HIV cure research: current strategies and challenges

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Barriers to cure

- Latently infected T-cells
- Residual viral replication
- Anatomical reservoirs

Eliminating latently infected cells

- Treatment during acute infection
- “Activating” latent infection
- Boosting HIV-specific immunity
- Allogeneic transplantation
- Reducing homeostatic proliferation(?)

Sustained remission off ART is rare but achievable


Current strategies to eliminate latently infected cells

Early ART limits persistence of HIV reservoir in all CD4+ T cell subsets

After 2 years of ART, integrated HIV DNA is undetectable in all subsets of Fiebig I individuals.

Nicolas Chomont and Jintanat Ananworanich
Post treatment control is rare following ART in acute infection

<table>
<thead>
<tr>
<th>Published studies</th>
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<tbody>
<tr>
<td>Optiprim</td>
<td>90</td>
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<tr>
<td>(Cheret A. Lancet ID 2015)</td>
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<tr>
<td>Spartac</td>
<td>165</td>
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<tr>
<td>(Stehr W, PLoS One 2013)</td>
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<tr>
<td>VISCONTI</td>
<td>14</td>
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<tr>
<td>(See-Corin A, PLoS Pathogens 2013)</td>
<td></td>
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<tr>
<td>Swiss HIV Cohort Study</td>
<td>32</td>
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<tr>
<td>(Ganella S, Antimoni Therapy 2011)</td>
<td></td>
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<tr>
<td>Primo-SHM</td>
<td>173</td>
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<tr>
<td>(Gieren ML, PLoS Medicine 2012)</td>
<td></td>
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<tr>
<td>ANRS C06 PRIMO</td>
<td>164</td>
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<tr>
<td>(Sogayar C, Antimoni Ther 2012)</td>
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<tr>
<td>CASCADE</td>
<td>259</td>
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<tr>
<td>(Lodi S, Arch Intern Med 2012)</td>
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Ananworanich, Keystone Symposium on HIV cure, April 2015

We need a biomarker that can predict “cure” or “remission”

- HIV DNA: SPARTAC, Swiss HIV Cohort Study
- CA-US HIV RNA: ACTG ATI Cohort Study
- PD1 expression on CD4 and CD8 (prior to ART): SPARTAC

Activating latent infection

Latency reversing agents: many now in clinical trials

Epigenetic modifiers
- HDACi
  - Methyltransferase inhibitor
  - Bromodomain inh

- TLR agonists
  - TLR7 (GS9620)
  - TLR3 (polyICLC)
  - TLR9
  - TLR4

Activators of NF-kB
- Prostratin
- Bryostatin
- Inogenol B / PEP 005
- SMAC mimetics

Other
- Disulfiram
- Quinolines
- IL-15

Adverse effects on HIV RNA splicing following activation with potent HDACi

<table>
<thead>
<tr>
<th>HDACi</th>
<th>Clinical development</th>
<th>HIV latency</th>
<th>US HIV RNA</th>
<th>Plasma RNA</th>
<th>HIV DNA</th>
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</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>Licensed (2006)</td>
<td>CTCL</td>
<td>Single dose$^1$</td>
<td>Intermittent$^2$</td>
<td>Continuous$^3$</td>
</tr>
</tbody>
</table>


CTCL – cutaneous T-cell lymphoma

HDACi have adverse effects on HIV-specific immunity (in vitro) and host gene changes

Changes over time for each LRA: Kruskal-Wallis; *** p ≤ 0.001; **** p ≤ 0.0001

Jones et al., PLoS Path 2014; Elliott et al., PLoS Path 2014
**TLR7 agonist activates HIV latency in SIV infected macaques**

Plasma SIV RNA

CD8 T cell activation

Human clinical trial of a similar TLR7 agonist currently enrolling

Whitney et al., CROI 2015, Seattle 2015

**Disulfiram dose escalation study to activate HIV latency**

Disulfiram dose escalation study to activate HIV latency

Elliott JH et al., CROI, Seattle 2015. Abstract 428LB

**High dose disulfiram increases cell associated and plasma HIV RNA**

A modest (2 fold) but significant increase in cell associated and plasma HIV RNA with disulfiram 2g/day

Elliott JH et al., CROI, Seattle 2015. Abstract 428LB

**Activation of non-canonical NFKB pathways: synergism with HDACi**

Activation of non-canonical NFKB pathways: synergism with HDACi

Pache et al., Cell Host Microbe 2015

**Boosting HIV-specific immunity**

“shock (tickle) and kill”

“reduce and control”

Latent infection

“shock”

HIV DNA

HIV US RNA

“kill”

HIV proteins

HIV virions

Cell death

**Therapeutic vaccination: bNABs and CMV vaccine**

Therapeutic vaccination: bNABs and CMV vaccine

Combination cure studies

Romedepsin + Vacc

Phase 1 human studies to start in 2016

Phase 1 human studies to start in 2016

Romedepsin + 3BNC117

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**Phase 1 human studies to start in 2016**

Romedepsin + bNABs

Phase 1 human studies to start in 2016

Romedepsin + Vacc

Phase 1 human studies to start in 2016

Romedepsin + 3BNC117
B cell follicles in lymph node might be a barrier

Exhausted T cell

CTLA-4

Blockine immune checkpoint markers to boost immune function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Target</th>
<th>Registration</th>
<th>HIV</th>
</tr>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>BMS</td>
<td>PD-1</td>
<td>FDA approved: melanoma</td>
<td>no</td>
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<tr>
<td>Pembrolizumab</td>
<td>Merck</td>
<td>PD-1</td>
<td>FDA approved: melanoma and lung cancer</td>
<td>no</td>
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<tr>
<td>BMS-932059</td>
<td>BMS</td>
<td>PD-L1</td>
<td>Phase III: solid organ malignancy</td>
<td>On hold</td>
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<tr>
<td>Ipilimumab</td>
<td>BMS</td>
<td>CTLA-4</td>
<td>FDA approved: melanoma</td>
<td>Case reports</td>
</tr>
</tbody>
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Wightman et al., AIDS 2015;29(4):504-6

ALT-803 (IL15 superagonist) acts as an LRA and boosts CTL

Ex vivo model using 500 million resting CD4+ T-cells (6 billion PBMC) from patients on ART co-cultured with autologous CTL

Brad Jones et al., Keystone Symposium on HIV Cure, Boston, MA, April 2015

Combination immune checkpoint blockade: greater efficacy in melanoma

Nivolumab plus Ipilimumab in Advanced Melanoma

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Role in HIV infection?

Trials update:
- Several Phase III trials ongoing modifying T cells (NCT01543152, NCT02256645, NCT02385941)
- First HSC trial anticipated opening July 2015

Gene therapy: ZFNs to knockout CCR5

Paula Cannon

Targeted nucleases: guide DNA break

Trials update:
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Paula Cannon
Targeted nucleases allow precise gene editing or site-specific gene addition

- Beyond gene (CCR5) knockout, this opens up the possibility of editing host genes such as restriction factors, or inserting anti-HIV genes at a specific site

Paula Cannon

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**Conclusion**

- Several interventions have been shown to significantly reduce the frequency of latently infected cells including very early ART and transplantation – but this rarely translates into prolonged remission
- Activation of latent HIV possible in vivo with HDACi, disulfiram and TLR7 agonists but remains a need for more potent, less toxic and more specific LRAs
- Combination activation and/or enhanced immunity through vaccination or immune check point inhibition currently being evaluated
- “Knock out” or “knock in” gene therapy may play a role

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GFP insertion at CCR5 in HSC

Ctrl. CCR5 ZFN mRNA + AAV-GFP donor

29%

GFP