Overview of scientific advances toward an HIV cure

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Outline

- Why can’t cART cure HIV?
- What are potential strategies to achieve a cure?
- Current clinical trials aimed at cure
- Current and future challenges
why can’t cART cure HIV?
Rapid rebound in virus when cART stopped

Years on HAART

0 1

off cART

HIV RNA

CD4 count

50
HIV DNA in infected cells is always detectable.

Chun et al., Nature 1997; 387:183; Finzi et al., Science 1997; 278:1295; Wong et al., Science 1997; 278:1291
No such thing as an “undetectable viral load”

Barriers to cure

- Latently infected T-cells
- Residual viral replication
- Anatomical reservoirs
HIV latency and infection of resting T-cells

Activated CD4+ T-cell → Resting CD4+ T-cell → Tissue chemokines

Latently infected T-cells

HIV Viral load

1
50

cART
Latent infection can be established in many T cells

Bone marrow → Thymus → Peripheral circulation

- Naïve T cells
- Effector/transitional
- Central memory

Multipotent progenitor cells → Naïve T cells → Transitional memory → Central memory

Latent reservoir

Residual replication
Immune activation associated with viral persistence in tissue

Spearman's rho: 0.65
P=0.012

Hatano et al., 6th IAS Conference, Rome, 2011
Anatomical reservoirs
Anatomical reservoirs

- DCs, macrophages, astrocytes

HIV Viral load

- cART

Levels: 1, 10, 50
GI tract is a significant viral reservoir on cART


N=8, time on cART with undetectable HIV RNA 2.8 – 12 years
What are potential strategies to achieve a cure?
Cure or remission?

**Cure**

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

**Sterilising cure**
Strategies for cure

- Eliminate residual virus replication
- Eliminate latently infected cells
- Make cells “resistant” to HIV
- Enhance HIV-specific immunity
current clinical trials aimed at cure
Eliminating viral replication: treatment intensification

Cell-to-cell infection not blocked by cART

Cell free infection

Cell-cell infection

e.g., lymphoid tissue

- cART

- Reduce immune activation
- Inhibit cellular not viral targets
- Enhance tissue penetration of cART

Sigal et al., Nature, 2011; 477(7362):95-8
Eliminate latently infected T-cells: activate latent HIV

- Activated CD4+ T-cell
- Resting CD4+ T-cell
- cART
Activating latent HIV

The Economist, July 17, 2011
Licensed drugs that activate latently infected cells

**Histone deacetylase inhibitors**
- Vorinostat
- Romidepsin
- Panabinostat
- Entinostat
- Belinostat
- Givinostat
- Others (9)

**Methylation inhibitor**
- 5-azacytidine

**Cytokine**
- Interleukin-7

**Anti-alcoholic**
- Disulfiram

* Total number of trials listed on [http://clinicaltrials.gov](http://clinicaltrials.gov) (July 2011)

Combination therapy: enhances potency of activation

Saleh et al., *Retrovirology* 2011 (in press)

Reuse et al., *Plos One* 2009; 4:e6093;
Perez et al., *Curr HIV Res*. 2010 Sep 1;8(6):418-29;
Van Lint, 6th IAS, Rome 2011
HDACi turn HIV genes “on”

Vorinostat (SAHA)

- Potent HDAC inhibitor
- Activates HIV from latency in vitro
- Licensed for cutaneous T cell lymphoma
- Multiple phase II trials for other malignancies including lymphoma, myeloma, solid tumors
- Oral administration
- Long term toxicities unknown

Will HDACi turn HIV genes on in vivo?

- n=20
  - 0,2,8 hours
  - Suppressive cART > 3 years
  - Vorinostat 400 mg/day

- * Rectal biopsy

- Primary endpoint
  - Cell associated HIV RNA
Latently infected cells are rare
Make cells “resistant” to HIV: gene therapy

- Activated CD4+ T-cell
- Resting CD4+ T-cell
- Silence or eliminate HIV
- Gene therapy
- Reduce CCR5

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.
Nucleases chop up DNA: eliminate CCR5 expression or eliminate HIV

Gene therapy to eliminate CCR5:
Sangamo Biosciences Inc, SB728-902

Aviremic HIV subjects on HAART (n=6) CD4 = 200-500/ml

Lalezari et al., 18th CROI, Boston, Feb 2011

SB728-T

n=6
Aviremic patients on cART
CD4>450
Treatment interruption

Ando et al., ICAAC, Chicago, Sept 2011
Gene therapy to eliminate CCR5: SB728T

Ando et al., ICAAC, Chicago, Sept 2011

% bi-allelic CCR5 modified cells correlated with viral suppression
current and future challenges for HIV cure
Scientific challenges

- Multiple barriers to eradication meaning a combination approach will be likely

- Better in vitro and animal models to evaluate new strategies, alone and in combination

- Drug development to increase potency and specificity for activating latently infected cells and/or enhanced tissue delivery

- Role of immune activation: driver of residual replication or a consequence of virus persistence?
Clinical and implementation challenges

- **Universal access** to cART must remain a top priority.

- PLWHA on cART are **doing well** so any intervention must have limited or no toxicity.

- **Clinical endpoints** for successful “eradication” unclear. When will a treatment interruption be OK?

- Multiple **unknowns with gene therapy**: safety of delivery vectors, DNA nucleases and long term impact of CCR5 suppression.
We need a cure that is scalable, deliverable and cheap

Funding for research toward a cure for HIV
Developing a road map for cure

International AIDS Society
Stronger Together

towards an HIV cure
people focused science driven

www.iasociety.org
The Rome Statement
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