IMMUNE CONTROL OF HIV

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Immune Response to HIV

- General Background

- Factors Driving the phenotypic and functional profile of HIV-specific T-cell responses

- Immune response profile associated with spontaneous long-term control of HIV replication

- Major immunological obstacles to HIV Functional Cure
Immune Response to HIV

- General Background

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- Major immunological obstacles to HIV Functional Cure
Natural course of HIV infection-1

Progressive disease (99% of cases) in the absence of ART

- Viral Load
- Exhausted T cell CD8+ T cell response
- Partial immune control of virus replication
- Total loss of viral control
- HIV specific CD8+ T cell response
- CD4+ T cell counts
- HIV specific CD4+ T cell response

Time after HIV infection (Years)

Magnitude

8-10 AIDS
Long-Term Non-Progressors/Elite Controllers

Long Term Non-Progressors (LTNP) and Elite Controllers, (1% of cases)

Immune control of virus replication

A minority of HIV-1 infected patients do not progress to AIDS, maintain normal CD4 counts in the absence of treatment for several years, have low (LTNP or viremic controllers) or even non detectable (elite controllers) viral replication in the blood.
Antibody Response in HIV infection

60-80% of subjects

<20% of subjects

No role of antibodies in the control of chronic HIV infection

Mascola and Montefiori, Annu. Rev. Immunol. 2010. 28:413-44

No role of antibodies in the control of chronic HIV infection
Immunological Measures Associated with Control of HIV Replication - I

- **Epitopes targeted**
  - Conserved among strains *(Turnbull, J Immunol, 2006)*
  - Mutations having a fitness cost *(Martinez-Picardo, J Virol, 2006)*

- **Immune Activation (lack of immune activation)** *(Many, Many Investigators)*

- **Genetic Factors**
  - Long-term nonprogressors (LTNP) and ‘Elite controllers’ (EC): spontaneous control of HIV-1 replication and preservation of high CD4 T-cell counts in the absence of ART
  - HLA-B*57, HLA-B*27 and HLA-B*5801 genotypes are associated with viral control *(Carrington M, Annu Rev Immunol 2003)*
  - Genome-wide association studies indicate that:
    - The HLA-viral peptide interaction is the main determinant of HIV-1 control *(Pereyra F, Science 2010)*
    - Specific amino acids in the HLA-B peptide-binding groove are important in HIV-1 control *(The international HIV controllers study, Science 2010)*
CD8 T-Cell Responses to Different HIV Proteins Have Discordant Associations with Viral Load

Dominant influence of HLA-B in mediating the potential co-evolution of HIV and HLA

Immunological Measures Associated with Control of HIV Replication - II

- **Functional profile**
  - Cytotoxic profile
    - Perforin/GrmB expression *(Hersperger, PLoS Path, 2010; Migueles et al., Immunity 2008)*
    - Inhibition of virus replication *(Freel et al., J Virol, 2010; Yang, JID, 2012)*

- **TCR clonotypes and protective role of HLA class I molecules** *(Chen et al. Nat Immunol, 2012)*


- **TCR avidity** *(Almeida et al., J Exp Med, 2007)*
Antigen-Specific Proliferation of CD8 T cells in Different Models of Immune Response

Subject 248
Gated on CD8+ T Cells
Flu 1.48%

Subject 248
Gated on CD8+ T Cells
EBV 1.76%

Subject 181
Gated on CD8+ T Cells
CMV 1.41%

LTNP 2073
Gated on CD8+ T Cells
HIV-1 12.8%

Patient 2092
Gated on CD8+ T Cells
HIV-1 0.68%

Zimmerli et al. 2005, PNAS
HIV-1-specific IFN-γ/IL-2-secreting CD8 T cells support CD4-independent proliferation of HIV-1-specific CD8 T cells

Simone C. Zimmerli, Alexandre Harari, Cristina Cellera, Florence Val Elle, Pierre-Alexandre Bart, and Giuseppe Pantaleo*
Functional Heterogeneity of Memory CD4 T Cell Responses in Different Conditions of Antigen Exposure and Persistence

Alexandre Harari, * Florence Valletlain, * Pascal R. Meylan, † and Giuseppe Pantaleo 2,*
Skewed representation of functionally distinct populations of virus-specific CD4 T cells in HIV-1–infected subjects with progressive disease: changes after antiretroviral therapy

Alexandre Harari, Stéphanie Petitpierre, Florence Valletian, and Giuseppe Pantaleo
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TCR avidity in HIV

- Functional avidity or antigen sensitivity has been shown to be a critical factor of antiviral immunity.


- Lower functional avidity was associated with a more polyfunctional profile in CMV and EBV and also in HIV infection (Harari A, et al. PNAS, 2007).


- Selective depletion of high avidity HIV-specific CD8+ T cells after early HIV infection (Lichterfeld, et al. JVI, 2007).
Inverse correlation between functional avidity of immunodominant HIV-specific CD8 T cell responses and HIV cell associated viral load
Avidity During Primary and Chronic HIV infection

- Cross-sectional study to assess the avidity of CD8 T cell responses at different stages of HIV infection
  - 85 HIV infected patients
    - 37 patients at very early stage of acute infection (PHI)
    - 39 patients with progressive chronic infection (CP)
    - 9 patients with non progressive chronic infection (LTNP)
  - 194 optimal HIV-1 derived CD8 T-Cell epitopes were used to assess HIV-specific CD8 T-cell responses
    9 to 11 mers, covering 60 different HLA Class I Alleles
No significant differences in the magnitude of HIV-specific CD8 T-cell responses

Vigano’ et al. PLOS Pathogens, 2013
Overall, lower functional CD8 T-cell avidity observed in PHI patients than in chronic or LTNP patients
Peptide-Specific Functional Avidity

Comparison of common epitopes recognized in the different cohorts

D

Common epitopes (n=23; P=0.0015)

Common epitopes (n=13; P=0.032)

Common epitopes (n=16; P=n.s.)

HLA-B*2705 – KK10
Association Between Magnitude and Functional Avidity of HIV-Specific CD8 T-Cell Responses

- PHI-B ($P=\text{n.s.}; r=0.06; n=45$)
- CP-B ($P=\text{n.s.}; r=0.22; n=40$)
- LTNP ($P=\text{n.s.}; r=-0.08; n=27$)

No significant association between functional avidity and magnitude of the immune response
Functional Profile of CD8 T-Cell Responses

Gated on CD8 T cells

IFN-γ, TNF-α, IL-2, Perforin

- PHI-B-07
  B*4402-AENLWTVYY
- CP-B-1021
  A*2601-EVIPMFSAL
- LTNP-013
  A*0201-FLGKIWPSYK
**Functional Profile of CD8 T-Cell Responses**

- Perforin expression higher in PHI patients
- IL-2 production higher in cell isolated from LTNP
- IFNγ producing cells mainly found in larger numbers in chronic progressor
Cytotoxic Granules in Acute HIV-1 Infection and Changes After ART

HIV-specific CD8 T-cell response during acute HIV-1 infection

Patient 1016
Gated on A*02-SLYNTVAL CD8 T-cells

<table>
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<tr>
<th></th>
<th>BSL</th>
<th>W144</th>
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<tbody>
<tr>
<td>GrmB</td>
<td>17</td>
<td>37.3</td>
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<tr>
<td>GrmK</td>
<td>10.2</td>
<td>41.1</td>
</tr>
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<td>GrmA</td>
<td>2.48</td>
<td>9.68</td>
</tr>
<tr>
<td>CD127</td>
<td>3.7</td>
<td>22.6</td>
</tr>
</tbody>
</table>

BSL, n=5
Year 3, n=5

* P<0.01

% of HIV-specific CD8 T-cells (mean±SE)

Perforin
Granzyme B
Granzyme A
Granzyme K
(Pies)
Black: BSL, n=5
Gray: Year 3, n=5
Expression of Inhibitory Receptors

Gated on CD8 T cells

- PHI-B-1037
  - B*1402-DRFYKTLRA
- CP-B-11
  - A*0201-SLYNTVATL
- LTNP-2081
  - A*0201-SLYNTVATL

Gated on  CD3 T cells

- CD27
- CD28

Gated on CD8 T cells

- CD8
- CD27
- CD28

- PD-1
- CD160
Expression of Inhibitory Receptors

Analysis performed on Tet^+ cells

- Higher proportion of cells expressing 2 (2B4 +CD160) or 3 co-inhibitory receptors (2B4, CD160, PD-1) in chronic and LTNP patients than PHI patients

- Most of the cells from PHI patients express no or 1 (2B4) inhibitory receptor
Impact of Early ART Treatment on CD8 T-Cell Functional Avidity

- Following early ART treatment HIV-specific CD8 T-cell responses may be lost, maintained or newly generated
- No differences in the functional avidity between responses that are either maintained, lost or newly generated
Changes in the Functional and Phenotypic Profile Following ATI

![Graphs and charts showing changes in HIV-1 RNA copies/ml and CD4 T cells/μl over weeks, with comparisons between PHI-T1Y (n=60), PHI-ATI (n=45), and PHI-T5Y (n=16).](image)

**Significance:**
- $P < 0.0001$
- $P = n.s.$
- $P = 0.0065$
- $P = 0.0002$
- $R = 0.66$

**PD-1 expression (MFI):**
- PHI-T1Y (n=21), PHI-ATI (n=10), PHI-T5Y (n=7)

**% of single IFN-γ-producing HIV-1-specific CD8 T cells:**
- Not specified

**% of max PD-1:**
- PHI-T1Y (n=21), PHI-ATI (n=10), PHI-T5Y (n=7)

**Correlation:**
- $P = 0.0022$
- $R = 0.66$
- $n=24$
Effect of Viral Rebound on Functional Avidity

Significant increase in CD8 T-cell avidity after treatment interruption in one patient
Effect of Viral Rebound on Functional Avidity

- Positive correlation was observed between the expression of inhibitory receptors and functional avidity.
- Statistical model to assess the evolution of functional avidity as a function of time and virus rebound. The model indicates that functional avidity does not change under steady-state conditions. However, an immediate increase of functional avidity of HIV-specific CD8 T-cells of about 1 log occurs after treatment interruption and this was not related to the duration of ART prior to treatment interruption.
Conclusions

- HIV-specific CD8 T cells generated during acute infection are of lower functional avidity when compared to responses measured during chronic progressive and non-progressive infection.

- Early treatment of HIV infection prevent the selection of high functional avidity CD8 T cells.

- No loss or preferential deletion of high functional avidity cells is observed.

- In the absence of high antigen exposure the functional avidity does not increase significantly over a short period of time.

- Acute antigen exposure of HIV-specific CD8 T-cells leads to a significant increase in functional avidity associated with a T-cell exhaustion phenotype and differentiation toward an effector phenotype.
Immunological Markers

- Preservation of HIV-specific CD4 and CD8 T-cell proliferation
- Polyfunctional profile
- Lack of expression of inhibitory receptors

The best immunological markers associated with virological control in HIV infected subjects with detectable viremia
Immune Response to HIV

- General Background
- Factors Driving the phenotypic and functional profile of HIV-specific T-cell responses
- Immune response profile associated with spontaneous long-term control of HIV replication
- Major immunological obstacles to HIV Functional Cure
Case Study: Patient 1010

Cyclosporine A

Stavudine + Lamivudine + Nelfinavir + Saquinavir

No treatment

HIV-1 RNA copies/ml

CD4 count (cells/µl)

CD8 count (cells/µl)

HIV exposure

Emergency room admission 15.03.99
Start of HAART and CsA 2 days later

Treatment interruption 31.12.00

Hypersensitive amplicor Assay (LOD: 5 c/ml)
Genetic background of patient 1010

**HLA class I genotype**

Two-digit PCR

- Locus A
- Locus B

**Four-digit:**

A*0301, B*0702, B*4002

**CCR5 genotype**

PCR-based assay

- 189-bp
- 157-bp

*Wild-type homozygous*

*Data generated by Erika Castro*
HIV replication in CD4 T-cells of Pt. #1010

MA.A336 : CD4+ T cell infection kinetic by HIVNL4-3BE

Data generated by Miguel Munoz and Amalio Telenti, Institut de Microbiologie - CHUV
HIV-1-Specific CD8 and CD4 T Cell Responses During Primary Infection in Patient # 1010

Baseline (prior to ART)

<table>
<thead>
<tr>
<th>Unstimulated</th>
<th>Pool GAG</th>
<th>Unstimulated</th>
<th>Pool GAG</th>
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</thead>
<tbody>
<tr>
<td>0.03</td>
<td>0.0</td>
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Gated on CD4 T cells

<table>
<thead>
<tr>
<th>IL-2</th>
<th>0.0</th>
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2 years after primary infection and 3 months after spontaneous treatment interruption

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<th>Pool GAG</th>
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<th>Pool GAG</th>
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<td>0.01</td>
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<td>0.01</td>
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Gated on CD8 T cells

<table>
<thead>
<tr>
<th>IFN-γ</th>
<th>0.0</th>
<th>0.29</th>
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<td></td>
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3 years after primary infection and 15 months after spontaneous treatment interruption

<table>
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<tr>
<th>Unstimulated</th>
<th>Pool GAG</th>
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<tr>
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<td>0.0</td>
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Gated on CD4 T cells

<table>
<thead>
<tr>
<th>IFN-γ</th>
<th>1.83</th>
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<tbody>
<tr>
<td></td>
<td>1.64</td>
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</table>
Functional Profile of HIV-1-Specific CD8 T-Cells Over Time in Patient #1010

Gated on CD8 T-cells

Week 3 (1999)

Week 135 (2001)

2005

2007

Unstimulated

B*0702 GPSHKARVL gag

B*0702 IPRRIRQGL env

A*0301 HMYISKKAK vif

IFN-γ

IL-2
HIV-1-specific CD4 and CD8 T-cell proliferation in Pt. # 1010

- **Unstimulated**
  - CD4: 0.19, 78.4
  - CD8: 0.062, 21.3

- **VDRFYKTLRAEQASQ** (gag)
  - CD4: 15.7, 67.4
  - CD8: 1.02, 15.9

- **B*0702-GPSHKARVL** (gag)
  - CD4: 60.4, 6.73
  - CD8: 4.93, 28
HIV-1-Specific CD8 T-Cell Responses in Patient #1010 in 2007

IFN-γ

IL-2

TNF-α

Perforin

Neg

GPGHKARVL (B*0702-gag)

IPRRIRQGL (B*0702-env)
Distribution of Perforin and Granzymes (A, B and K) in HIV-Specific CD8 T Cells in Patients 1010 as Compared to Different Groups of Patients
Differentiation Stage of HIV-1-Specific CD8 T-Cell Responses in Patients #1010, #1017 and #1023

Pt# 1010
B*0702-GPGHKARVL

Pt# 1017
B*0702-GPGHKARVL

Pt# 1023
B*0702-GPGHKARVL
Differentiation Stage of HIV-1-Specific CD8 T-Cell Responses in Patients 1010, 1017 and 1023
Conclusions

The prototypic immunological profile of an HIV-1 infected patient (#1010) with optimal virological control in the absence of ART, i.e. very low DNA load in blood and gut CD4 T-cells (about 10 HIV DNA copies per $10^6$ cells, no isolation of infectious virus, viremia below 5 HIV RNA copies has the following characteristics:

- **Central memory differentiation stage:** >80% of CD8 T-cells CD127+, CCR7+, CD27+ and CD28+

- **Central memory functional cytokine profile:** highly polyfunctional (>3/4 of CD4 and CD8 T-cells secreting IL-2)

- **Central memory proliferation profile:** extensive CD4 and CD8 T-cells proliferation capacity

- **Central memory cytotoxic profile:** lack of expression of cytotoxic granules such as perforin and GrmB critical for the cytotoxic activity of CD8 T-cells
Loss of virus control
Evolution Of The Magnitude Of HIV-Specific CD8 T-Cell Responses

- Decrease of Gag B*0702 (49 and 49a) and RT pol A*0301 (127) responses
- Increase of Gag A*0301 (8), B*4001 (15), Env B*0702 (82), Vif A*0301 (152)
Cumulative HIV-Specific CD8 T-Cell Responses Overtime

% of HIV-specific CD8 T cell responses of CD8 T cells

- 8  RLRPGGKKK  A*0301  gag
- 15  IEIKDTEAL  B*4001  gag
- 49  GPGHKARVL  B*0702  gag
- 49a  GPGSKARVL  B*0702  gag
- 82  IPRRIRQGL  B*0702  env
- 92  QVPLRPMTYK  A*0301  nef
- 127  GIPHPAGLK  A*0301  RT-pol
- 131  AIFQSSMTK  A*0301  RT-pol
- 135  IEELRQHLL  B*4001  RT-pol
- 139  QIYPGIKVR  A*0301  RT-pol
- 152  HMYISKKAK  A*0301  vif
Evolution Of The Functional Profile Of All HIV-Specific CD8 T-Cell Responses

- RLRPGKKK
- IEIKDTKEAL
- GPGHKARVL
- GPGSKARVL
- RPRIRQGL
- GIPHPAGLK
- AIFQSSMTK
- IEELRQHLL
- QIYPGKVR
- HMYISKKAK

- A*0301
- B*4001
- B*0702
- B*0702
- B*0702
- A*0301
- A*0301
- B*4001
- A*0301
- A*0301

- gag
- gag
- gag
- env
- RT-pol
- RT-pol
- RT-pol
- RT-pol
- vif

% of HIV-specific CD8 T-cell responses

- IFN-γ
- IL-2
- TNF-α

- 2007
- 2009
- 2010
- 2011
Evolution Of The Functional Profile Of The Three Initial HIV-Specific CD8 T-Cell Responses

(Gated on IFN-γ-producing CD8 T cells)

The response to peptide 49 gag (B*0752) decreases after virus rebound (from 6 to 2%) however the cytokine profile does not change dramatically. Slight increase in the proportion of IFNγ+TNF+ secreting cells after viral rebound.
Evolution Of The Functional Profile Of The Three Initial HIV-Specific CD8 T-Cell Responses

(Gated on IFN-γ-producing CD8 T cells)

These responses increase after virus rebound. In this case the cytokine profiles changes dramatically:

- for 82 env: increase in IFNγ+TNF+ producing cells and decrease IL-2 production, i.e. change towards an effector cell cytokine profile
Case Study: Patient 1010

HIV-1 RNA copies/ml

Cyclosporine A

Stavudine + Lamivudine + Nelfinavir + Saquinavir

No treatment

HIV exposure

Emergency room admission 15.03.99
Start of HAART and CsA 2 days later

Treatment interruption 31.12.00

Hypersensitive ampicor Assay (LOD: 5 c/ml)
Lesson Learned from Patient #1010

- Patient #1010 has been treated within 15 days from HIV exposure. He therefore fits very well within the beneficial effect observed in other cohorts of patients treated early during primary infection.
- HIV in Patient #1010 has come back after almost 10 years.
- It is slowly taking over the immune control.
- Caution should be exerted in considering patients with long term virological control cured from HIV.
- Nonetheless Patient #1010 is a perfect example of what should be achieved with HIV functional cure, i.e. extended period of time with full virus control in the absence of ART.
Immune Response to HIV

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- Factors Driving the phenotypic and functional profile of HIV-specific T-cell responses

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The First T-Cell Response to the Transmitted/Founder Virus Contributes to the Control of Acute Viremia in HIV-1 Infection

**Virus sequence changes emerge both early and rapidly at multiple sites across the HIV-1 proteome**

<table>
<thead>
<tr>
<th>Days after infection</th>
<th>Gag I</th>
<th>Gag TW10</th>
<th>Gag TW10</th>
<th>Env (334-351)</th>
<th>Env (350-368)</th>
<th>Env (597-614)</th>
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<tbody>
<tr>
<td>0</td>
<td>0%</td>
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<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Numerous CD8 T cell responses induced following HIV infection
- Extremely rapid appearance of mutations driven by CD8 T-cell responses in the first few days of infection
- Responses to the transmitted form of the virus disappeared after selecting early virus escape mutants
Why Does HIV Persist In Infected Individuals?

Two Main Hypotheses

Latent HIV Reservoir

- Size: $10^5$-$10^7$ cells
- Half life memory CD4 T cells: 43 months
- Estimated time for eradication: ~70 years under full virus suppression by ART
- Not susceptible to ART
- Not susceptible to the immune system

Residual HIV Replication

- Covert cellular reservoir
- Privileged anatomic compartment
- Resistant to HIV cytopathic effect
- Poorly accessible to cytotoxic CD8 T cells
- Minimal virus spreading
- Replenishment of the latent cellular reservoir
Follicular Helper T cells Serve as the Major CD4 T cell Compartment for HIV-1 Infection, Replication, and Production

Mathieu Perreau, Anne-Laure Savoye, Elisa De Crignis, Jean-Marc Corpataux, Rafael Cubas, Elias K. Haddad, Laurence De Leval, Cecilia Graziosi, and Giuseppe Pantaleo
Tfh Cells and CXCR5-PD-1+ CD4 T-Cells Are Enriched in HIV-Specific CD4 T-Cells

CNA#2066 32250 HIV RNA copies/mL
  Gated in CD3+CD4+CD45RA+ cells

Unstimulated
  Gag Pool 1
  Gag Pool 2
  Pol Pool 1
  Pol Pool 2
  Pol Pool 3
  Env Pool 1
  Env Pool 2
  Env Pool 3

GAG-specific responses (N=22)

- CD45RA
  - PD-1
  - CXCR5

POL-specific responses (N=33)

- CD45RA
  - PD-1
  - CXCR5

Frequencies of total
HIV-specific responses (N=11)

- CD45RA
  - PD-1
  - CXCR5

* p < 0.05
Tfh Cells and CXCR5-PD-1+ CD4 T-Cells Are Enriched in CD4 T-Cells Containing HIV DNA
Tfh Cells and CXCR5-PD-1+ CD4 T-Cells Are the Most Efficient in Supporting Production of HIV

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High viremia
(>15000 HIV RNA copies/mL)

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CNA#2132 57690 HIV RNA copies/mL

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<thead>
<tr>
<th>CXCR5-PD-1^-</th>
<th>CXCR5-PD-1^+</th>
<th>CXCR5^+PD-1^-</th>
<th>Tfh cells</th>
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<tbody>
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<td>0.0572</td>
<td>0.0249</td>
<td>0.0527</td>
<td>0.0248</td>
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anti-CD3/CD28 stimulation

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% of max

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CFSE

---

D0

---

Collection of SNs

---

D2

---

p24 detection

---

D5

---

Anti-CD3/CD28

---

Gated on CD3+CD4+ cells

---

* P<0.05

---

NS

---

0.1 to 100 ng/mL

---

0 to 6 days

---

STEMCELL Technologies Inc. 2021
HIV Isolation from Patients with Low (<1000 HIV RNA copies/mL of plasma) in Different CD4 T-Cell Populations

- Tfh and CXCR5⁺PD-1⁺ but not CXCR5⁻PD-1⁻ and CXCR5⁺PD-1⁻ CD4 T-cells efficiently support virus isolation and production in patients with low viremia levels.
The Percentage of Tfh Cells Correlates with HIV Viremia Levels

- Percentage of CXCR5^PD-1^ CD4 T cells
  - $R = -0.3900$
  - $N = 23$
  - $P = 0.0658$

- Percentage of CXCR5^PD-1^ CD4 T cells
  - $R = 0.1489$
  - $N = 23$
  - $P = 0.4977$

- Percentage of CXCR5^PD-1^ CD4 T cells
  - $R = 0.2543$
  - $N = 23$
  - $P = 0.2417$

- Percentage of Tfh cells
  - $R = 0.6035$
  - $N = 23$
  - $P = 0.0023$
Sequencing Results

- Sequencing of HIV in plasma and in different memory CD4 T-cell populations has indicated that the virus isolated from Tfh cells is identical to that found in plasma.

- PD1+CXCR5 CD4 T-cells contains HIV almost identical to that circulating in plasma.

- These results demonstrate that Tfh cells are mostly responsible for the production of circulating HIV.
Events Occurring in the Germinal Centers in Viremic HIV-Infected Patients

- High levels of HIV replication and production within $T_{FH}$ cells. Correlation with viremia levels.
- Defective Tfh help to B-cells and decreased Ig production.
Events Occurring in the Germinal Centers in ART HIV Suppressed Patients – Non-HIV Ag Stimulation

- B-cell zone
- SCS macrophage
- primary follicle
- FDC
- T-cell zone
- Non-HIV Ag stimulation
- B-cell
- antigen presentation
- BCR
- DC
- CD4 T cells proliferation
- pre-GC
- TFH cells
- TH cells
- HIV
- germinal center
- B-cell
- centroblasts proliferation
-/pre-GC
- TFH cell
- plasma cells
- (early response)
Events Occurring in the Germinal Centers in ART HIV Suppressed Patients – Non-HIV Ag Stimulation

Transient bursts of HIV replication and production within $T_{FH}$ cells. Responsible for virus blips?
Primary Anatomic Sites of HIV Replication

- Lymphoid tissues represent the primary site for HIV infection and replication even during the asymptomatic clinical phase of infection (Pantaleo et al., 1991; Pantaleo et al., 1993; Embretson et al., 1993 and Brenchley et al., 2004).

Pantaleo et al., Nature 1993
Regulation of T-Cell Entry Within GCs

- Loss of CCR7 expression
- Expression of CXCR5
- Production of CXCL13 (ligand for CXCR5) by FDCs
- Therefore, access of cells to GCs is highly selective
- CD8 T-cells have very limited access to GCs, e.g. small proportion express CXCR5
Low CXCR5 expression on HIV-specific CD8 T-cells

Untreated HIV-infected donor #CNA 2066 (HIV RNA 32250 copies/ml)

Gated in memory CD8 T cells

- PD-1
- CXCR5
- Tetramer
- Viability dye
- CXCR5

A*03 Gag RLRPGKKK

Total memory CD8 T cells

PD-1

CXCR5

Tetramer

Viability dye

PD-1

CXCR5

Percentage of PD-1+ memory CD8 T cells

Percentage of CXCR5+ memory CD8 T cells

Percentage of HIV-specific CD8 T cells

* p< 0.05
*** p< 0.0005
**** p< 0.0001

Total memory CD8 T cells

HIV-specific CD8 T cells

PD-1

CXCR-5

- - + +
Conclusions

- Tfh Cells Serve as the Major CD4 T-Cell Compartment for HIV Infection, Replication and Production (Perreau et al. *JEM* 2013)

- Tfh Cells and CXCR5⁺PD-1⁺ Cells May Represent the Primary Obstacle for Achieving Functional HIV Cure/Eradication

- HIV infected Tfh cells reside in a privileged anatomic site, i.e. germinal centers, with limited accessed to HIV-specific cytotoxic CD8 T-cells
THE FUTURE
Multivalent Biological Approach

Therapeutic Vaccine i.m.

Generation / Boosting of HIV-specific CD8 T-cells

Potentiation

Activation of HIV Replication

Reactivation/Boosting HIV Replication

Potentiation

HDACi

PD-1

CD4

ADC Bi-specific Abs:

PD-1/HIV env

CD4/HIV env

PD-1/CD4

Killing of HIV infected CD4 T-cells

Killing of HIV infected CD4 T-cells
Final Considerations

- The solely potentiation of the HIV-specific immune response is not sufficient to achieve control of HIV replication.

- Major reduction in the pool of CD4 T-cells containing replication competent HIV is necessary in order to promote immune-based virus control.

- Therefore, therapeutic interventions targeting and causing massive depletion of memory CD4 T-cell populations containing HIV replication competent is required to achieve HIV functional cure.
IMMUNE CONTROL OF HIV

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