Immune-based approaches to HIV cure

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HIV pathogenesis research 1.0

What causes AIDS in HIV infection?
Why SIV doesn’t cause disease in African monkeys?

Viral factors
Host factors

Chronic immune activation
Defective immune responses
Lack of immune regeneration
Immune senescence

HIV pathogenesis research 2.0

What causes HIV residual disease under ART?
How can we eliminate the reservoirs & achieve a full immune recovery?

Viral factors

Host factors
OUTLINE

1. The NHP model for pathogenesis/cure research

2. The “Cure” as an immunological problem

3. Testing concepts & interventions
   - shock & kill
   - soothe & schmooze
   - push & vanish
   - star wars

4. Where to go next
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Opportunities provided by NHP models in studies of HIV cure

1. Control for various clinical parameters that are virtually impossible to control in humans (Identity, dose, and route of virus challenge, time of infection, duration of ART etc).

2. Comprehensive cellular and anatomic characterization of both active and persistent reservoirs (including elective necropsy).

3. Pilot trials of in vivo eradication conducted in a timely and controlled fashion; treatment interruption is possible.

4. Testing of “risky” interventions (i.e., combination therapy, cell depletion studies, stem cell-based interventions etc)

Currently, key limitations to these studies are cost and lack of a standardized animal resource.
Five-Drug cART Regimen in SIV_{mac239}-infected Indian Rhesus Macaques

Figure 2. Suppression of plasma viremia with novel cART regimen in SIV_{mac239}-infected RM. (A) Individual and (B) Mean plasma viral loads. Dotted line represents the lower limit of detection of the assay (60 SIV RNA copies/ml of plasma). Undetectable values are plotted at half the lower limit of detection.
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Residual disease in ART-treated HIV-infected individuals

- Persistent Reservoirs
- Residual Immune Disfunction

Viral factors
Host factors

Residual HIV disease
Embracing the complexity of the CD4 pool to develop immunologically “sound” approaches to HIV cure

Different life-span of memory T-cells → “stem cells” of latent reservoirs?

Different pathways of CD4 differentiation

Th1  Th2  Th17  Tfh  Treg

Different levels of “resting”

Resting  Activated

Naïve

T_{SCM}

T_{CM}

T_{TM}

T_{EM}
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The “shock & kill” concept

What is the role of CTLs in controlling viremia on ART? and what if SIV is “reactivated” by HDAC-I?

Experimental design: CD8+ lymphocyte depletion in ART-treated SIV-infected macaques.

If viral blips are observed, and if ART is 100% effective, the observed virus comes from already infected, long-lived cells (i.e., latently infected).

CD8+ lymphocyte depletion has a major effect on CD4+ T cell activation that peaks one-to-two weeks after the nadir of depletion (Klatt, PLoS Pathogens 2010)
CD8+ lymphocyte depletion results in "early" vs "late" rebounds in viremia.
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Soothe and schmooze concept

Residual immune activation and immune dysfunction
IL-21 treatment in SIV-infected macaques on ART
(Luca Micci & Mirko Paiardini)

16 RM: 8 treated with ART+IL-21 vs 8 treated with ART alone

Does IL-21 improve the recovery of intestinal Th17 and Th22 cells?

Does IL-21 limit residual immune activation/inflammation?

Does IL-21 reduce residual viremia and/or size of the latent SIV reservoir?
Repeated measures analyses: percentages of RMs with undetectable viremia over time is significantly higher in IL-21 treated animals than controls (P=0.03)

Limit of detection: 3 copies/mL (Jeff Lifson)
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PD-1+ central memory CD4+ T cells as a key component of the reservoirs of latently HIV-infected cells

Increasing contribution of Tscm to HIV reservoir over time (M. Lichterfeld)

Lichterfeld et al., Nature Medicine 2013
The “push & vanish” concept

Naïve           Memory SC     TCM            TTM1          TTM2           TEM

PUSH

VANISH
Examples of “push & vanish” approaches:

1. Promote the differentiation of latently infected CD4 T\textsubscript{CM} with combinations of cytokines (IL-7, IL-15) and co-inhibitory blockade (PD1, LAG-3, TIGIT).

2. Promote CD4 T\textsubscript{SCM} differentiation with inhibitors of the signaling pathways involved in the self-maintenance or “stem cell-ness” of this cell subset.

3. Maraviroc monotherapy before ART initiation to ‘push’ the virus in CD4 T\textsubscript{EM} by exploiting the higher CCR5 levels in these cells as compared to T\textsubscript{CM}.
Testing the “push & vanish” concept in SIV-infected sooty mangabeys

Paiardini et al., Nat Med 2011
Chahroudi et al., Science 2012
Cartwright et al. J Immunol 2014

Persistence of TSCM (and TCM) reservoirs

Absence of TSCM (and TCM) reservoirs
ART suppresses SIV replication in SMs
Post-ART virus control in SMs?

Graph showing SIVsmm RNA copies/mL over days on ART with ART regimen PMPA + FTC + RLT + DRV.
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Reconstructing Berlin: HSCT & Gene therapy

Zinc Finger Nuclease
Auto-HSCT in SHIV-infected, ART-treated macaques

- 3 experimental RM: SHIV infection + aHSCT
- 3 paired non-transplanted control RM: SHIV infection

Harvest + cryopreserve HSC

RT-SHIV Infection

TBI (Total Body Irradiation) 3 x 3.6cGy

G-CSF

Blood samples collected throughout the study

Full necropsy
Auto-HSCT in SIV-infected RMs: summary of results

- Through cytoreduction by TBI and successful engraftment following a-HSCT we conducted a massive “reset” of the lympho-hematopoietic compartment (including 95-99% of CD4+ T cells).

- Rapid plasma viral rebound in 2/3 transplanted RMs following ART interruption indicates that this drastic hematopoietic “reset” in the setting of ART was not sufficient to eradicate the infection.

- Encouraging signs?
  The 3rd transplanted RM had undetectable plasma viremia and SIV-DNA in PBMCs 15 days after ART interruption. However, virus was detected in the spleen and some LNs at necropsy.

- Future directions:
  - Allogenic HSCT (harness the “graft vs reservoir effect”)
  - Gene therapy intervention to knock out CCR5

Mavigner et al., PLoS Pathogens, 2014
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1. Curing HIV infection is not a virological problem only, but instead a virological AND immunological problem.

2. Eradication of the persistent reservoir of latently infected CD4+ T cells will most likely require approaches that take fully into account the remarkable complexity of this immune cell population.

3. Extensive use of the animals models (NHP & humanized mice) will be crucial to test innovative concepts and interventions to cure AIDS.
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