Advances Toward a Cure for HIV

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Financial Relationships With Commercial Entities

Dr. Siliciano has served on the scientific advisory board for Gilead Sciences, Inc. Her lab has received a grant from Gilead Sciences, Inc. (Updated 08/3/20)

Learning Objectives

After attending this presentation, learners will be able to:
• Describe basic mechanisms that allow HIV to persist despite antiretroviral therapy (ART)
• Recognize how proliferation of latently infected resting CD4+ T cells contributes to viral persistence
• Describe 1 current approach for achieving an HIV cure
**Magnitude of the problem**

- 38,000,000 infected
- 23,000,000 on ART
- 3 people cured

**HIV replication dynamics**

- HIV replication dynamics
- Set point
- ART intensity
- 1/2 life of virus: 1d
- 1/2 life of cells: 14d

**Physiology of resting and activated CD4+ T cells**

- Naive
- Memory
Establishment and maintenance of a latent reservoir

HIV gene expression depends on inducible host factors

A stable latent reservoir for HIV
Reactivation of latent HIV

Quantitative viral outgrowth assay

Slow decay of latently infected CD4+ T cells
Quantitative viral outgrowth assay

Comparison of assays for the latent reservoir

Most HIV proviruses are defective
Digital droplet assay for intact proviruses

Intact proviral DNA assay

Large scale IPDA analysis in pts on ART

- The IPDA measures the reservoir, not active viral replication
- The IPDA measures viral DNA in infected CD4+ T cells, not free virus particles in the plasma.
- The IPDA is almost always positive even in people on ART who have plasma virus levels below the limit of detection.
- The clinical utility of the IPDA is in analysis of curative interventions as it measures the cells that are a barrier to cure.
Intact proviruses decay more rapidly than defective proviruses

- Cells with intact proviruses decay more rapidly than cells with defective proviruses
- This may indicate some immune pressure on infected cells during ART.
- This decay is slow! In first 7 years, $t_{1/2}$ is close to 44 months. Subsequently, even slower.

Response of resting T cells to antigen

Infected cells can also proliferate
Residual viremia

Proliferation of infected cells

Time post entry (d)

Proviral sequences from resting CD4+ T cells

Activated Plasma

- These sequences reflect extensive proliferation of a clone of infected cells
- The cells we want to eliminate can proliferate in vivo!

Tobin et al, J Virol 2005

Clonal nature of residual viremia

Maldarelli et al, Science 2014
Wagner et al, Science 2014
Cohn et al, Cell 2015
The latent reservoir

Clones of latently infected cells

Clones of latently infected cells
Infected cells can also proliferate

Slow decay of the latent reservoir in resting CD4+ T cells

Clones of latently infected cells wax and wane
Clones of latently infected cells wax and wane
The “shock and kill approach” to HIV cure

TLR7 agonists
PKC agonists
SMAC mimetics

Histone deacetylase inhibitors:
Vorinostat
Romidepsin
Panobinostat

Assessing LRA efficacy

Might cause blips

Might cause blips
Should reduce reservoir as determined by QVOA or IPDA
Assessing LRA efficacy

- Might cause blips
- Should reduce reservoir as determined by QVOA or IPDA
- Should delay rebound on interruption of ART

Clinical trial of romidepsin

- Neutralize diverse HIV isolates
- Arise slowly, generally after virus has already escaped
- Can be administered passively as infusion or with AAV vectors
- Block infection and target infected cells for killing

Broadly neutralizing antibodies

- Neutralize diverse HIV isolates
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- Block infection and target infected cells for killing
**Effects of antibodies**

- Neutralization of free virus particles
- Killing of infected cells

**Clinical trials of bNABs**

- bNAb VRC01 infused just prior to and during analytical treatment interruption (ATI)

  - VRC01 infused prior to and during ATI
  - Plasma HIV viral load
  - Limit of quantification
  - Months

- Pre-existing or newly arising viral variants resistant to VRC01 monotherapy were selected during rebound
- Reservoir size was not changed indicating that bNABs alone do not decrease the latent reservoir and that short ATIs do not increase reservoir.
Conclusions

- The latent reservoir in resting CD4+ T cells is the major barrier to cure.
- Accurate measurement of the reservoir is important for evaluating cure interventions and requires distinguishing intact proviruses from defective ones. This can be done with a novel assay, the IPDA.
- The reservoir is maintained by the proliferation of infected cells in response to antigens. This is a serious problem for cure efforts.
- Eliminating the reservoir through the “shock and kill” strategy will require finding better ways to turn on latent HIV and better ways to induce the killing of productively infected cells.
- Broadly neutralizing antibodies are of great interest in the HIV vaccine field and may also be useful to enhance killing of infected cells.