How Can Oncology Help HIV Cure Strategies?

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• Disclosure COI
• MSD
• BMS
• Genzyme
HIV cure

• Eradication or remission? 

Eradiation

Remission

ART
Can Oncology help HIV eradication?

One case of HIV eradication: Berlin’s patient T. Brown
Treatment of leukemia with bone marrow allograft

The challenge = be alive after two bone marrow allografts and a graft versus host disease (mortality = 30%)… Unacceptable

Kent et al. Lancet Infect Dis 2013
HIV remission?

- Spontaneous and post-treatment controllers: HIV remission is possible
- Undetectable HIV RNA in plasma, very low HIV DNA and no decrease of the CD4 T cell count in the long term

What are the main obstacles to achieve HIV remission?

1. HIV persists in latently infected resting memory CD4 T cells
   
   \[ T_{EM} < T_{TM} < T_{CM} < T_{naive} < T_{scm} \]

   Murray et al. JI 2016

2. Post-integration HIV latency is complex and very stable

3. HIV persists in tissues despite ART (lymph nodes, gut, brain, adipose tissue...)

4. The HIV-specific immune response is not functional

5. The question of an insufficient biodiffusion of ART in tissues
   (Lorenzo-Redondo et al. Nature 2016)
HIV cure… not for tomorrow morning…
Think different: do the parallel with the residual cancer cells

HIV cure

Cancer cure

Goal = to kill or control rare « events »

Latently infected CD4 T cells
Quiescent poorly immunogenic cancer cells « invisible for the immune system »

– No good test to detect these cells
– Intrinsic properties favoring persistence and survival
– Extrinsic obstacles
– Defects of the immune system
– Deleterious role of the tissular microenvironment
How to control the cancer cells escape?

The cancer cells and their microenvironment are tightly dependent.
How to control the persistent HIV-infected CD4 T cells?

Many common mechanisms facilitate the persistence of our target cells

Active HIV replication in CD4 T cells

Latently HIV-infected CD4 T cells

Soluble immunosuppressive products inhibiting anti-HIV immunity
What are the strategies we have to develop?

- Action on the HIV-infected cells
  - Reduction of the size of the reservoirs
  - « Shock and kill » strategies
- Improve the immune control of the HIV-infection
  - Example of HIV controllers

- Action on the cancer cells
  - Targeted therapies against oncogenic pathways
- Improve the immune control of cancer
- Spontaneous cancer regression (role of the immune system)
Reduction of the size of the HIV reservoirs: the « Shock and kill » strategies with Latency Reactivating Agents (LRAs)

Multiple targets to reactivate HIV-1 from latency

Vorinostat (SAHA)
Panobinostat
Romidepsin

Prostratin
Bryostatin
Disulfiiram
TLR7 and TLR 9 agonists

Anti-JAK
ruxolitinib

5AZA, 5AZAdC

Most of the Latent Reactivating Agents (LRA) used in the « shock and kill » strategies come from oncology.

Toxicity is known
Doses are lower than in cancers: better tolerance

Does it work in the HIV field?
iHDACs are able to mobilize HIV reservoir in blood but not to reduce its size

Sogaard et al. Plos Path 2015
How Oncology can help HIV remission strategies?

- In oncology, drugs used as Latent Reactivating Agents (LRA) are used in combination with other anticancer strategies and during a prolonged time.

ClinicalTrials.gov

**TLR9 Agonist SD-101, Ipilimumab, and Radiation Therapy in Treating Patients With Low-Grade Recurrent B-cell Lymphoma**

- **Conditions:** Extranodal Marginal Zone B-cell Lymphoma of Mucosa-associated Lymphoid Tissue; Nodal Marginal Zone B-cell Lymphoma; Recurrent Grade 1 Follicular Lymphoma; Recurrent Grade 2 Follicular Lymphoma; Recurrent Marginal Zone Lymphoma; Recurrent Small Lymphocytic Lymphoma; Splenic Marginal Zone Lymphoma

**Panobinostat or Placebo With Bortezomib and Dexamethasone in Patients With Relapsed Multiple Myeloma**

- **Condition:** Multiple Myeloma


**Sequential treatment with 5-aza-2'-deoxycytidine and deacetylase inhibitors reactivates HIV-1.**

Bouchat S1, Delacourt N1, Kula A1, Darcis G2, Van Driessche B1, Corazza F3, Gatot JS1, Melard A4, Vanhulle C1, Kabeya K5, Pardons M1, Avetrand-Fenoel V4, Clumeck N2, De Wit S5, Rohr O6, Rouzioux C4, Van Lint C7.
Can Oncology help HIV remission strategies?

• If LRAs are used alone, the risk of failure is high because HIV-infected cells can survive (Shan et al. Immunity 2013)

• We need to boost simultaneously the HIV-specific immune response
  – Immunotherapies using
    • vaccine strategies
    • broadly neutralizing antibodies mediating ADCC
    • immune check-point blockers (ICB)
    • Gene and cell therapies

(Lu et al. Science 2016, Bruel et al. Nat Com 2016)
Can Oncology help HIV remission strategies?

- Immune check-point (ICP) blockers have revolutionized cancer therapeutic strategies

- ICP control T cell activation

- Ipilimumab (anti-CTLA4): melanoma

- Nivolumab and pembrolizumab (anti-PD1)
  - Melanoma
  - NSC lung cancer
  - Hodgkin
  - Renal cell cancer

Anti PD-1 and cancer

- Phase III, Lung
- 272 patients
- Nivolumab versus docetaxel
  - AE ≥ grade 3
    - 7% Nivo
    - 55% docetaxel

Brahmer et al; NEJM 2015

Durable responses after anti-PD1 stop
Anti PD-1 and anti PD-L1 boost the cancer-specific CD8 T cells present in the cancer microenvironment.

Extended Data Figure 7 | Biomarker analyses for a responding patient receiving MPDL3280A. A patient with PD-L1-positive (IHC IC 3) renal cell staining from a tumour biopsy of a shrinking lesion during week 4 of treatment with MPDL3280A that demonstrates an increase in CD8⁺ T-cell infiltration.

Anti-PD-L1, Herbst et al., Nature 2014
Immune activation is associated with exhaustion of the immune system in HIV: role of the PD-1 / PD-L1 axis

- PD-1 expression on CD8 and CD4 T cells correlates with disease progression
- Functional improvement of CD4 T and CD8 T cells if PD-1/PD-L1 blockade

Increase of IL-2 production

PD-1 blockade in CD4 in HIV infection

Increase of cytotoxicity

PD-1 blockade in CD8 in HIV infection

PD-1 blockade in vivo: the NHP model

14 Indian macaques: 9 with anti-PD-1 + 5 with Ig
4 doses humanized anti-PD-1 day 0,3,7,10
Increase of SIV-specific CD8 T cell responses (polyfunctionality and cytotoxicity)
Increase of the production of SIV-specific antibodies
Decrease of the plasmatic viral load
Decrease of immune activation (Shetty et al. JCI 2012)
Safety OK

Increase of the survival
Perspectives for anti-PD1 in HIV

• Optimization of the immune response
  – CD4 T, CD8 T
  – Immunomodulation

• Reduction of the HIV lymphocyte reservoir?

Chomont et al. Nat Med 2009

PD-1$^+$ and follicular helper T cells are responsible for persistent HIV-1 transcription in treated aviremic individuals

Riddhima Banga$^1$, Francesco Andrea Procopio$^1$, Alessandra Noto$^1$, Georgios Pollakis$^2$, Matthias Cavassini$^3$, Khalid Ohmiti$^3$, Jean-Marc Corpataux$^4$, Laurence de Leval$^5$, Giuseppe Pantaleo$^{1,6}$ & Matthieu Perreau$^1$
Can ICB as anti-PD1 help HIV remission strategies?

Yes but adaptations are necessary

- Use different isotypes of ICB
  - To block (nivolumab, pembrolizumab…. IgG4)
  - To deplete via ADCC (IgG1)
- Find specific protocols of administration
- Better know the roles of the different immune check points in HIV infection (TIGIT, LAG3…) in blood and in tissues++ to define ICB associations

Triple positive PD1+ TIGIT+ LAG3+ CD4 T cells are enriched in latently infected cells (Fromentin et al. Plos Path 2016)
Can ICB as anti-PD1 help HIV remission strategies?

- To better know
  - the adverse events of anti-PD1 and other ICB (autoimmunity++)
  - how to manage these adverse events
- Collaborative work with oncologists
- Trials in HIV-infected patients with cancers

Trials in HIV infection

- NCT02028403 (oral presentation CROI 2016)
- Safety and Immune Response of BMS-936559 (anti-PD-L1) in HIV-Infected People Taking Combination Antiretroviral Therapy
- A Phase I, Double-Blind, Placebo-Controlled, Ascending Single Dose Study
- This study has suspended participant recruitment: retinal toxicity in NHP

- NCT02408861
- A Phase I Study of Ipilimumab and Nivolumab in Advanced HIV Associated Solid Tumors With an Expansion Cohort in HIV Associated Solid Tumors (Anal, lung)
- Sponsor: National Cancer Institute (NCI)
- Recruiting

- NCT02595866
- Pembrolizumab in treating patients with HIV and relapsed, refractory, or disseminated malignant neoplasms
- Sponsor: National Cancer Institute (NCI)
- Recruiting

- France: two trials phase II: Nivolumab in NSCLC and in Hodgkin disease (start end of 2016)
- France: ANRS Cohort ONCOVIH for all patients treated for cancer by anti PD1, PD-L1, CTLA4
Can Oncology help HIV remission strategies? Cellular therapies

Chimeric Antigen Receptor (CAR) T cells!

Can Oncology help HIV remission strategies?
Cellular therapies

Table 1. Current Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial Registry Identifier(s)</th>
<th>Manufacturer/Sponsor(s)</th>
<th>Phase</th>
<th>Estimated Study Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early ART in combination with autologous HIV-specific cytotoxic T lymphocyte (CTL) infusion</td>
<td>NCT02231281</td>
<td>Yongtao Sun, MD, PhD, Tangdu Hospital, the Fourth Military Medical University</td>
<td>Phase III</td>
<td>December 2016</td>
</tr>
<tr>
<td>Reconstitution of HIV-specific immunity against HIV</td>
<td>NCT025563509</td>
<td>Guangzhou 8th People’s Hospital</td>
<td>Phase I/II</td>
<td>December 2016</td>
</tr>
<tr>
<td>HXTC: HIV 1 antigen expanded specific T cell therapy</td>
<td>NCT02208157</td>
<td>University of North Carolina, Chapel Hill</td>
<td>Phase I</td>
<td>September 2018</td>
</tr>
</tbody>
</table>

JCI The Journal of Clinical Investigation

Public T cell receptors confer high-avidity CD4 responses to HIV controllers

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First published April 25, 2016 - More info

CAR T cells with an « ideal » TCR?
To conclude…

How Can Oncology Help HIV Cure Strategies?

• To share information in basic science
• To set up clinical trials combining different therapeutic strategies
It is the time to think about HIV cure as cancer cure

Antiretroviral drugs

Many targets and weapons... Combine strategies

ICB as Anti-PD1....

CD8 T  NK  B cell  bNabs

LRAs

CCR5
Do not forget some points which are not, today, a limit in cancer… but in HIV

- The patients and their acceptability for new treatments
- The physicians and their acceptability for new treatments
- The feasibility of HIV remission strategies on a large-scale
From 1980 to 20…

• 1995
  - Ritonavir, indinavir, saquinavir are combined with AZT, d4T, ddl…
  - HIV was controlled
  - Lipodystrophies, lactic acidosis, neuropathy…
  - Many pills

• 2015
  - Tenofovir, emtricitabine, rilpivirin, dolutegravir, raltegravir
  - HIV is controlled
  - Limited and acceptable AE
  - One or few pills

• 20… = HIV remission!
  - Combination of optimized ART (tissue diffusion) + LRAs + immunotherapy + Nab antibodies

• 2010-2015
  - Targeted therapies
  - Ipilimumab, nivolumab, pembrolizumab
  - Frequent adverse events / costs++
  - Frequent infusions IV

• 2020-20…. 2nd generation!
  - …ab, ….ib, used in combination
  - Limited and acceptable AE
  - A simplified way of administration (subcutaneous…)
  - Lower costs+++
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Jean-Philippe Spano
Dominique Costagliola

HIV-infected patients

www.iasociety.org
Cocktail of 3 broadly neutralizing antibodies + 2 LRAs (vorinostat + BETi) + anti-CTLA4

Broadly Neutralizing Antibodies and Viral Inducers Decrease Rebound from HIV-1 Latent Reservoirs in Humanized Mice

Ariel Halper-Stromberg,1 Ching-Lan Lu,1,2 Florian Klein,1 Joshua A. Horwitz,1 Stylianos Bourmazos,3 Lilian Nogueira,1 Thomas R. Eisenreich,1 Cassie Liu,1 Anna Gazumyan,1 Uwe Schaefer,4 Rebecca C. Furze,6 Michael S. Seaman,6 Rab Prinjha,5 Alexander Tarakhovsky,4 Jeffrey V. Ravetch,3 and Michel C. Nussenzweig1,7,*

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http://dx.doi.org/10.1016/j.cell.2014.07.043
To conclude…

How Can Oncology Help HIV Cure Strategies?

• To share information in basic science
• To set up clinical trials combining different therapeutic strategies
Diffusion très insuffisante des ARV dans les ganglions

Fletcher C et al. PNAS 2014
Anti-PD1 and cancer

Role of the levels of expression of PD-L1

Garon et al. NEJM2015
PD-1 blockade in vivo: the monkey model

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Brief Report
PD-1 blockade during chronic SIV infection reduces hyperimmune activation and microbial translocation in rhesus macaques

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Gordon J. Freeman², Guido Silvestri¹,³ and Rama Rao Amara¹,⁴