Towards an HIV Cure: where are we now and where are we going?

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Why do we need a cure for HIV?

- Life expectancy remains reduced and ongoing morbidity on cART

- For every one patient who initiates cART there is one new infection

- Funding lifelong cART for all who need it is unlikely to be sustainable
HIV eradication: cure or remission

### Cure

**Infectious Diseases model**

- Elimination of all HIV-infected cells
- HIV RNA < 1 copy/ml

**Sterilising cure**
HIV cure is possible

- **The Berlin patient** (7 years off ART)
  - Bone marrow transplant from a donor naturally resistant to HIV infection

- **The Mississippi baby** (2 years off ART)
  - Very early treatment, 30 hours post delivery

- **Post treatment controllers**
  - ART in acute infection (VISCONTI; n=14; 8 years off)
  - ART in chronic infection (Belgium; n=4; 6 months off)

Outline

- What are the major barriers to cure?
- Clinical strategies being tested
  - Eliminating latently infected cells
  - Making cells “resistant” to HIV: gene therapy
- Future challenges
what are the major barriers to cure?
Barriers to cure

- Latently infected T-cells
- Residual viral replication
- Anatomical reservoirs
Latency occurs in central and transitional memory CD4+ T-cells
Preferential persistence of cells with similar integration sites in vivo

Wagner et al., CROI, March 2014; Cohen J, Science 2014: 343; 1188
The reservoir might be 60 fold bigger than originally thought

Ho et al., Cell 2013; 155: 540-551
eliminating latently infected cells
Eliminating latently infected cells

- Treatment during acute infection
- “Activating” latent infection
- Boosting HIV-specific immunity
- Allogeneic stem cell transplantation
Treatment of early acute HIV Infection: how might this work?

Very early ART

1. Limit number of latently infected cells
2. Prevent chronic immune activation (that fuels ongoing viral replication)
3. Preserve HIV-specific immunity

Achieve functional cure (Undetectable plasma HIV RNA without ART)
Very early ART during acute infection significantly reduces latently infected cells

Chomont, Ananoworanich et al., ICAAP 2013
Early ART leads to functional cure in a small number of patients: why?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Frequency of post ART control</th>
<th>Time of ART initiation</th>
<th>ART duration before interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mississippi baby</td>
<td>Case report</td>
<td>31 hours after birth</td>
<td>18 months</td>
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<tr>
<td>Persaud D, NEJM 2013</td>
<td></td>
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<tr>
<td>French</td>
<td>15% (n=70)</td>
<td>2-3 mos from exposure</td>
<td>3 years</td>
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<tr>
<td>Sáez-Cirión A, Plos Pathogen 2013</td>
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</table>
Activating latent infection

Latent infection

“activate”

HIV US RNA

HIV proteins

HIV virions

Cell death

HDACi

Cytokines eg., IL7

disulfiram

quinolines

Methylation inh

Histone methyl transf inh

BET inh
The HDACi vorinostat activates latent HIV

No change in the viral reservoir ie HIV DNA
No change in plasma HIV RNA – is virus being produced?

14 days of vorinostat in patients on stable ART (n=20)
Significant increase in CA-US RNA with the HDACi panobinostat

n=16

Plasma RNA – qualitative NAT screening test
Odds ratio **10.5 (95% CI 2.2;50.3)** for positive test on-treatment compared to baseline

Rasmussen et al., CROI, Boston, March 3-6., 2014
## Trials of other latency “activating” agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Design</th>
<th>PI (location)</th>
<th>Status</th>
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<tr>
<td>HDACi</td>
<td></td>
<td></td>
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<tr>
<td>Vorinostat</td>
<td>3 days on / 3 days off</td>
<td>Margolis (US)</td>
<td>No additional benefit (CROI2014)</td>
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<tr>
<td>Vorinostat + vaccine</td>
<td>10 days (acute treated HIV)</td>
<td>Frater (UK)</td>
<td>Approved</td>
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<tr>
<td>Disulfiram</td>
<td>14 days 500mg/day</td>
<td>Deeks (US)</td>
<td>Transient increase in plasma RNA (Spivak CID 2014)</td>
</tr>
<tr>
<td></td>
<td>3 days 500mg-2g/day</td>
<td>Elliot/Lewin (Australia)</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>
Latently infected cells are rare
HDACi induce prolonged changes in host gene expression

14 days of vorinostat in patients on stable ART (n=20)

Ghheim et al., CROI, Boston, March 2014
Will “activation” of HIV transcription be enough?

HIV DNA

Latent infection

“activate”

Cell death

“kill”

post transcriptional blocks?

therapeutic vaccine

Anti-PD1 or anti-PDL-1
Blocking PD1-PDL1 to boost immune function

**Study design:**

- **SIV Infection**
- **Start ARV**
  - PMPA 20 mg/kg QD SC
  - FTC 30 mg/kg QD, SC
  - RAL 200 mg BID, PO
  - ATV 400mg BID, PO

- **PD-L1 blockade**
  - 2 weeks
  - 6 weeks

- **ARV Ti**

- **Viral load rebound off ARV**

- **BMS-936559 (8)**
- **Isotype control (5)**
Anti-PDL1 led to successful virus control following ART in half the monkeys

ACTG: single infusion of anti PDL-1 (BMS) to start in 2014
The Berlin patient: CCR5 negative stem cell transplantation

The Emerging Race To Cure HIV Infections

Timothy Ray Brown’s startling fate has pushed to the front a daunting research challenge that long seemed a fool’s errand.
The Boston patients: “regular” stem cell transplantation

The Boston patients: “regular” stem cell transplantation

- CCR5+ (WT)
- Allogeneic BMT
- Reduced intensity irradiation (RISC)
- cART
- HIV DNA neg
- HIV RNA neg

HIV+ Lymphoma (n=2)

Henrich et al., *J Infect Dis* 2013: 207(11):1694-702
How low do you need to go?
making cells resistant to HIV
Making cells resistant to HIV: gene therapy

- Host gene – CCR5
- HIV itself
Gene therapy to eliminate CCR5

Leukapheresis
CD4+ T-cell isolation

CD4 + T-cells

ZFN modification of CCR5

Re-infuse

+ cyclophosphamide
Infusion of CCR5 modified cells is safe and cells survive

Tebas et al., *N Engl J Med* 2014; 370:901-10
Cyclophosphamide improves engraftment of modified cells

Blick et al., CROI 2014
future challenges?
Future challenges

- What are acceptable risks and toxicities of interventions in a population doing well on stable cART?

- What surrogate marker(s) of viral persistence accurately predict control post treatment interruption?

- Expectations of study participants in early “proof of concept” studies

- Universal access to cART must remain a top priority
Summary

- Early ART and stem cell transplantation can significantly reduce the viral reservoir although unclear what biomarker will best predict post treatment control.

- Activating HIV latency is possible in vitro and in vivo but unclear that this alone will produce virus and/or eliminate latently infected cells.

- Unlikely that success will be achieved by purely reducing the size of the reservoir. Enhanced immune control also likely to be needed.

- Significant additional challenge to find a strategy that ultimately is cheap, scalable and widely available.
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