Correlates of vaccine induced T cell immunity

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T cell vaccination?

[Graph showing RNA particles/ml plasma over time with two lines: one for Placebo and one for Vaccine.]
STEP Trial Results
Impact on set-point viral load

RNA particles/ml plasma

Time

Vaccine: 40,000
Placebo: 26,000
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
Relative number of subjects

RNA copies/ml plasma

Elite Controllers 1/300
The International HIV Controllers Study

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.
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?

![Graph showing the proportion of individuals with CD4 > 350 over years since diagnosis for EC (N=313, 20 failed) and VC (N=555, 69 failed)].

Pereyra et al
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

Patient isolate → RT-PCR → Gag-Pro → Generate chimeric NL4-3 viruses
HIV+ cells (GFP)

Forward Scatter

% GFP+

Day

Brockman et al, 2007
Average of 2 experiments

\[ p < 0.0001^* \]

Miura, Brockman et al
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

Pereyra et al, JID 2008
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

Spearman r 0.1881

Pereyra et al
CD4 cells in elite controllers: Negative immunoregulatory molecules

Kaufmann et al, 2007
The magnitude of HIV antibody response vs plasma HIV virus load

Spearman r 0.3346

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?

Average of 2 experiments

slope value (day 2-6)

EC (N=52)  CP (N=41)

p<0.0001*
HLA influences viral replication capacity

Miura, Brockman et al
HLA influences viral replication capacity

- $p=0.0002^*$
- $p=0.0245^*$
- $p=0.6889$
- $p=0.0074^*$
- $p=0.0489^*$

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

TSTLQEQQIAW

---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

Miura, Brockman et al
### TW10 sequence in plasma: Progressors

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<th>DRLHPV</th>
<th>HAGPIAPGQM</th>
<th>REPRGSDIAGT</th>
<th>TSTLQEIQIGW</th>
<th>MTNNPP</th>
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<td>------V------L</td>
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<td>------S---</td>
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</table>

Miura, Brockman et al
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

CD8:CD4 1:10
CD8:CD4 1:1
CD4 uninfected
CD4 infected with HIV-1 (X4) MOI 0.1

p24 pg/ml

Day

0 1 2 3 4 5 6 7 8 9 10 11 12 13

1 10 100 1000 10000 100000 1000000

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
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  – Paul de Bakker, Mary Carrington
• Virology
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