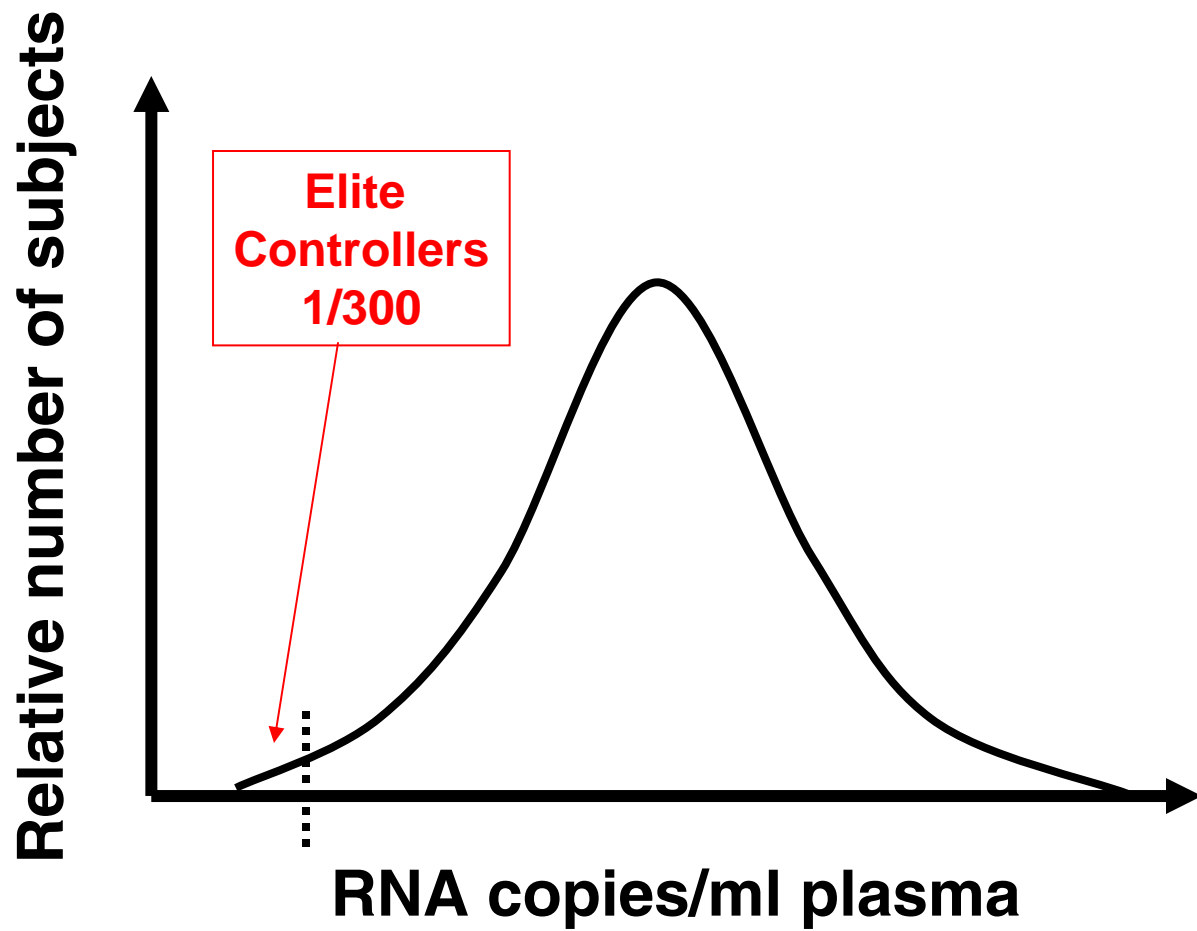


What will a successful T cell vaccine be?

- A vaccine that allows for infection but keeps the virus in check
 - Decreased chance of transmission to others
 - Decrease chance of disease progression

A model for “successful” vaccination?

- Elite controllers (EC):
 - VL < 50 RNA Copies/ml plasma
- Viremic controllers (VC)
 - VL < 2000 RNA Copies/ml plasma



www.hivcontrollers.org

Address  http://www.hivcontrollers.org/

The International HIV Controllers Study

 INTERACTIVE INTERNATIONAL MEMBER MAP

Search the Site

- About HIV Controllers
- About the Study
- Study Members
- Enrolling in the Study
- For Health Professionals
- Funding Source
- News Center
- Contact



Are you HIV positive with a low viral load, without medications? You could help us better understand HIV. Consider enrolling in our study.

The goal of the International HIV Controllers Study is to help scientists understand why some people are able to control HIV infection without the need to take any medications. These findings could assist in the development of vaccines and new therapies.

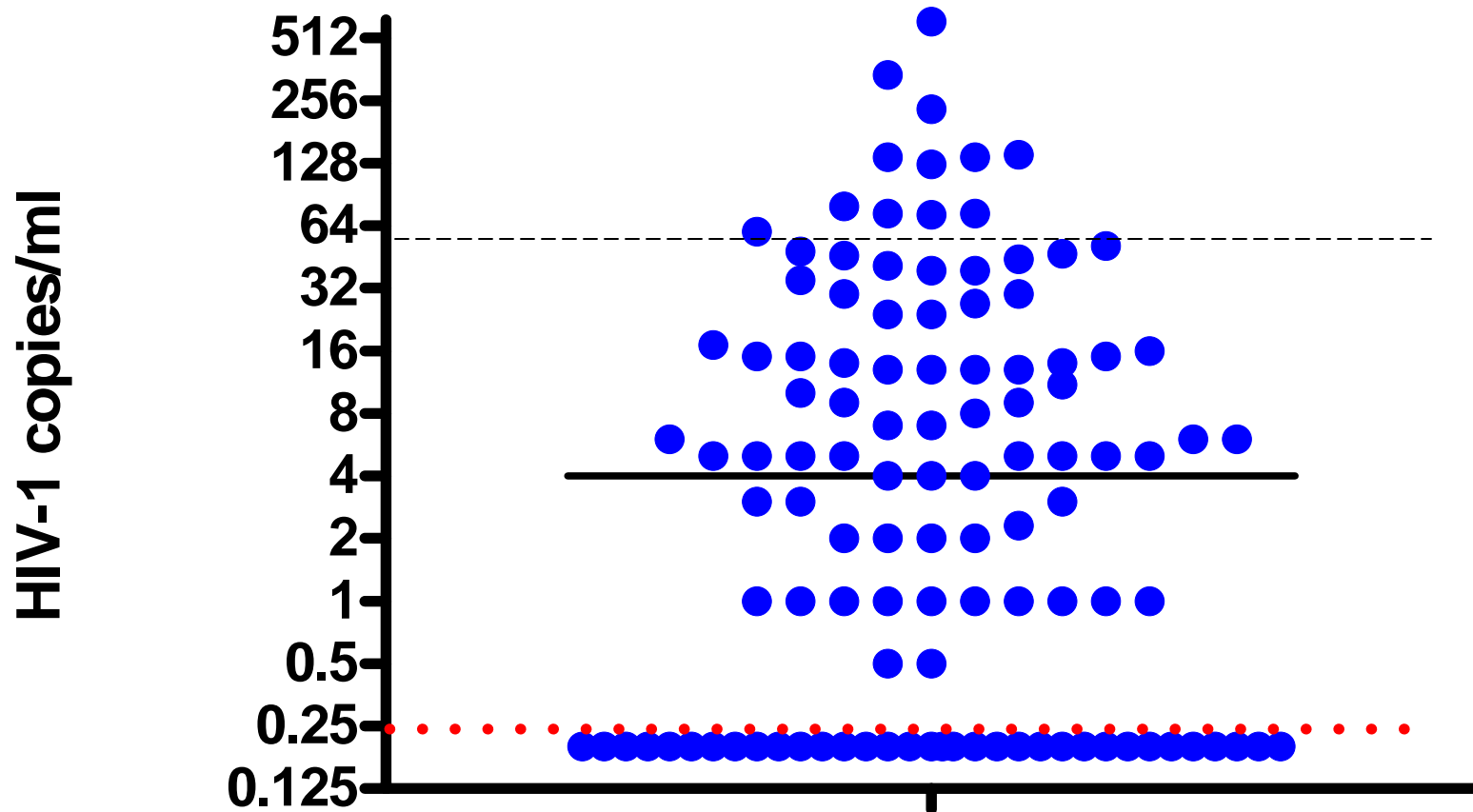
© 2008 The International HIV Controllers Study
Partners AIDS Research Center • 149 13th Street, Room 5224 • Charlestown, MA 02129
617-726-5536 / 617-643-3643 • elitecontrollerstudy@partners.org
[Admin Login](#)

 Local intranet

Recruitment

- Elite controllers (EC):
 - VL < 50 RNA Copies/ml plasma
 - 419 subjects
- Viremic controllers (VC)
 - VL < 2000 RNA Copies/ml plasma
 - 729 subjects

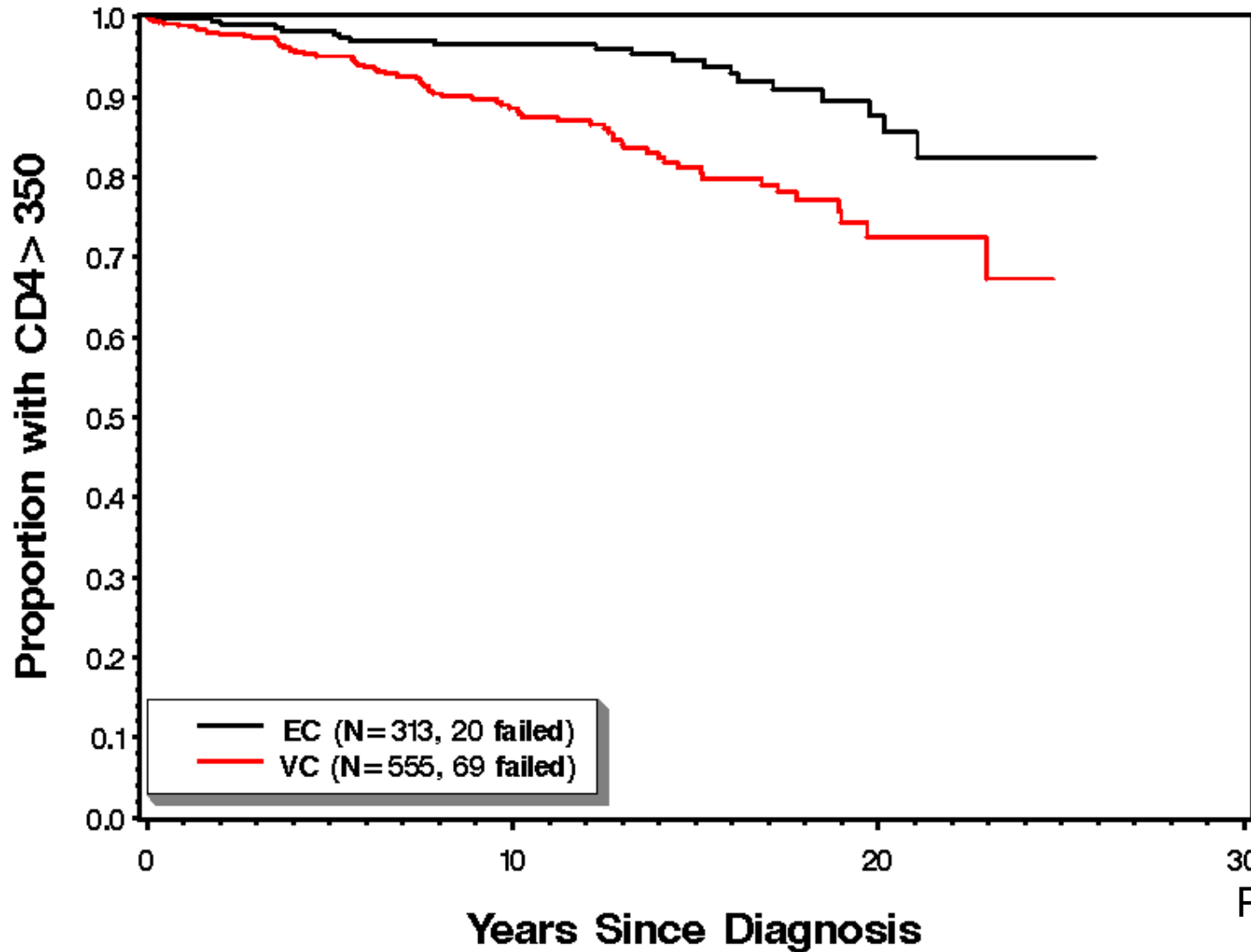
Viral load in Elite Controllers: Increased sensitivity RNA assay



n= 84 Elite Controllers

Palmer, Coffin et al

Do HIV Controllers Progress?



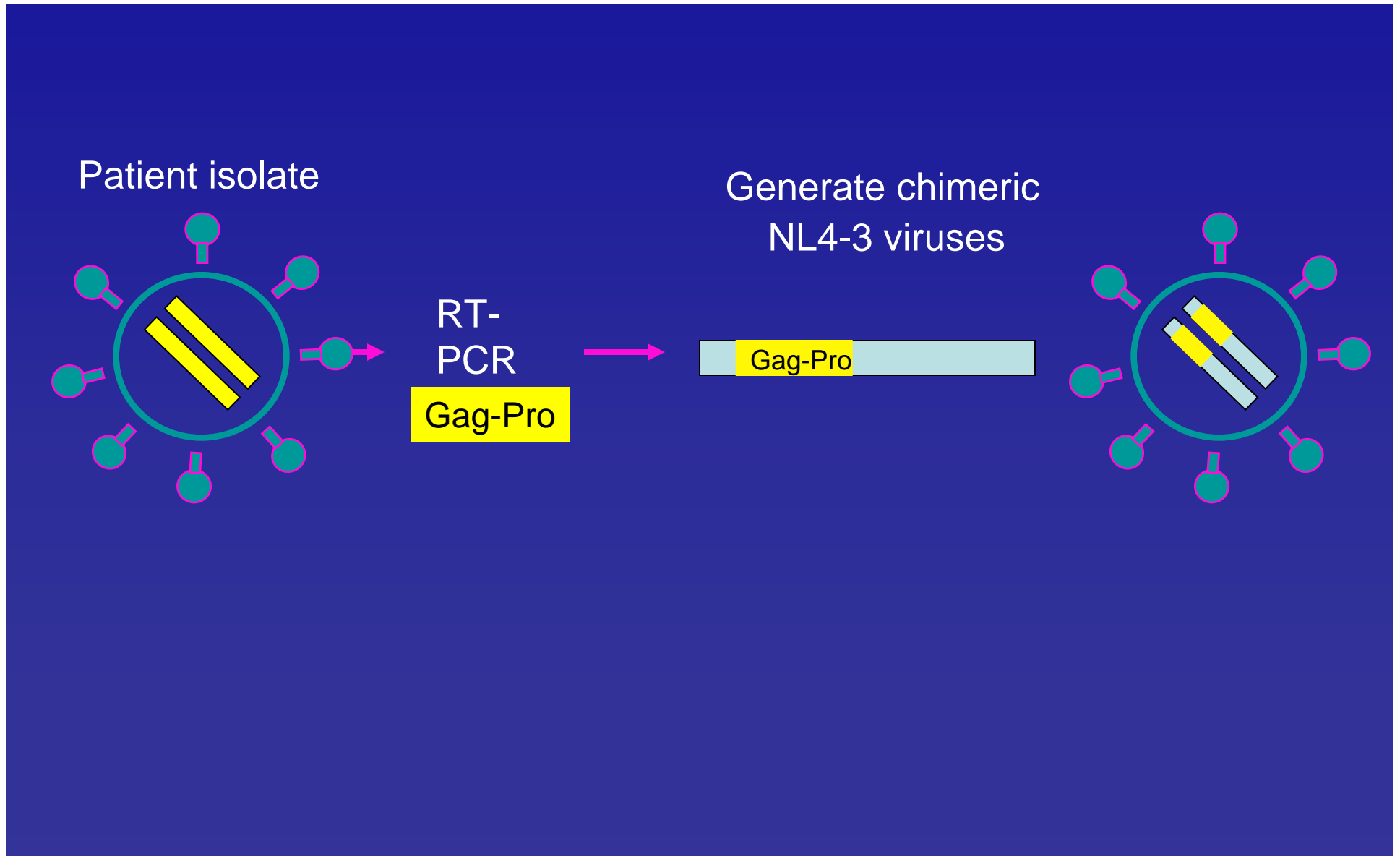
What accounts for elite control?

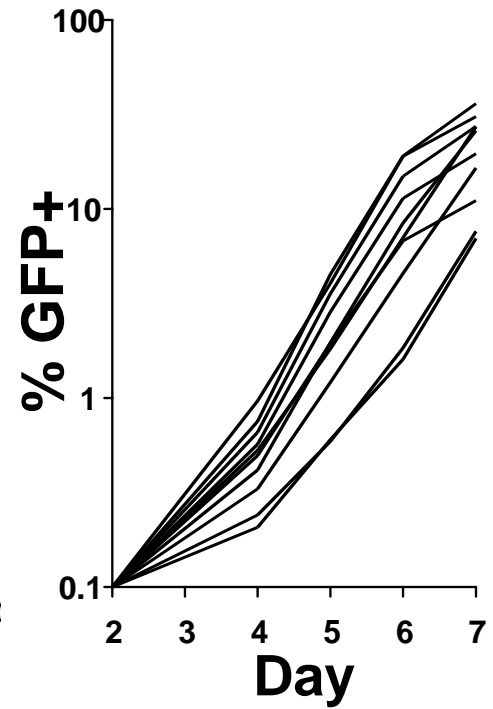
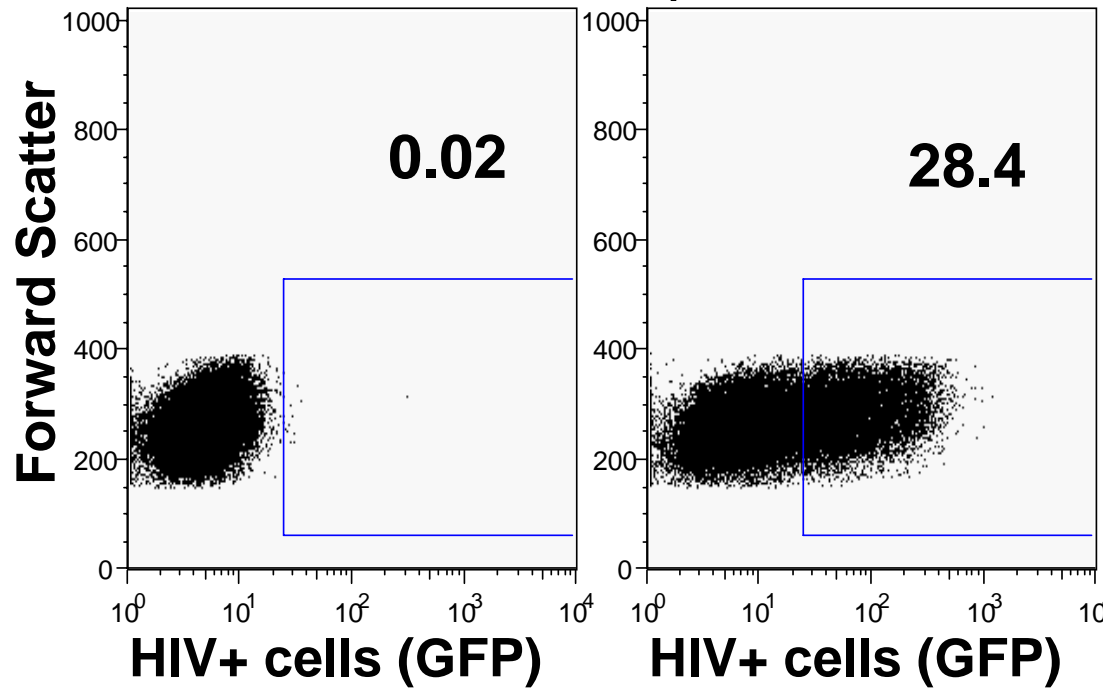
- Virology
- Host Genetics
- Immunology

Does reduced viral replicative capacity contribute to elite control?

- Subjects
 - 52 elite controllers (VL < 50 copies)
 - 41 chronic progressors (median plasma VL 80K)
- Methods
 - Construct chimeric viruses
 - Measure replication rate

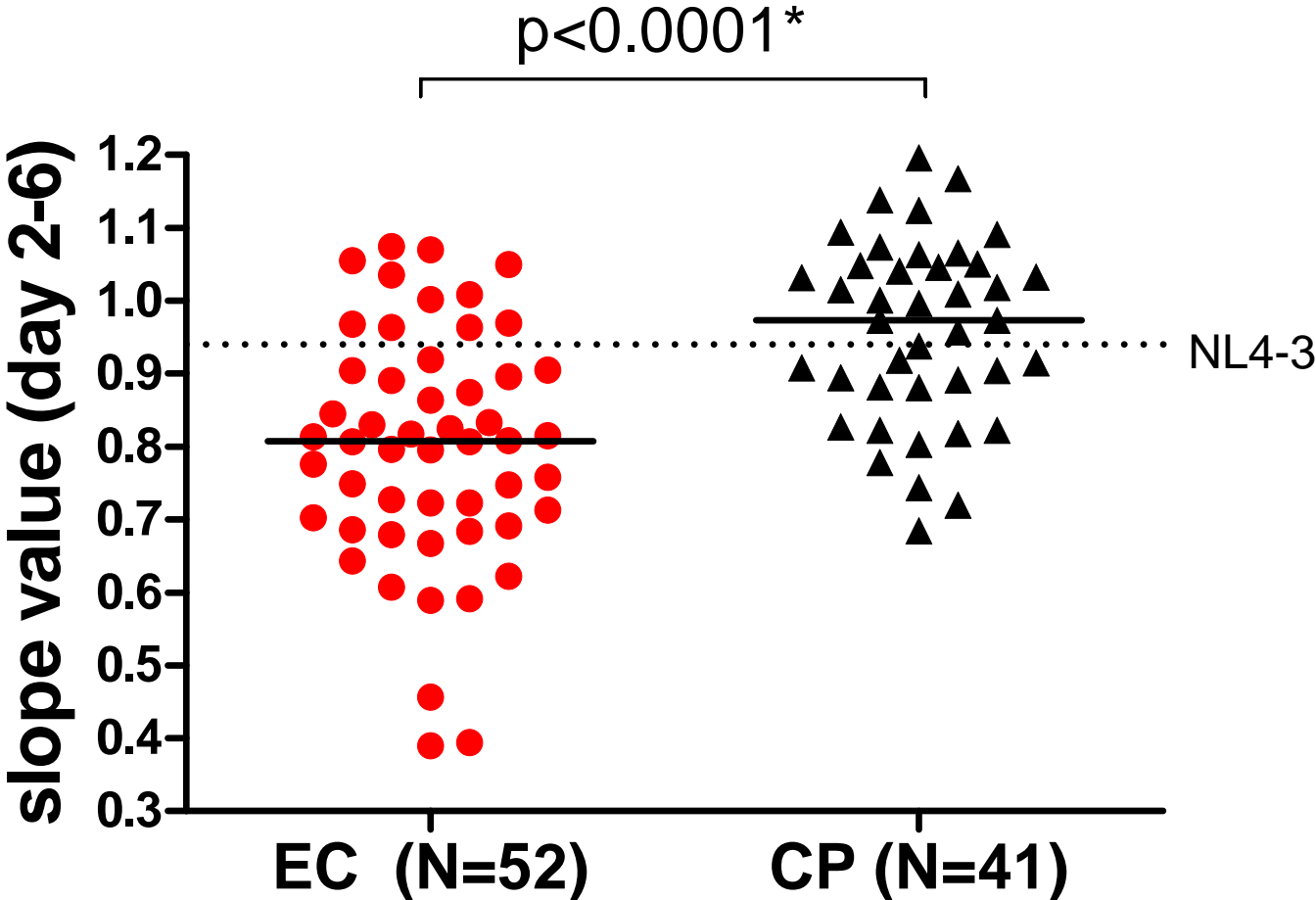
Generation of chimeric viruses using Gag-Pro sequences from clinical isolates





Brockman et al, 2007

Average of 2 experiments



Conclusion I

- Elite controller viruses exhibit reduced replication capacity

- Virology
- **Host Genetics**
- Immunology

Genome wide association scan on HIV Controllers

- Completed
 - 601 Controllers
 - 912 Progressors
 - 650,000 SNPs per patient
- Pending in queue
 - 234 Controllers
 - 1230 Progressors
 - 1M SNPs
- Recruitment goal
 - 2000 Controllers
 - 3000 Progressors

1513 subjects
601 Controllers, 912 Progressors

Pre-scan filters
DNA quantity/conc
fingerprint genotyping
49 samples removed

1466 samples submitted
to Illumina platform

Scanner Error
31 samples removed

Call rate below 95%
102 samples removed

Fingerprint mismatch
7 samples removed

1326 samples available for data freeze
525 Controllers, 801 Progressors

1326 samples available for data freeze
525 Controllers, 801 Progressors

Sample Duplicates
9 samples removed
(6 Controllers, 3 Progressors)

Misclassified Controllers
20 samples removed

Ethnicity Cleanup
Re-grouped obviously misclassified samples

EIGENSTRAT Outliers
66 Samples Removed
(26 Controllers, 40 Progressors)

Asian Samples
20 samples removed
(9 Controllers, 11 Progressors)

1211 samples available for analysis
464 Controllers, 747 Progressors

Population Stratification

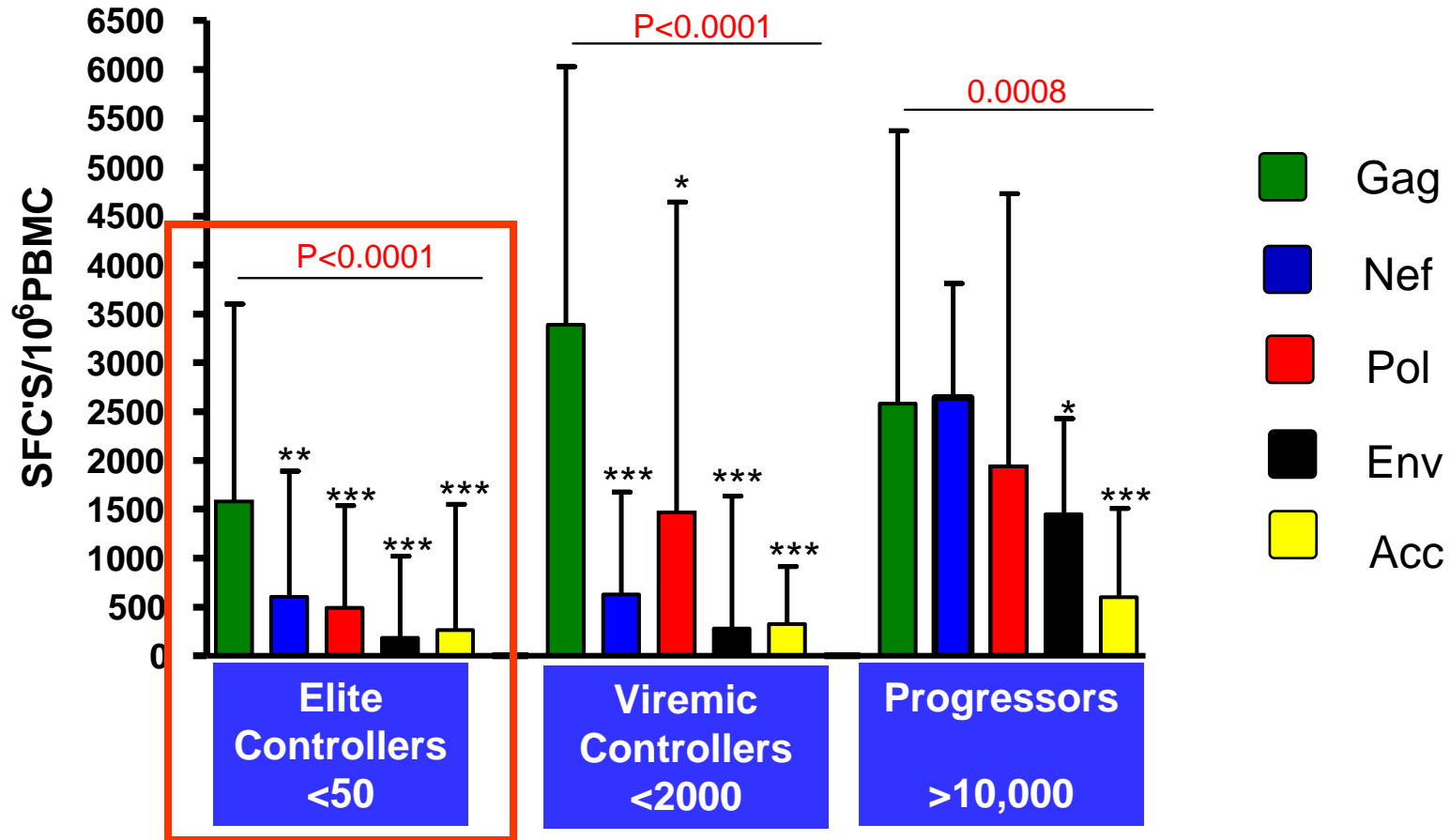
- Ignoring fundamental genetic differences within samples will lead to spurious associations
- Solution: Analyze 3 groups separately (white, black, hispanic) and combine results in meta-analysis

Conclusion II

- SNPs with strong genome wide significance are present in the MHC, suggesting an immune mediated mechanism

- Virology
- Host Genetics
- Immunology

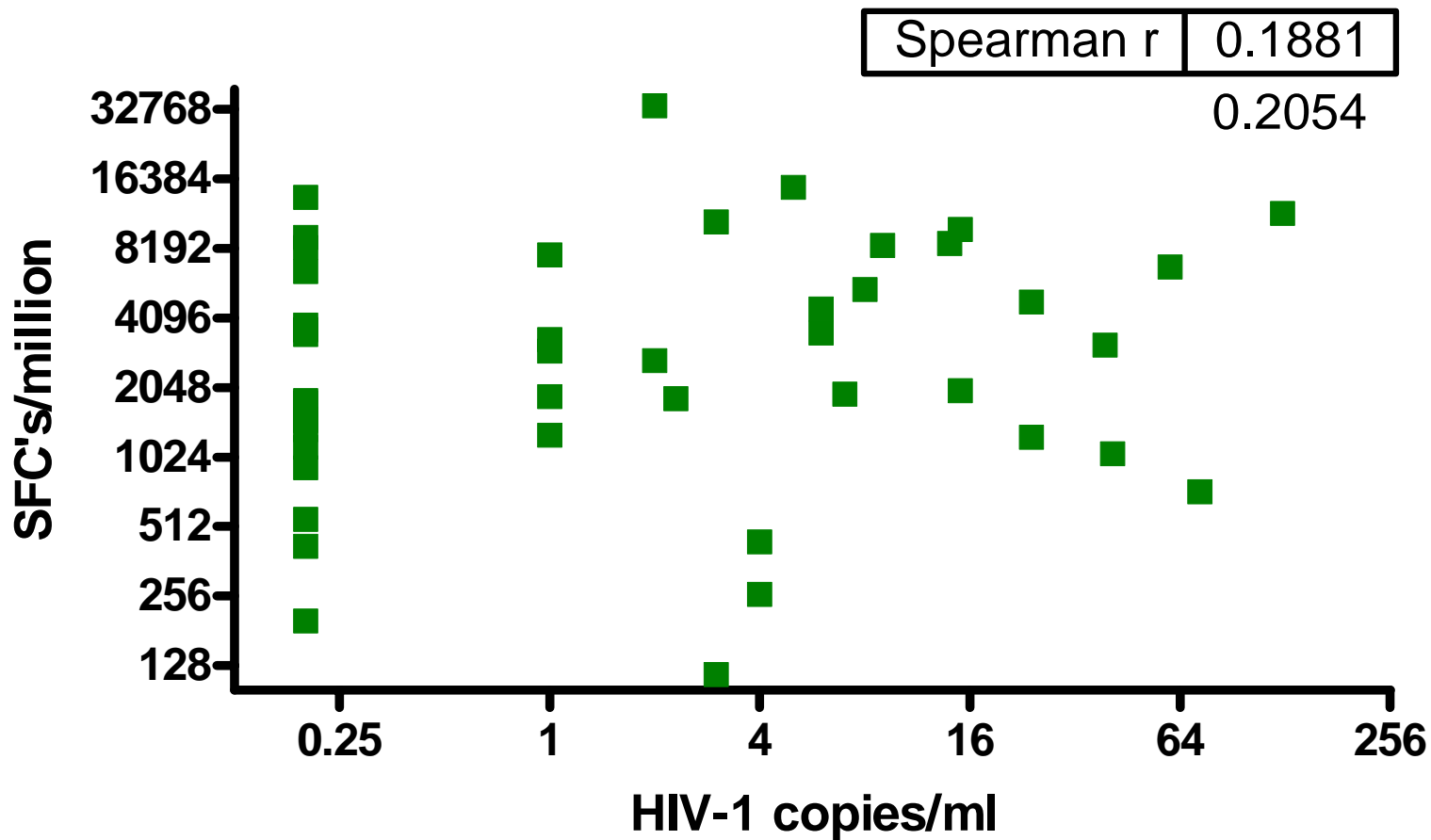
CD8 T cell responses are weaker but more Gag-focused in Elite Controllers



What are the immunologic characteristics of extreme control?

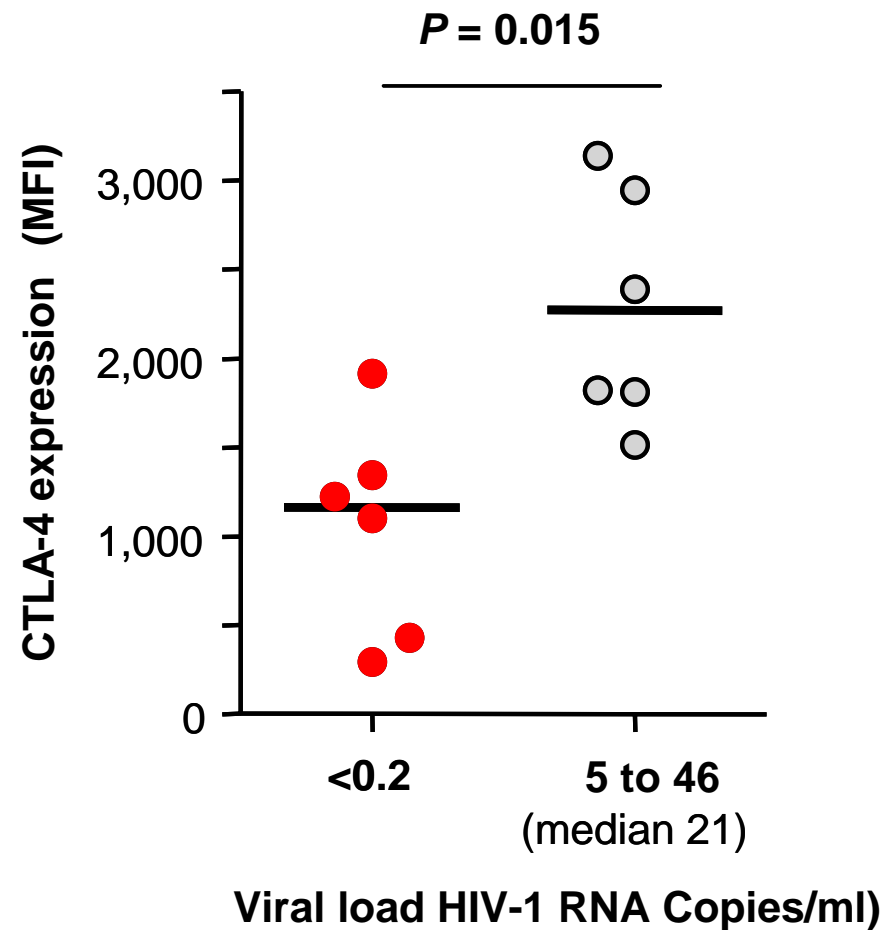
- Subjects
 - 88 Elite controllers with known VL < 50 copies
- Methods
 - CD8 T cell responses by IFN-g Elispot
 - CD4 T cell responses by functional phenotype
 - Nab responses to reference viruses
 - WB analysis

Magnitude of CD8 T cell responses

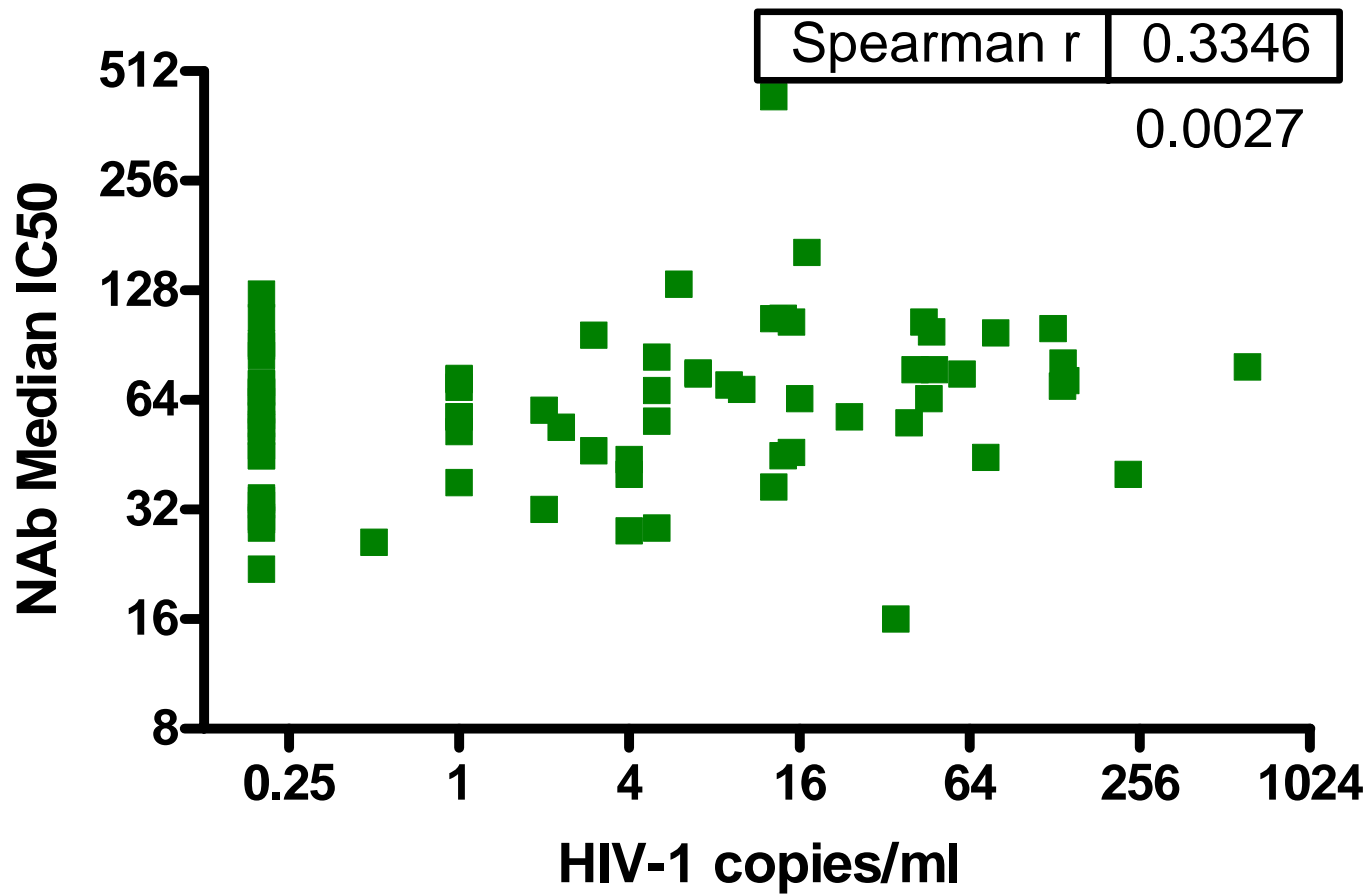


Pereyra et al

CD4 cells in elite controllers: Negative immunoregulatory molecules



*The magnitude of HIV antibody response vs
plasma HIV virus load*

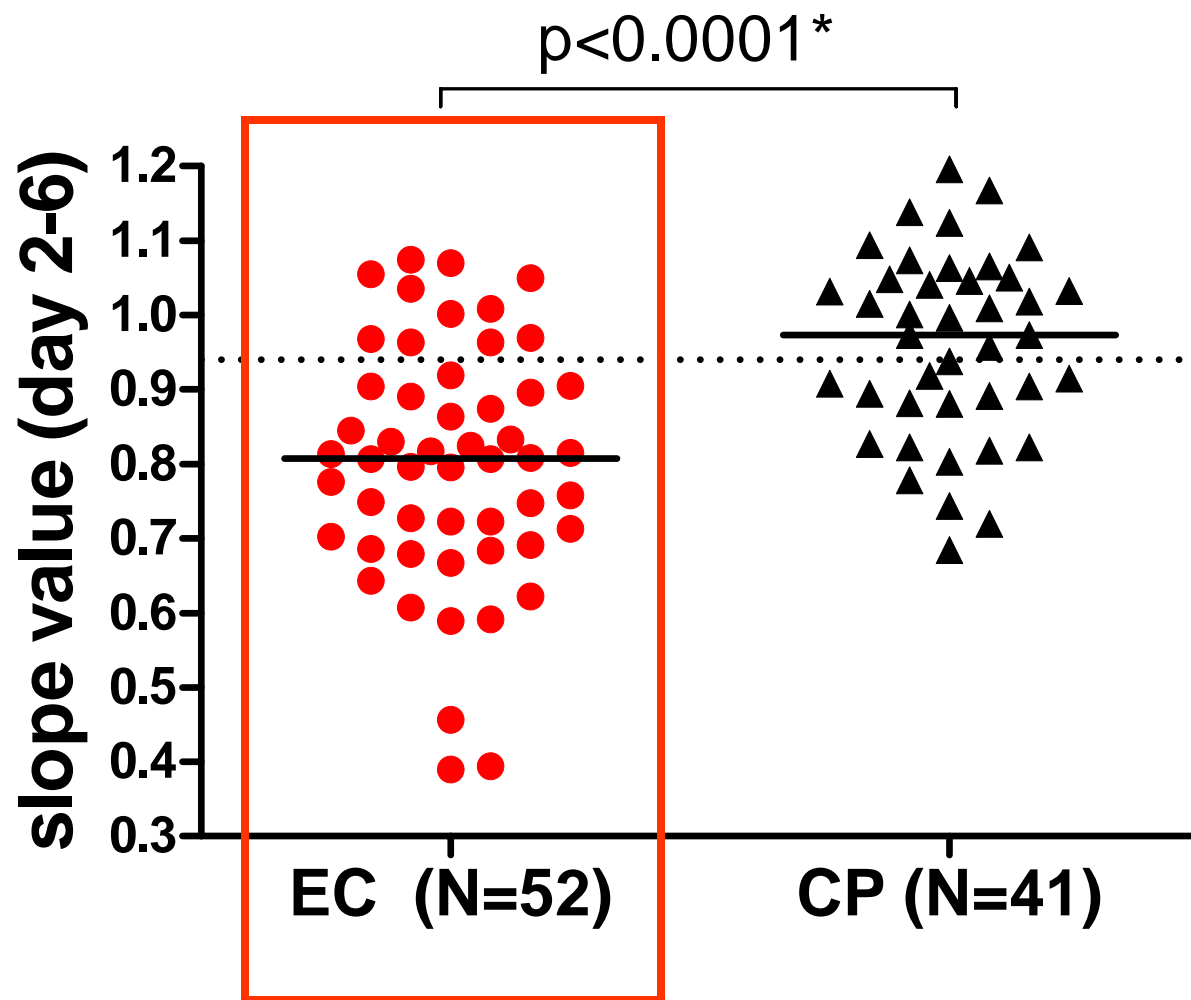


Pereyra et al

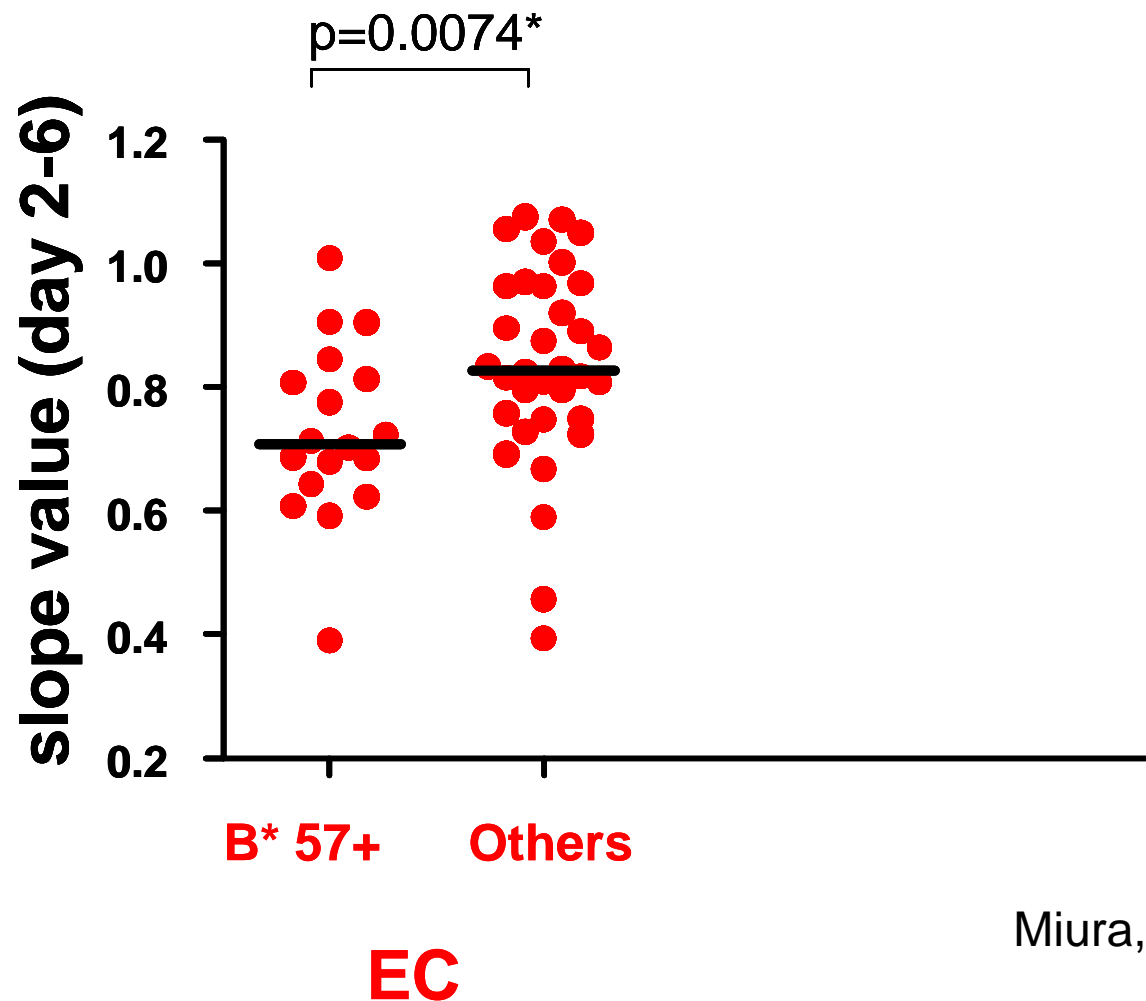
Conclusion III

- Some elite controllers maintain such low viral loads that HIV-specific immune activation is extremely weak

Is there a link between immune responses
and viral fitness?

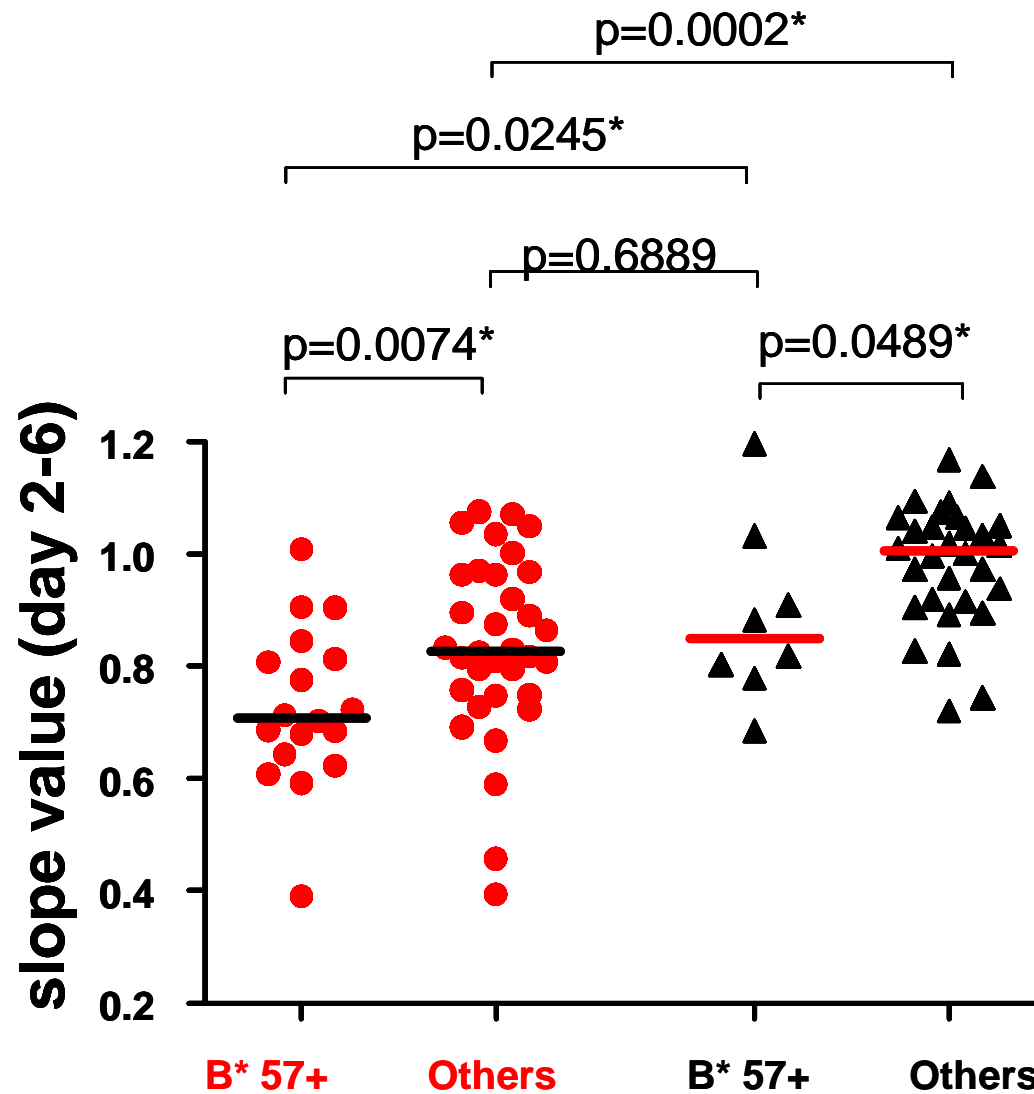


HLA influences viral replication capacity



Miura, Brockman et al

HLA influences viral replication capacity



EC

CP

Miura, Brockman et al

Is there a link between HLA,
viral replication capacity, and
HIV-specific CD8 T cell induced mutations?

TSTLQEQIAW

TW10

--**N**-----

T242N Escape

Examine viral fitness under B*57/5801 selection pressure

- Subjects
 - 23 Elite Controllers
 - 27 Viremic patients
- Methods
 - Sequence plasma viral RNA
 - Construct mutations into NL4-3
 - Examine effects on viral fitness

TW10 sequence in plasma: Progressors

DRLHPV	HAGPIAPGQM	REPRGSDIAGT	<u>TSTLQEQIGW</u>	MTNNPP
-----A	Q-----P---	I-----	--N-----T-	-----
N-----	-----V-----	-----	--N-----	-----
--T--X	-----V-----	-----	--N-----	--S---
-----	-----P----L	-----	--N-----	-----
--M---	-----	-----	--N-----	--S---
-----	Q---V----L	-----	--N-----A-	--H---
-----X	-----X-----	-----	--N-----	--S---
-----	-----V-----	-----	--N-----	-----
-----	-----	-----	--N-----A-	-----
-----	-----	-----	--N-----	-----
-----	-----L	-----	-----VQ-	I-----
-----	-----V----L	-----S	-----	--S---

Why is the mutation that causes a fitness defect (T242N) more prevalent in persons with higher viral loads?

TW10 associated mutations in HLA B*57 positive elite controllers

TW10 Gag epitope

TSTLQEQIAW ---

Wild type

--**N**-----

Escape in Progressors

---**D**---**X**

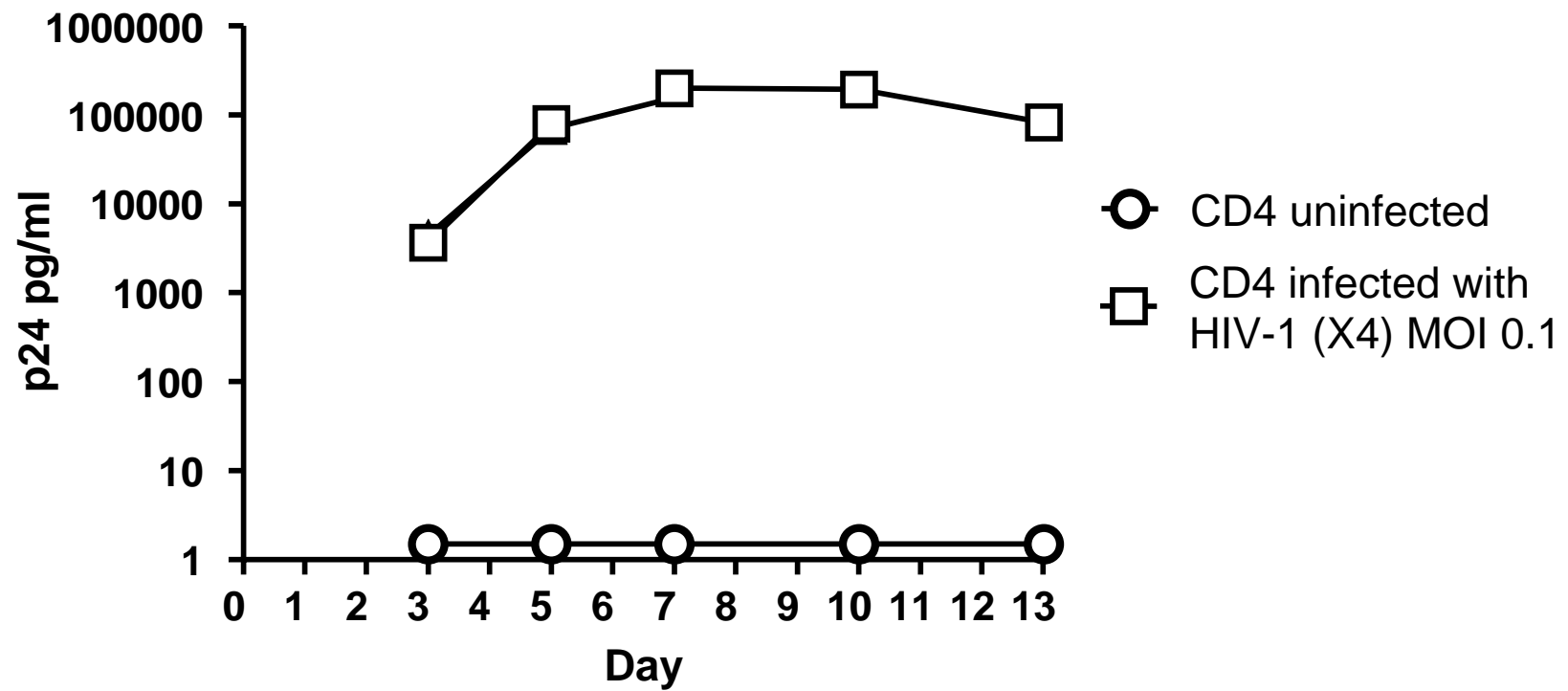
Escape, only in Controllers

Conclusions IV

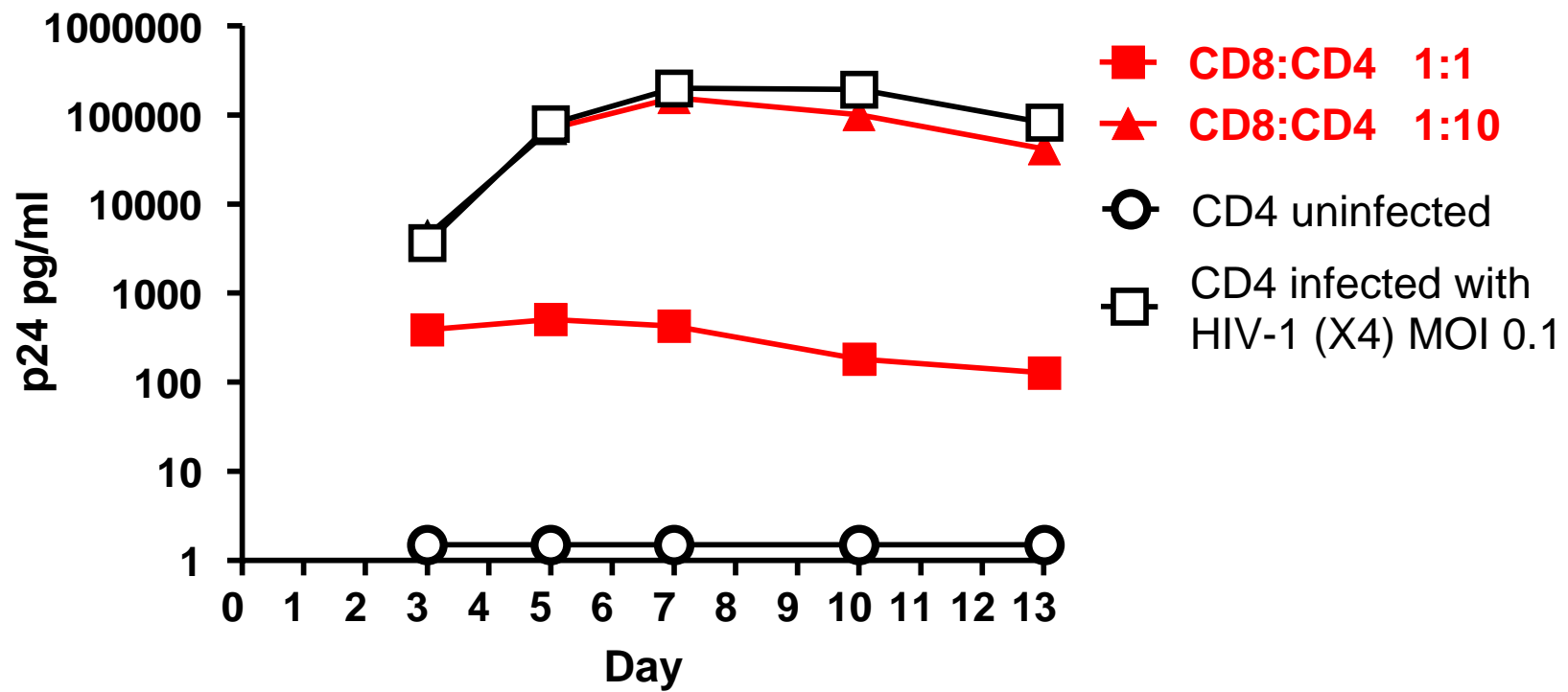
- The CD8 T cell response is inducing a less fit virus, and the less fit virus is targeted by a de novo CD8 T cell response

Can CD8 T cells be functionally linked to an antiviral effect?

- Methods
 - Infect CD4 cells with HIV
 - Add back CD8 cells
 - Measure p24 antigen production



See also: Saez-Cirion et al, PNAS 2007



B. Juelg et al

To what extent can CTL responses predict viral control?

- Subjects
 - HIV controllers (N=150)
 - HIV Progressors (N=102)
- Methods
 - Define all targeted optimal epitopes
 - Calculate the contribution of the pattern of recognition to immune control

Conclusions V

- The epitopes targeted have a greater ability to predict viral load than does HLA
- HLA mediates its effect through CTL epitope recognition

If CTL exert strong selection pressure, will circulating viruses evolve to escape CTL?

- Subjects
 - 2800 persons with chronic HIV infection
 - 9 cohorts, 5 continents
- Methods
 - HLA typing
 - Virus sequencing in Gag
 - Analyze the relationship between HLA prevalence and detection of escape mutations

Y Kawashima, K Pfafferott, John Frater, P Matthews et al

Summary:

HIV Controllers and Immune Correlates

1. CTL alter viral virulence
2. The CTL epitopes targeted explain the predictive value of class I alleles
3. Not all CTL contribute to control
4. There are clearly epitopes that are associated with durable control
5. CTL are shaping HIV evolution, and strongly targeted epitopes are being lost at a population level
6. We still don't understand the precise mechanisms of persistent control of HIV, but specificity clearly makes a difference
7. The fact that there are so many indicators of CTL being involved in durable control in humans offers hope for a T cell based vaccine

International HIV Controllers Study

Project Leaders

- Clinical Cohort
 - Steve Deeks, Florencia Pereyra
- Genetics
 - Paul de Bakker, Mary Carrington
- Virology
 - Matt Henn, Todd Allen
- Immunology
 - Marcus Altfeld, Sylvie Le Gall
- Bioinformatics
 - Chanson Brumme, David Heckerman
- International HIV Controller Consortium
 - S. Deeks, S. Little, A. Telenti, V. Marconi, M. Markowitz, P. Goepfert, O. Yang, R. Harrigan, N. Bernard, G. Tambussi, J. Eron, H. Schuitemaker, H-J. Stellbrink, M. Lederman
 - www.hivcontrollers.org

- Huabiao Chen
- Mark Brockman
- Florencia Pereyra
- Toshi Miura
- Boris Juelg
- Marylyn Addo
- Alicja Trocha

- Paul De Bakker
- Noel Burt
- David Altschuler

- Sarah Palmer
- John Coffin
- Terri Wrin
- Chris Petropolous
- Michelle Nussenzweig
- Johannes Scheid



- Paul de Bakker
- Sherman Jia
- Sara Pulit



- Noël Burt
- Lauren Gianinny
- Gabe Crawford
- David Altshuler
- GAP



- Florencia Pereyra
- Marylyn Addo
- Boris Juelg
- Huabiao Chen
- Toshi Miura
- Mark Brockman
- Zabrina Brumme
- Chanson Brumme
- Alicja Trocha
- Brian Block
- Alissa Rothchild
- Brett Baker
- JJ Proudfoot
- Cheryl McClurg
- Jeffrey Lian
- Emily Cutrell



- Dan Kuritzkes
- David Haas

- All the participants, providers and collaborators who have contributed samples

- Yuka Kawashima¹
- Katja Pfafferott
- John Frater
- Philippa Matthews
- Rebecca Payne
- Marylyn Addo
- Hiroyuki Gatanaga
- Mamoru Fujiwara
- Atsuko Hachiya
- Hirokazu Koizumi
- Nozomi Kuse
- Shinichi Oka
- Anna Duda
- Andrew Prendergast
- Hayley Crawford
- Zabrina Brumme
- Chanson Brumme
- Todd Allen
- Christian Brander
- Richard Kaslow
- James Tang
- Eric Hunter
- Susan Allen
- Joseph Mulenga
- Songee Branch
- Tim Roach
- Mina John
- Simon Mallal
- **Anthony Ogwu**
- **Alasdair Leslie**
- Roger Shapiro
- Julia Prado
- Oliver G. Pybus
- Paul Klenerman
- Thumbi Ndung'u
- Rodney Phillips
- Patricia D'Sousa
- David Heckerman
- P. Richard Harrigan
- Masafumi Takiguchi
- Philip Goulder

Acknowledgements

- IAVI
 - SAAVI
 - HHMI
 - NIH/CFAR
 - Wellcome Trust
 - Microsoft
-
- Mark and Lisa Schwartz Foundation
 - Bill and Melinda Gates Foundation
 - Philip and Susan Ragon Foundation