Enlisting Effector Cells to Clear HIV Infection

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Disclosures

• Gilead: common stock
• Merck: consulting
• Will discuss the experimental use of licensed drugs, but no treatment recommendations are made
Other Challenges:

• Clearance of infected cells
• Clearance of virions
• Complete block of new infection

A first step to eliminate latent HIV infection

A second step to eliminate latent HIV infection

Immunotherapy

Latency Reversal

Latently Infected Cells
Aiming for sustained “remission” off ART

Cohen J. Science 2014
**Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy**


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**14 daily doses of vorinostat**

Elliot PLoS Path 2014

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**Thrice weekly cycles of Panobinostat**

Rasmussen Lancet ID 2014

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**Weekly Romidepsin**

Sogaard PLoS Path 2015

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Challenges to clearing persistent infection after latency reversal

- Recent absence of antigen – low frequency of HIV-specific antiviral responses
- Immune dysfunction, deletion, or exhaustion
- Archived viral diversity, including immune escape
- Viral antigen is rare, dispersed, compartmentalized, and may be transient
- Latency Reversing Agents (LRAs) are host-targeted, and alone or in combination may alter antiviral immune response
Two step problem:

*Persistent HIV infection despite ART*

- Given assay variance, a more than 6-fold RCI decrease would have likelihood 0.023 (2.3%)
- Therefore a measurable goal is therapy that can reduce the latent reservoir by half a log
From Siliciano Nature Med. 2003
Testing interventions in vivo

LRAs
Immunodulators
HIV vaccines
Novel approaches

Reduction in:
- Resting CD4 cell infection
- Low-level viremia

Baseline

- Leukapheresis for QVOA and ca-HIV RNA
- SCA
- Immune assays
- Host cell assays & biomarkers
- **Novel assays, eg. Quanterix Simoa**

After intervention

- Leukapheresis for QVOA and ca-HIV RNA
- SCA
- Immune assays
- Host cell assays & biomarkers
- **Novel assays, eg. Quanterix Simoa**
Viral Inhibition Assay to Assess Effector Clearance Using Lymphocytes from HIV-Infected ART-Suppressed Patients

1. Deplete CD8$^+$ cells from patient PBMCs
2. Activate 2-3 days
3. Infect with autologous reservoir (AR) virus [obtained from prior outgrowth assay using patients’s own resting CD4$^+$ T cells following mitogenic stimulation]
4. Incubate ± Autologous effector cells or reagents
5. Co-culture for 7 days
6. Supernatant harvested for HIV-1 gag p24 ELISA
Ex-Vivo Latency Clearance Assay:

A modified quantitative viral outgrowth assay

PBMCs

CD8+ by negative selection

Resting CD4+ cells by negative selection

Culture Resting CD4+ cells

Latency Reversing Agent

Add Effectors

CD8+, HXTCs, or DARTs

or

Limiting Dilution Co-culture

Measure HIV Production at 2 weeks

or

No Effectors
HIV specific Ex-vivo Expanded T cells (HXTCs)

PBMC → Immature DC + gag/pol/nef peptides → Mature DC

PHA blast + K562 Irradiated

Mature DC + IL-7, IL-15

CD80/86 4-IBBL

Mature DC + CD32

Irradiated

PHA blast

ARVs

HIV Specific CTL
HXTCs Reduce Recovery of Virus from autologous resting CD4+ T cells stimulated with:

![Graph showing the number of positive wells (out of 12 total) for different patients and conditions.](image)

**Sung et al. JID 2015**
Dual Affinity ReTargeting (DARTs) Molecules for HIV

- Do not require pre-existing HIV specificity
  - Not impacted by archived CTL escape variants

- Anti-Env arm based on well characterized mAbs with
  - Breadth in binding to CD4 inducible epitopes and ADCC activity
  - Little to no binding to free virions
Targeting Conserved Env Epitopes on HIV-Infected Cells with non-neutralizing ADCC-mediating mAbs

V1-V2 loop
PGT145

C1-C4 (gp120 cluster A)
A32

Glycan-V3 loop
PGT121

CD4-binding site
VRC01

gp41 cluster I
7B2

MPER
10E8
A32 and 7B2 mAbs: Broad and Potent mediators of ADCC

- 25 mAbs tested for Antibody Dependent Cellular Cytotoxicity activity against 22 IMCs
- 7B2 (gp41) and A32 (gp120) chosen based on potency and breadth of specificity

<table>
<thead>
<tr>
<th>IMC Recognized</th>
<th>A32</th>
<th>7B2</th>
<th>pos. ctl.</th>
<th>neg. ctl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>95</td>
<td>91</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>Mean Max %SL</td>
<td>43.69</td>
<td>39.58</td>
<td>48.25</td>
<td>9.73</td>
</tr>
<tr>
<td>Range %SL</td>
<td>12-86</td>
<td>15-74</td>
<td>24-84</td>
<td>2-22</td>
</tr>
</tbody>
</table>

Sung, et al. JCI 2015
HIVxCD3 DART-Mediated Killing Activity Using Lymphocytes from HIV-Infected ART-Suppressed Patients

N=8 (left panel), N=5 (right panel)

*indicates p<0.05 by Dunnett's test for multiple comparisons

Combo (1:1 mix of A32xCD3 and 7B2xCD3)

Sung, et al. JCI. 2015
HIVxCD3 DART Mediated Clearance of Resting Patient CD4 Cells Exposed to Vorinostat

HIVxCD3 DART-mediated virus clearance in 4 of 4 patients (longer time needed for Pt 795)

Sung, et al. JCI 2015
Enhancing HIV-specific immunity

- Provides all 3 signals required for adaptive immune response (TCR, CD28, IL 12) in context of patient’s own Gag, Rev, Nef, Vpr
- Produces memory T cells for a durable response
- Does not require CD4+ T cell help
Multi-functional immune responses to the total antigen RNA payload in participants treated with 4 doses of AGS-004

Memory CD28+ CD45RA-CTL recall responses ex vivo to AGS-004 at baseline and week 16 in 6 participants treated during AHI and aviremic for more than 6 months

- BrdU+
- CD107a+
- GrnB+
- IFN γ+
- IL22+
- TNFα+

*p<0.005
Steps to eliminate HIV infection

Productively Infected Cells

Immunotherapy

Latent Infection

Latency Reversal

Finally: the addition of durable immunotherapy for protection if rebound occurs