HIV: Towards a sustainable remission?

Françoise BARRE-SINOUSSI
35 years of HIV Science
A good example of translational research

A new era since cART in 1996….
“Which kind of “HIV Cure” are we looking for?”

HIV Reservoirs on cART....

Cure

Elimination of all latently infected cells

Sustainable Remission

Persistent reduction and control:
Long term health without cART and without risk to transmit

Berlin Patient?

Proof of concept...
HIV remission is rare but possible

Viral load

ART

STOP 2-4 weeks Boston A 3 months

Boston B 8 months

ART started early in infection

Mississippi child 28 months

Visconti, French Teenager

Challenges.....
HIV Reservoirs and immune activation...

Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys


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HIV reservoirs in many cell subsets and lymphatic tissues

- **Major reservoirs** are resting central & transitional CD4+ memory T cells (Persistent and stable on cART >10 years);

- **Other reservoir cells**: naive T cells, memory stem T cells, T follicular helper cells (EC), myeloid cells, astrocytes, hematopoietic progenitor cells, etc...

- **Anatomic reservoirs**: GI & genital tract, lymphoid tissue, CNS...

**Residual viral replication**

**T cell survival**

**Homeostatic Proliferation** (clonal expansion): expression of Immune checkpoints molecules (PD-1, LAG-3, TIGIT, CTLA-4), negative regulators of T cell responses, contributing to immune exhaustion...
Opportunities?
Activating latent infection: the “shock”

Latent infection

“shock”

HIV DNA

HIV US RNA

HIV proteins

HIV virions

Cell death

Latency reactivating agents (LRA)
eg., modify chromatin

LRA accelerating cell death
eg., disulfiram, TLR agonists
Distinct classes of Latency Reversing Agents (LRAs)

LRAs may activate latency in vivo but none eliminate latently infected cells

<table>
<thead>
<tr>
<th>Latency reversing agent</th>
<th>Site of action</th>
<th>HIV latency</th>
<th>US HIV RNA</th>
<th>Plasma RNA</th>
<th>HIV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>HDACi</td>
<td>Single dose&lt;sup&gt;1&lt;/sup&gt; Intermittent&lt;sup&gt;2&lt;/sup&gt; Continuous&lt;sup&gt;3&lt;/sup&gt;</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>HDACi</td>
<td>Intermittent dose&lt;sup&gt;4&lt;/sup&gt;</td>
<td>↑</td>
<td>+/-</td>
<td>↔</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>HDACi</td>
<td>Weekly dose&lt;sup&gt;5&lt;/sup&gt;</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↔</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>AKT activation</td>
<td>High dose 2g/day&lt;sup&gt;6&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Bryostatin</td>
<td>PKC agonist</td>
<td>Low dose 10-20ug/m²</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

HDACi = histone deacetylase inhibitor; US HIV RNA = unspliced HIV RNA

Killing HIV-infected Cells

Dual-Affinity Re-Targeting Therapy (DART)

CD8

Genetically engineered T cells
(CAR T cells)

NK

Broadly Neutralizing Antibodies (bNAbs)

HIV-infected Cell

Vaccines

Jintanat Ananworanich, Joep Lange Memorial Lecture, IAS 2017, Paris
HIV vaccination + TLR7 (adjuvant or latency reversal) leads to SIV control off ART

TLR7 agonist (Gilead) and Adenovirus (Ad26) + Modified Vaccine Ankara (MVA, Janssen)

Borducchi et al., Nature 2016
Protective efficacy of V2 env specific antibodies (PGDM1400 and CAP256-VRC26.25-LS) against SHIV-325c in rhesus macaques.

Single injection of bNabs before viral challenge

Boris Julg et al.,
Sci Transl Med 2017;9:eaal1321
Broadly neutralising antibodies eliminate infected cells and prolong time to rebound off ART.


HIV viral load, log copies/ml
CD4+ T-cell count, cells/ml

HIV-infected individuals on ART
Antiretroviral treatment interruption 2 days after first infusion

ACTG = historical controls;
Group A = 3BNC1017x2 infusions;
Group B = 3BNC1017 x 4 infusions

19<sup>th</sup> JNI, Nantes, du 13 au 15 juin 2018
Bi-specific Abs: “shock and kill”

Sung et al., J Clin Inv 2015; Pegu et al., Nat Comms 2015

- BITEs and DARTs mediate killing of HIV-infected cells in vitro
- Little in vivo data for treatment of HIV, even in animal models, but ongoing studies
- Products exist and have entered clinical trials for cancer
Targeting cell trafficking to the gut? Sustained virus control following $\alpha4\beta7$ blockade

- $\alpha4\beta7$ is an integrin and enables migration of CD4+ T-cells to GI tract
- $\alpha4\beta7$ is a co-receptor for HIV infection
- $\alpha4\beta7$ expression predicts HIV outcome
- $\alpha4\beta7$ antibody (vedalizumab) is licensed for IBD

Byareddy et al., Science 2016

Vedraluzimab now in clinical trials in HIV-infected individuals on ART
HIV Persistence and cancer

Similar challenges...

Chronic Inflammation

Immune Suppression

Cancer/HIV persistence
HIV Persistence and cancer:
Similar therapeutic strategies...

- LRA (HDAC inhibitors; JAK/STAT inhibitors; PKC agonists)
- TRL4/7 agonists
- Cytokines and/or anti-cytokines (IL-1, IL-21, IL-15, anti-IFNα, anti-IL-7...)
- ICB blockers (anti-PD1, PD1-L or anti CTLA-4...)

Chronic Inflammation

Immune Suppression

Cancer/HIV persistence
<table>
<thead>
<tr>
<th>Immune checkpoint blocker</th>
<th>Study design</th>
<th>Patient population</th>
<th>Study name (Location)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti PD1 (Merck)</td>
<td>Multi-dose phase 1B</td>
<td><strong>Malignancy</strong>: AIDS-defining or non-AIDS</td>
<td>CITN; US</td>
<td>Reservoir substudy</td>
</tr>
<tr>
<td>Anti PD1 + Anti CTLA4 (BMS)</td>
<td>Phase 1 Dose escalation</td>
<td><strong>Malignancy</strong>: HIV-associated tumors including lung, anal and KS</td>
<td>AMC; US, Sydney</td>
<td>Reservoir substudy</td>
</tr>
<tr>
<td>All ICB</td>
<td>Observational study</td>
<td><strong>Malignancy</strong>: melanoma or small cell ca of lung</td>
<td>Australia, US, Denmark, Germany</td>
<td>Ongoing</td>
</tr>
<tr>
<td>All ICB</td>
<td>ANRS OncoVIH cohort</td>
<td>All cancer patients</td>
<td>France</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Nivolumab (anti PD1)</td>
<td>Phase 2 trials</td>
<td>NSCLC and Hodgkin</td>
<td>France</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

ACTG = AIDS Clinical Trials Group; CITN = Cancer Immunotherapy Network; AMC = AIDS Malignancy Consortium; ANRS Clinical trials and cohorts

Adapted from Rasmussen T et al., Curr Opinion HIV/AIDS 2016
HIV reservoir decrease in one patient with lung cancer treated with nivolumab


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**Figure 1.** Immunovirological modulations under anti-PD-1 therapy in an HIV-infected patient treated for lung cancer. (A) CD4 cell count, interleukin (IL)-6 plasma levels, HIV-1 plasma viral load measured with ultrasensitive technique (USVL), and total HIV-DNA (DNA copies/million cells) through time. (B) PD-1 expression on total CD4+ and CD8+ T cells, on HIV Gag-specific CD8+ T cells, and on HIV RT/Nef-specific CD8+ T cells. Results are expressed as absolute number of total PD-1+ T cells/mm³ or as mean fluorescence intensity (MFI) for HIV-specific T cells. (C) HLA-DR and CD38 activation markers expression on total CD4 and CD8 peripheral T cells. (D) Frequencies of HIV Gag, RT/Nef, and Epstein Barr Virus (EBV)-specific IFNγ+CD8+ T cells (stimulation with optimal CD8 peptides).
“Block and Lock” Strategy

Epigenetic silencing by Curaxin 100 (CBLO100), an inhibitor of transcriptional elongation

Tat inhibitor like dCA (didehydrocorstatin)
Gene/cell therapy?

Re-infusion of ZFN-CCR5 modified T cells in few patients: sustained decline in HIV DNA and CD4+T cell increase over one year (Sangamo study by Dale Ando et al.)

What are the best strategies?

- Gene editing using CRISPR-Cas9 (modified CCR5, siRNA, CARs, TCRs...)?
- Which Cell (T cells or human stem cells, autologous vs. allogeneic) to engineer?
- HSC engraftment concerns?
- Animal models and best patients for clinical studies?
- Safe, effective, affordable and scalable approach?

Hua et al. PNAS 2015; Liao et al. Cell Cycle 2015
Excising HIV Provirus with Gene Editing

Elimination of HIV-1 Genomes from Human T-lymphoid Cells by CRISPR/Cas9 Gene Editing
R Kaminski, K Khalili et al.

In Vivo Excision of HIV-1 Provirus by saCas9 and Multiplex Single-Guide RNAs in Animal Models
C Yin, W Hu et al.
Where are we going?
HIV Cure strategies currently in human studies

MINIMIZE RESERVOIR
Limit reservoir with early treatment
Antiretroviral therapy
Broadly neutralizing antibodies

URGENT NEED for novel biomarkers predictive of efficacy!

SHOCK
Reactivating latently infected cells
Inhibit histone deacetylase
Inhibit bromodomain extraterminal domain
Activate toll-like receptors

Combinations
BLOCK and LOCK
Latency Promoting Agent (LPA)

KILL
Viral clearance by the immune system
bNabs
Therapeutic vaccines
anti-PD1 or PD1-L

Curaxin100 (CBLO100): inhibitor of transcriptional elongation.
dCA (tat inhibitor didehydroxycorsatin)

HIV RESISTANT CELLS or DESTROY HIV
Transfusing cells with modified CCR5 gene
Gene-editing therapy using CRISPR-Cas9
Bone marrow or cord blood transplantation

Personalized cure therapy?
Affordable and scalable strategies ($<1400$)
Advisory Board to Implement a Global Multidisciplinary, Integrated and Coordinated Scientific Agenda...

- **Funding**: 2012-2016: Investment x 3
- **New concepts, new generation**
- **Interaction between Basic + Clinical Science**
- **Social and Economical Science**
- **Community engagement**
- **Cross-talk with other scientific disciplines**
- **Int. scientific collaborations**
- **Cooperation public + privates sectors**
- **Platforms of Information & Data exchanges**

**Towards an HIV cure**

*people focused science driven*

**Launch of the Rome Statement for an HIV Cure**

**Monday, 18 July,**... Associate Director for AIDS Research and Director of the Office of AIDS Research at the National Institutes of Health. 

19th JNI, Nantes, du 13 au 15 juin 2018
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