Targeting nucleic-acid sensors in Dendritic Cells differentially restores frequencies vs polyfunctionality of HIV-1 specific CD8+ T cells on treated chronic HIV-1 infected patients

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Anti-retroviral therapy cannot eradicate HIV infection

10 Things to Know About HIV Suppression by NIAID

Siliciano, Nat Med, 2003
Mechanisms contributing to HIV-1 persistence

Latently infected CD4+ T cells with integrated HIV

Exhaustion CTL

PERSISTENCE

Latently infected resting memory CD4+ T cells

Memory cell turnover

Cognate or cross reacting antigen

Free virus

Homocysteine

Integration site dependent proliferation

Current strategies to eliminate the latent HIV-1 reservoir: *Shock and kill strategy*

Can we potentiate the CTL response with Dendritic cells?
TBK-1 activation is associated with specific CTL responses in EC

Single cell RNAseq identifies an antiviral response of DC from EC marked by IFN signature

Increased polifunctional CTL responses against Gag peptides

Martin-Gayo, et al, Genome Biol 2018
TBK-1 activation is associated with specific CTL responses in EC

Single cell RNAseq identifies an antiviral response of DC from EC marked by IFN signature

Induction of highly functional DC phenotype depends on TBK-1 activation

Martin-Gayo, et al, Genome Biol 2018
Can we induce TBK-1 artificially to potentiate DC function?
Activation of MDDCs from patients in response to TBK-1 adjuvants

Individual or combined adjuvants induce the expression of costimulatory molecules on DC.
In vitro system to activate HIV-1 Gag-specific CTL responses in the presence of DC

Chronic HIV+ patients in ART

- N patients: 21
- Y under ART: 8 [1-21]
- Sex: 19 M; 2 F
- Age: 43 [27-73]
- CD4: 826 [158-1676]
- Ratio CD4/CD8: 0.97 [0.40-2.44]

Activation of Gag-specific CD8+ T cell responses (IFNγ+) in the presence of DC and Gag peptides

Polyfunctionalily (IFNγ+, CD107a+)

Magnitude

Quality
**In vitro** system to induce HIV-1 Gag-specific CTL responses

Proportions of IFNγ+ on gated CD8+ T cells

Fold-change of IFN+ CD8 T cells

<table>
<thead>
<tr>
<th>LT + MDDC</th>
<th>Gag</th>
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Gag responders.

Non-Gag responders.

Wilcoxon test
**In vitro** system to induce HIV-1 Gag-specific CTL responses

![Proportions of IFNγ+ on gated CD8+ T cells](image)

- **Gag responders.**
- **Non-Gag responders.**

**Fold-change of IFNγ+ CD8 T cells**

- **LT**
  - + + + +
- **MDDC**
  - + + + +
- **Gag**
  - - + + +
- **STING**
  - - - + +
- **PIC**
  - - - - +

**Wilcoxon test**
**In vitro** system to induce HIV-1 Gag-specific CTL responses

Proportions of CD107a+ cells from gated IFNγ+ CD8+ T cells

- Gag responders.  
- Non-Gag responders.

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In vitro system to induce HIV-1 Gag-specific CTL responses

**Gag responders.**

**Non-Gag responders.**

>10 Y ART Chi Square P=0.0195

- LT + MDDC
- Gag

<table>
<thead>
<tr>
<th>Less than 5 years</th>
<th>11%</th>
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<tr>
<td>5 - 9 years</td>
<td>22%</td>
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<tr>
<td>More than 10 years</td>
<td>67%</td>
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</table>
Functional test of CTL responses from chronic patients

Chronic HIV+ patients In ART

- N patients: 11
- Y under ART: 8 [1-20]
- Sex: 9 M; 2 F
- Age: 52 [39-61]
- CD4: 828 [643-1676]
- Ratio CD4/CD8: 1.11 [0.34-1.78]

5 days
GM-CSF, IL4

PBMC

MDDC

2’3’-c-di-AM(PS)2

Poly I:C

Gag peptides

Autologous CD8 T cells

Autologous CD4 T cells

Violet tracing

Romidepsin Raltegravir

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p24+ cells

CD4

HIV p24

p24/HIV
0.19
Intracellular p24 expression is basally detected in CD4 T cells but not in MDDC.

Treatment with Romidepsin does not induce significant increase of p24 at 24h in the presence of Raltegavir.
Functional test of CTL responses from chronic patients:
2 groups of chronic patients with different P24-specific CD8 T cell activity
Conclusions

DCs from ART chronic patients treated with TBK-1 adjuvants can enhance the activation of autologous Gag-specific CTL in vitro.

Impact of TBK-1 treated DC on CD8 T cell activation depends on differential basal response to Ag stimulation in HIV-chronic individuals associated with treatment duration.

Differential impact of TBK1-MDDC in functional abilities of CD8 T cells to eliminate p24+ CD4 T cells in different patient populations, depending on immune exhaustion levels.

PERSONALISED TBK-1 DC BASED STRATEGIES MIGHT BENEFIT DIFFERENT HIV-1 CHRONIC PATIENT POPULATIONS FOR THERAPEUTIC PURPOSES.
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