Les stratégies anti-cancéreuses dans les perspectives de « HIV cure »

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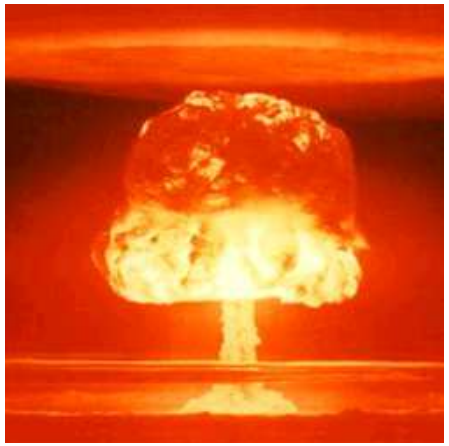
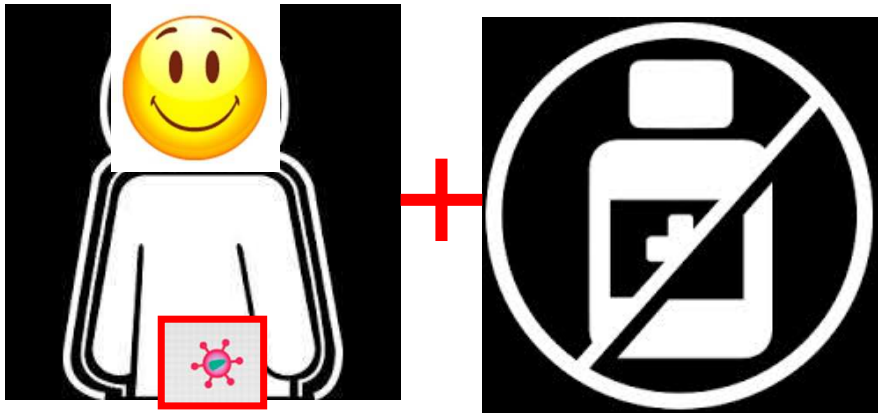
Cancer VIH 1ère journée nationale

HIV cure

- Eradication ou rémission ?





Eradication

Rémission

HIV cure: mythe ou réalité ?

- Le patient de Berlin = guérison de type éradication ?
- Le défi = survivre à deux allogreffes de moelle…..

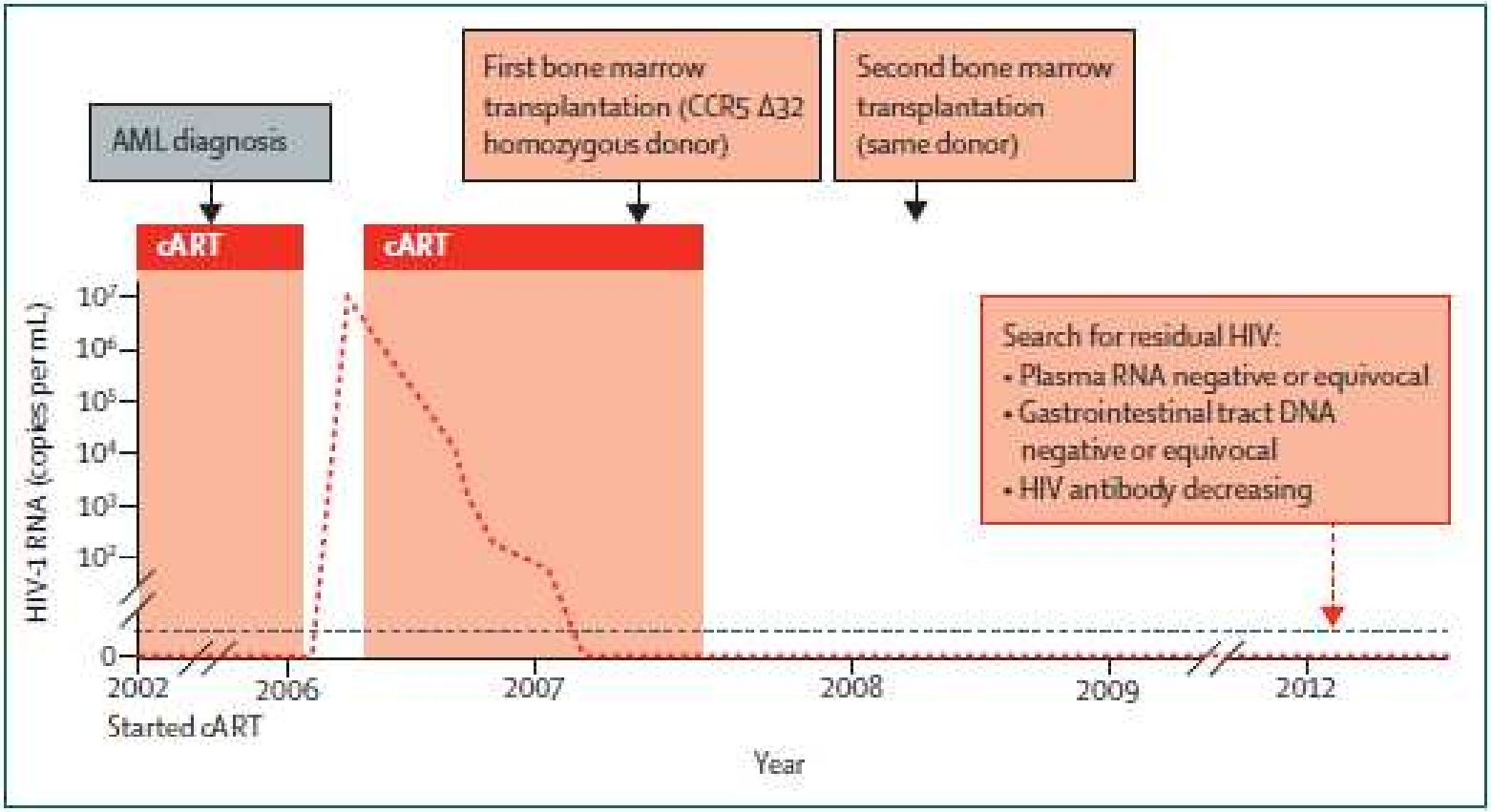


Figure 1: Timeline for treatment of the Berlin patient

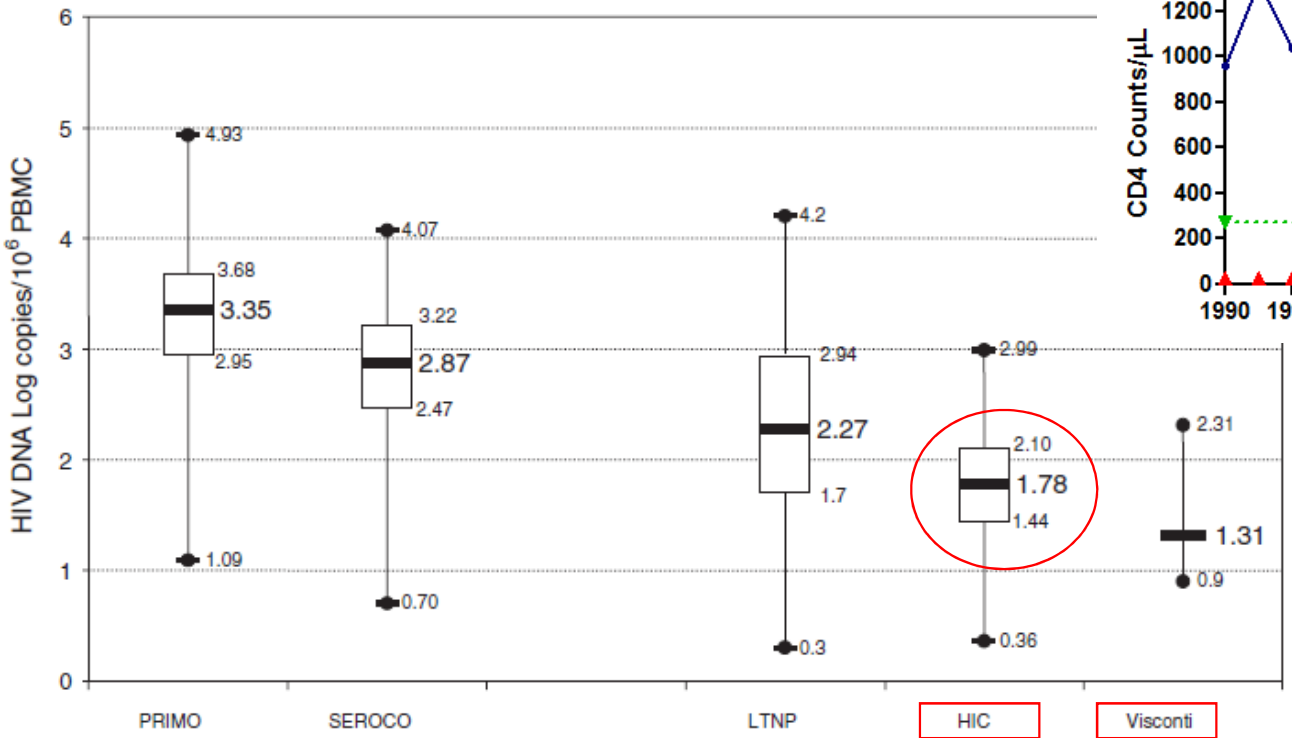
Kent et al. Lancet Infect Dis 2013

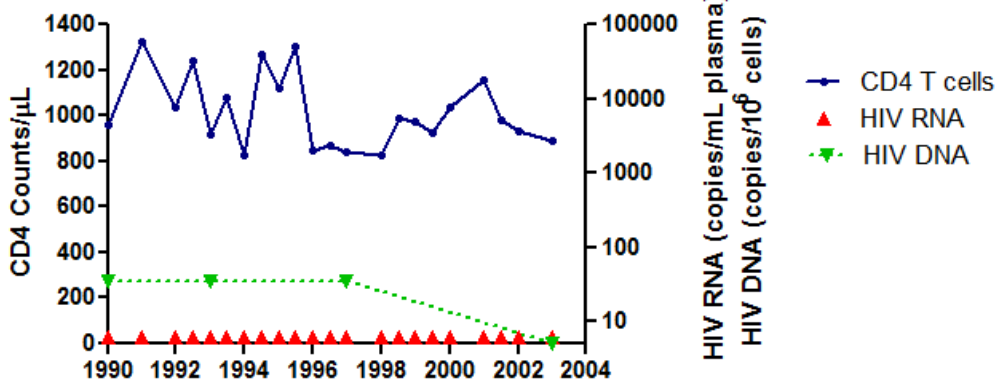
HIV cure: mythe ou réalité ?

Les patients HIV controllers: une guérison fonctionnelle / rémission ?

- Les controllers post traitement (Etude Visconti)
- Les patients HIV Controllers « spontanés »

= niveaux d'ADN VIH les plus bas





Lewin S et al. AIDS 2011

Réduire la taille des réservoirs viraux contribue probablement au succès d'une stratégie de « cure »

- Connaissance des mécanismes de persistance du VIH
- Etre capable d'agir contre ces mécanismes
- Chez un grand nombre de patients
- Coût accessible

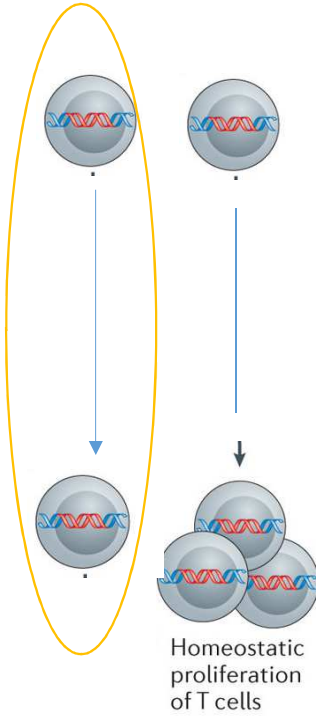
1997 : L'éradication virale envisagée se heurte à la persistance du virus dans un réservoir

Lymphocytes T CD4+ quiescents DR- infectés de manière latente

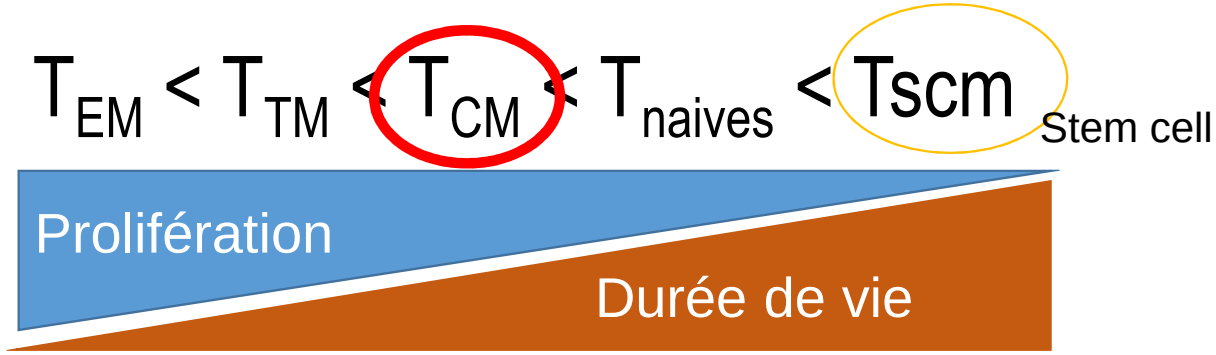
virus compétent pour la réplication sous forme d'ADN viral intégré

Finzi et coll., Science 1997, Wong et coll., Science 1997, Chun et coll., PNAS 1997

Le réservoir cellulaire le mieux caractérisé est le réservoir lymphocytaire T CD4 quiescent



Virus intégré latent = pas de transcription = pas de détection par le système immunitaire



Persistance car longue durée de vie des cellules réservoirs et prolifération homéostatique (IL-7)

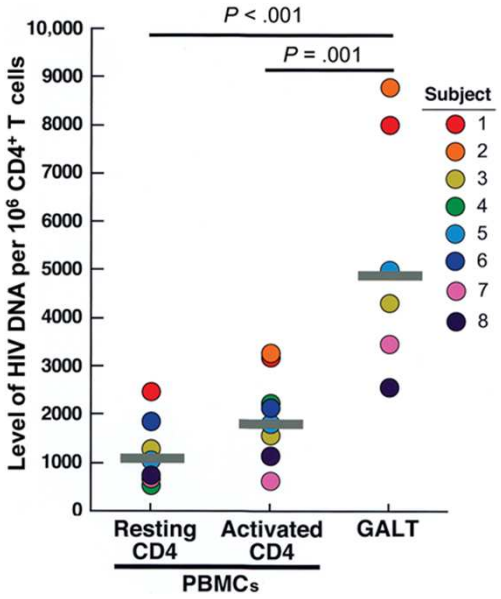
Réduire le réservoir lymphocytaire T CD4 ?

- Modèles mathématiques : > 60 ans de tt anti-rétroviral pour éliminer les réservoirs TCD4

= impossible

- 4 obstacles !

1. La stabilité intrinsèque du réservoir lymphocytaire
2. Les autres réservoirs – les tissus
   - Macrophages et lymphocytes T CD4 résidents
   - Cellules folliculaires dendritiques
   - Sites réservoirs anatomiques (SNC…)
3. Une réplication virale résiduelle liée à une efficacité insuffisante des ARV dans les tissus (Lorenzo-Redondo et al. Nature 2016)
4. L'absence de réponse spécifique anti-VIH efficace



Chun et al JID 2008, Erikson Plos Path 2013, Yukl et al. JID 2013, Yukl et al. AIDS 2014

HIV cure… not for tomorow morning…

- Persistance du VIH

1. Mécanismes intrinsèques du LTCD4 infecté de manière latente ↔ latence VIH, biologie de la cellule cible

2. Mécanismes extrinsèques dans les tissus

- Interactions cellulaires : déficit immunitaire anti-VIH, rôle du microenvironnement
- Diffusion des ARV

Think different: the parallel with the residual cancer cells

HIV cure

Cancer cure

- Goal = to kill or control rare « events »

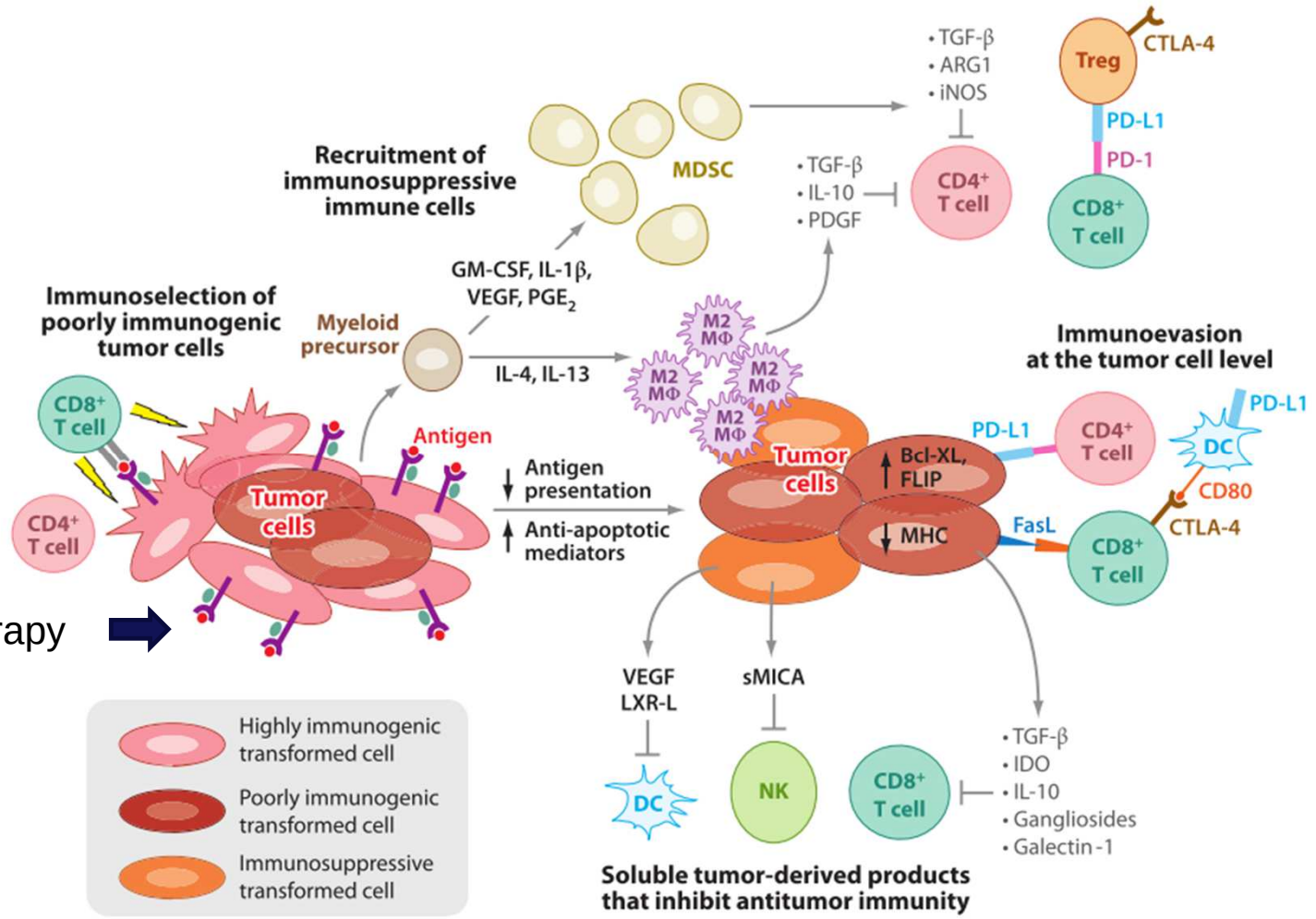
Latently infected CD4 T cells
Quiescent cancer cells

« invisible for the immune system »

- Defects of the immune system
- Deleterious role of the tissular microenvironment

How to control the cancer cells escape?

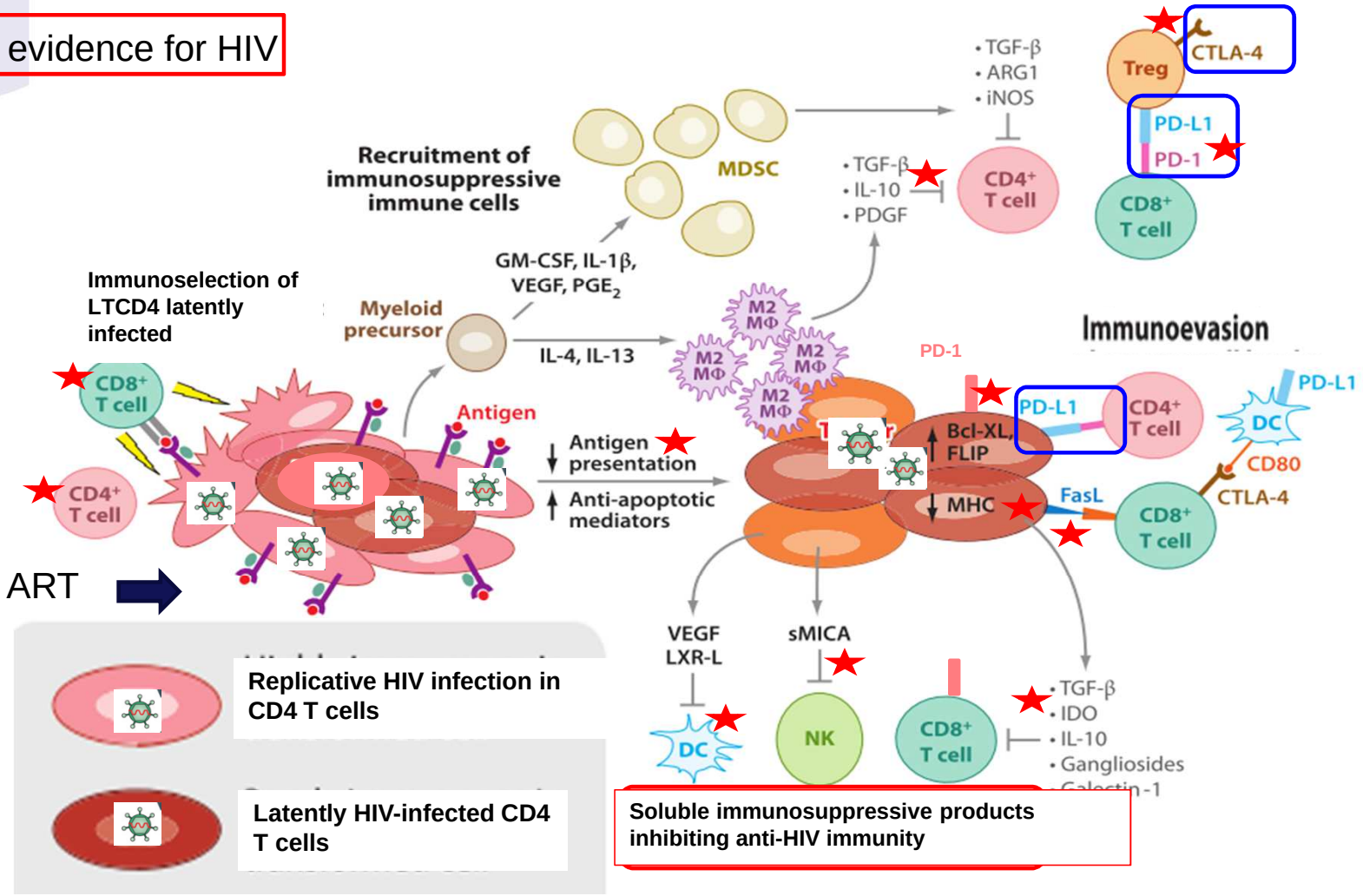
Chemotherapy



Vesely et al. Annu Rev Immunol 2011

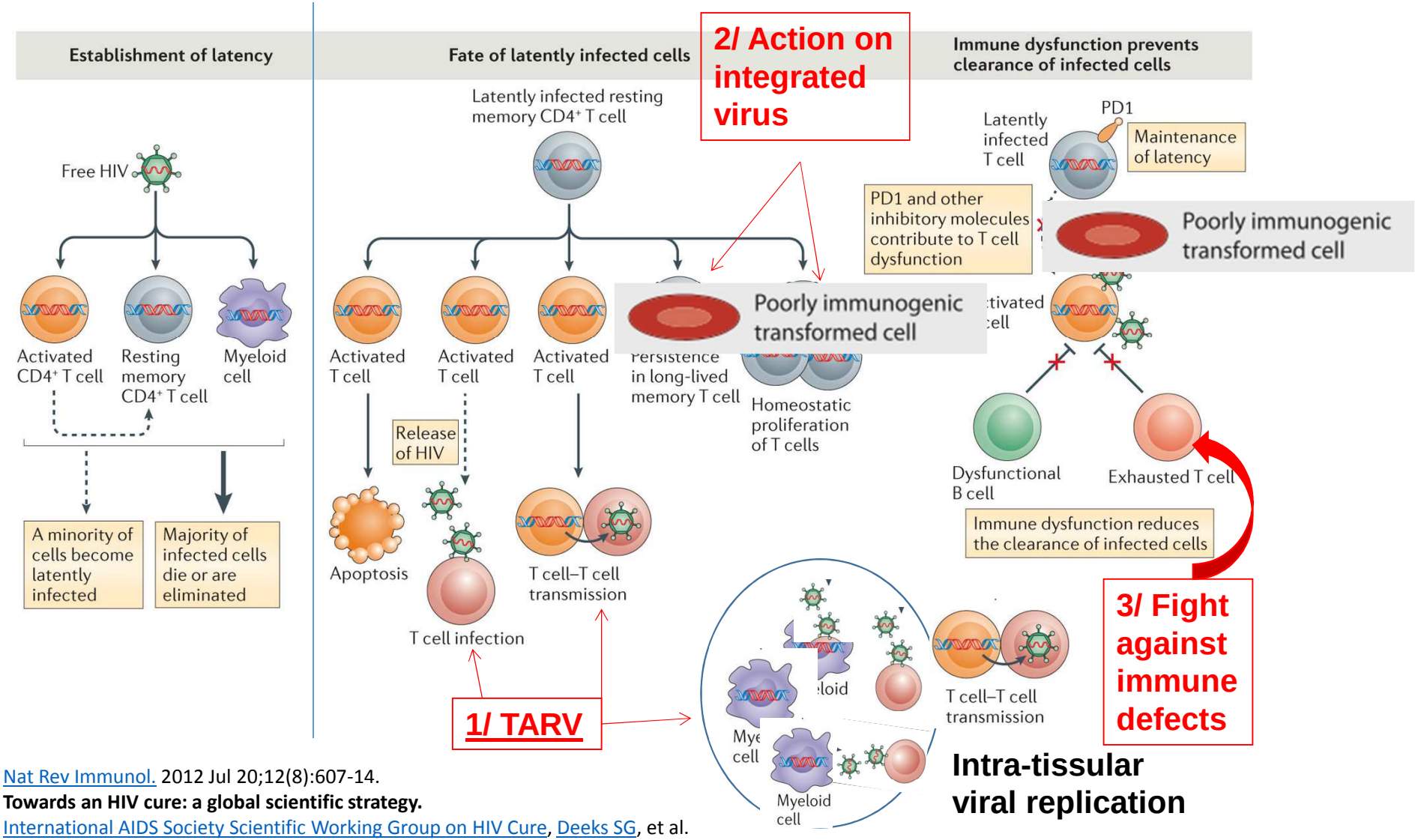
How to control the persistent HIV-infected-CD4 T

★ = evidence for HIV



Vesely et al. Annu Rev Immunol 2011

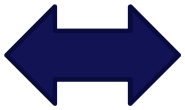
How to get remission ?



Nat Rev Immunol. 2012 Jul 20;12(8):607-14.
Towards an HIV cure: a global scientific strategy.
International AIDS Society Scientific Working Group on HIV Cure, Deeks SG, et al.

What are the strategies we have to develop?

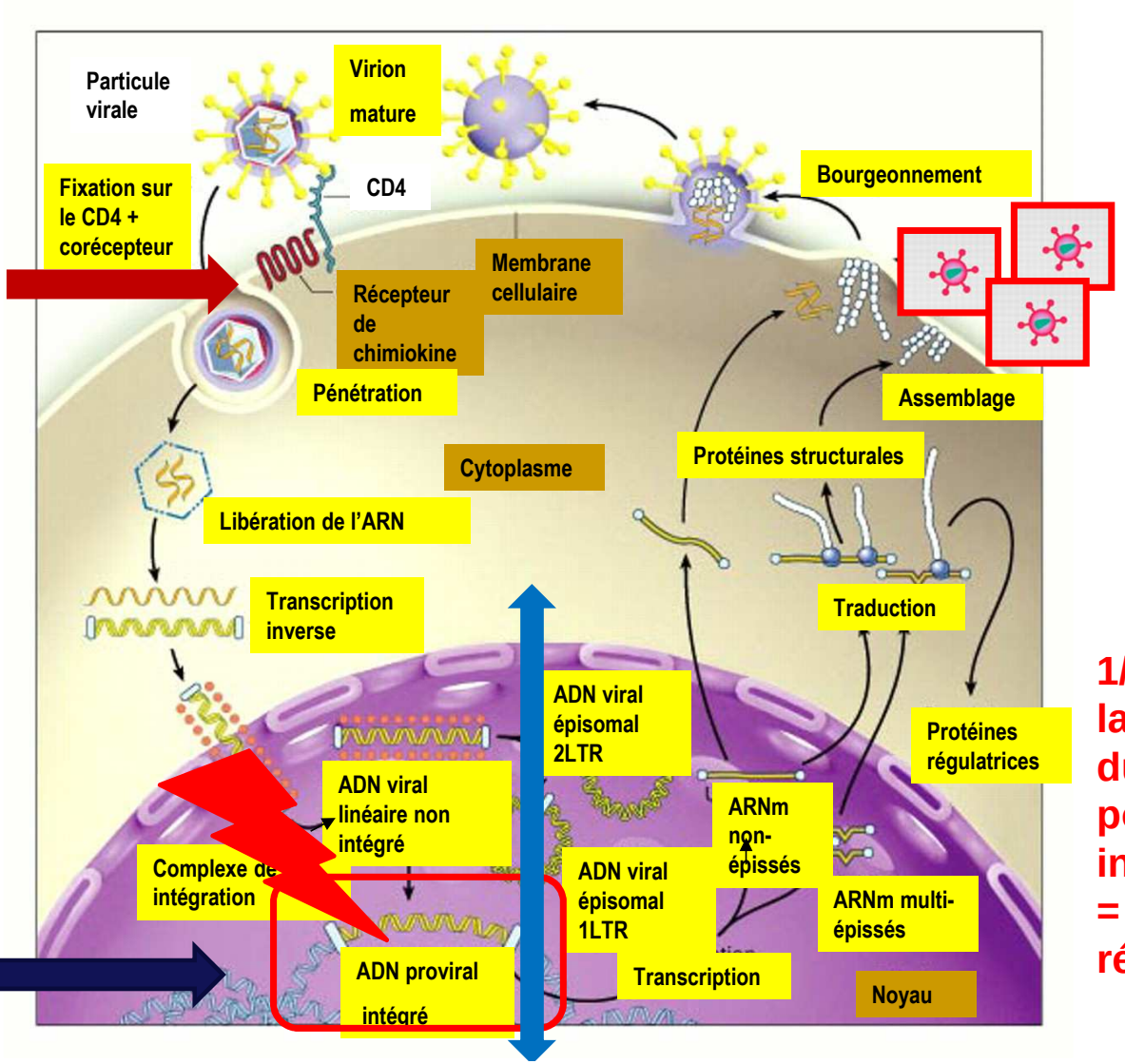
- Action on the infected cells
  - « Shock and kill » strategy
  - Reduction of the size of the reservoirs
- Improve the immune control of the HIV-infection
- Example of HIV controllers



- Action on the cancer cells
  - Targeted therapies with improved knowledge of the oncogenic pathways
- Improve the immune control of cancer

Il existe plusieurs stratégies ciblant les LTCD4 réservoirs du VIH (adapté de Furtado MR et al. NEJM, 1999 ; 1614-22)

2/ Cibler CCR5 (analogie avec le patient de Berlin)

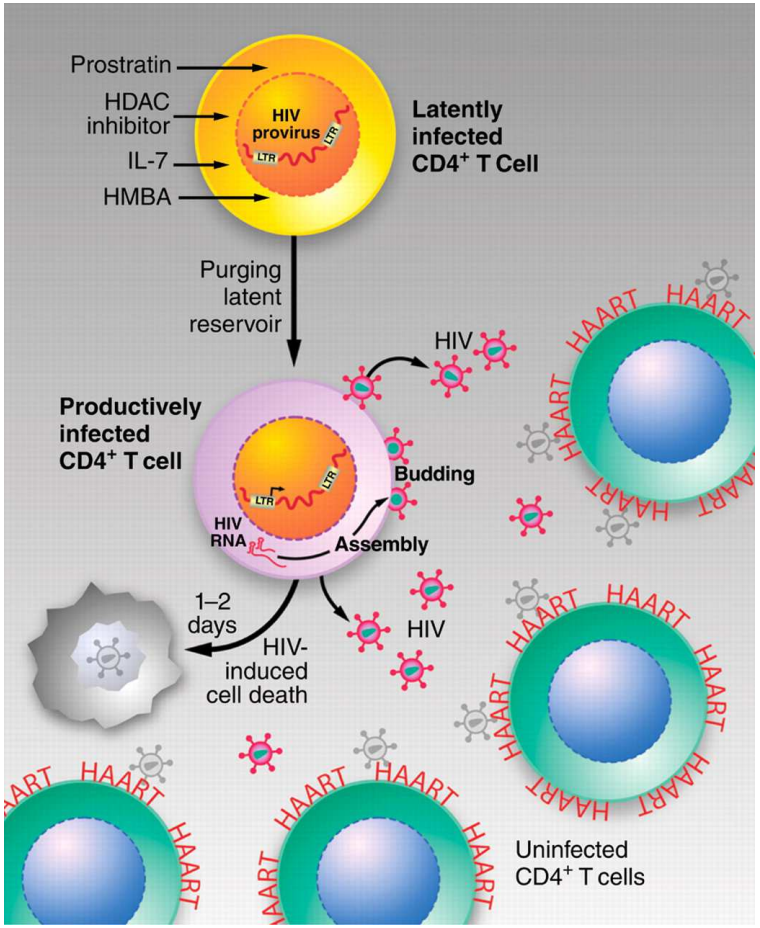


3/ Maintenir la latence post-intégration

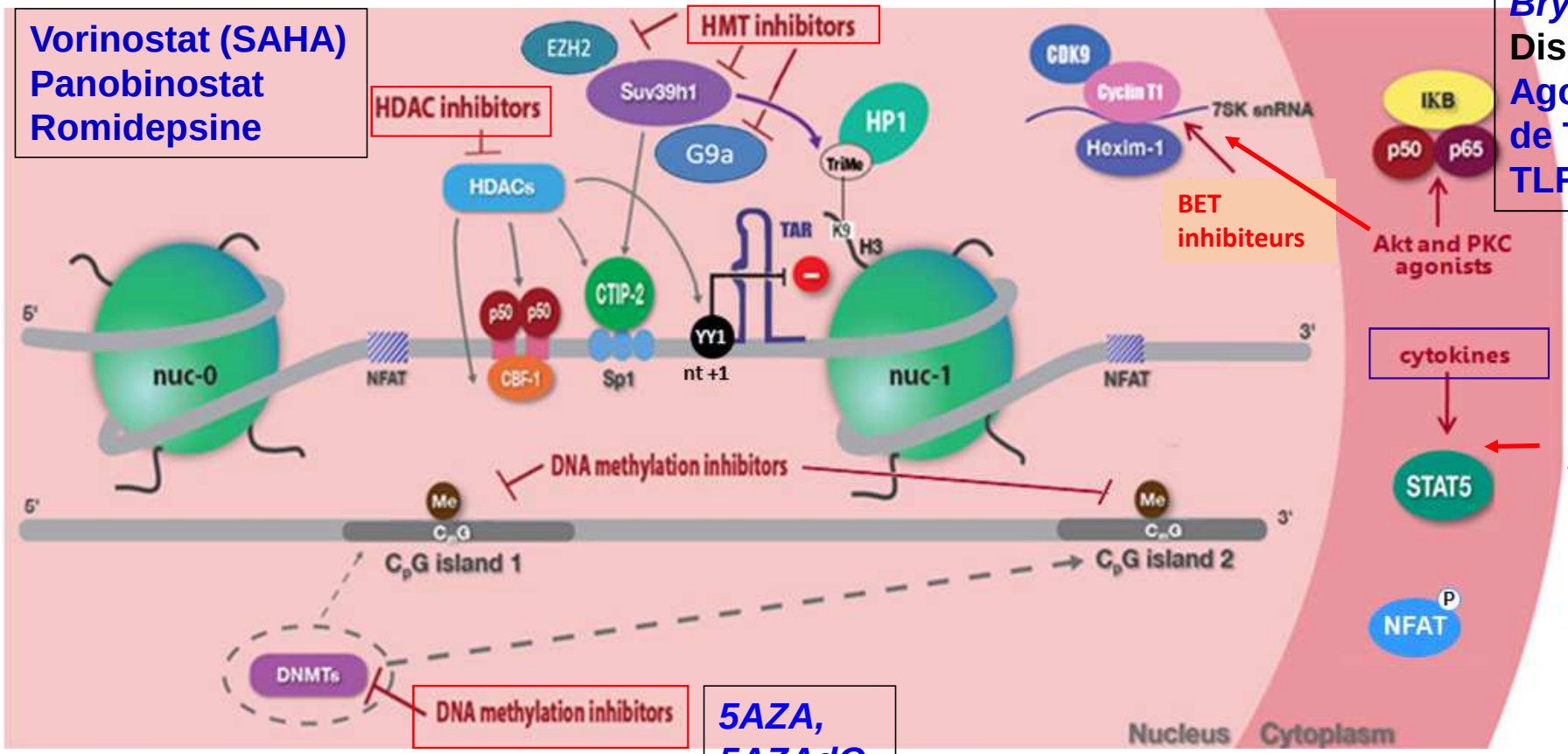
1/ Cibler la latence durable post-intégration = réactivation

Le LTCD4 mémoire infecté = cible n°1 des stratégies de cure

- 1/ Selon le modèle de R Siliciano, la réactivation d'un LTCD4 infecté de manière latente = son élimination
- Stratégie du « shock and kill »
- Comment réactiver une telle cellule réservoir ?
  - Connaître les voies de contrôle de latence du VIH
  - Avoir un TARV optimisé



Multiple targets to reactivate HIV-1 from latency



Prostratine
Bryostatine
Disulfirame
Agonistes de TLR7 et TLR 9

Archin et al. Nature 2012, Sogaard et al. Plos Path 2015
Rasmussen et al. Lancet HIV 2014
Spivak et al. Clin Infect Dis 2014

Essais thérapeutiques pour réactiver les virus latents

	Intervention	Study population (patients chronically infected with HIV-1)		ClinicalTrials.gov
		Study population	Main endpoint	
ERAMUNE 01	Interleukin 7+ART intensification with raltegravir and miraviroc	29 patients with HIV RNA <50 copies per mL on ART and HIV DNA between 10 and 1000 copies per 10^6 PBMC	Decrease of 0·5 log_{10} HIV DNA from baseline at 56 weeks	NCT01019551
ERAMUNE 02	HIV rAD5 vaccine+ART intensification with raltegravir and miraviroc	28 patients with HIV RNA <50 copies per mL on ART and HIV DNA 10–1000 10^6 PBMC; negative AD5 antibody	Decrease of 0·5 log_{10} HIV DNA from baseline at 56 weeks	NCT00976404
Disulfiram	Disulfiram: 500 mg/day for 14 days	20 patients on ART with HIV RNA <50 copies per mL	2 weeks frequency of replication, competent HIV-1 in resting CD4 T cells	NCT01286259
Vorinostat	Vorinostat: 200–600 mg per day	30 patients with HIV RNA <30 copies per mL	HIV expression in resting CD4 T cells	NCT01319383
Vorinostat	Vorinostat: 400 mg/day	20 patients with HIV RNA <50 copies per mL and CD4 cell >500 per mL	HIV unspliced RNA in resting CD4 T cells at 28 days	NCT01365065
Panobinostat	Panobinostat: 20 mg three times a week, two of three weeks	16 patients with suppressed viraemia and CD4 cell count >500 per mL	HIV unspliced RNA in resting CD4 T cells change from baseline	NCT01680094
CD4 T cells modified at CCR5 by zinc-finger nuclease	Autologous CD4 T cells modified at CCR5 gene by zinc-finger nuclease SB-728	30 patients with suppressed viraemia and CD4 cell count >500 per mL on antiretroviral therapy	Safety; persistence and activation of CCR5+ T cells in peripheral blood of infused autologous T cells	NCT01252641
CD4 T cells modified at CCR5 by zinc-finger nuclease	Autologous CD4 T cells modified at CCR5 gene by zinc-finger nuclease	18 patients: three cohorts of HIV-positive patients, either failing ART or with suppressed viraemia	Safety	NCT00842634
Lentivirus vector rHIV7-shI-TAR-CCR5RZ-transduced haemopoietic progenitor cells	Autologous CD34+haemopoietic cells modified by lentivirus-transduced non-functional CCR5RZ gene	10 patients with AIDS-related lymphoma undergoing haemopoietic stem-cell transplantation	Safety and durability of transduced cells	NCT00569985
Interferon alfa-2b	Interferon alfa-2b intensification	Recruiting, non-randomised, one-group assignment	Efficacy: viral RNA levels in blood and sequence diversification	NCT01295515

ART=antiretroviral therapy. PBMC=peripheral blood mononuclear cells.

Table 1: CURE-related clinical pilot trials in progress in 2012

SAHA = Vorinostat > ↑ ARN VIH dans LTCD4 mais rien d'autre

Panobinostat > ↑ ARN VIH dans LTCD4 et dans le plasma mais pas de baisse du réservoir

Katlama et al. Lancet 2013

Est-ce que ça marche ?

- Travaux prometteurs sur l'acide valproïque (Lehrman et al Lancet 2005) puis sur le SAHA (Archin et al. Nature 2012) puis le panobinostat (CROI 2014) : non confirmés = pas d'effet sur la mesure d'ADN total
- Une molécule prometteuse: la romidepsine?

PLOS | PATHOGENS

RESEARCH ARTICLE

The Depsipeptide Romidepsin Reverses HIV-1 Latency *In Vivo*

Ole S. Søgaard[1]*, Mette E. Graversen[1,2], Steffen Leth[1,2], Rikke Olesen[1], Christel R. Brinkmann[1], Sara K. Nissen[1], Anne Sofie Kjaer[1,2], Mariane H. Schleimann[1,2], Paul W. Denton[1,2,3], William J. Hey-Cunningham[4], Kersten K. Koelsch[4], Giuseppe Pantaleo[5], Kim Krogsgaard[6], Maja Sommerfelt[6], Remi Fromentin[7], Nicolas Chomont[7,8], Thomas A. Rasmussen[1], Lars Østergaard[1,2], Martin Tolstrup[1,2]

1 Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark, **2** Institute of Clinical

Plos Path 2015

Une molécule prometteuse? la romidepsine

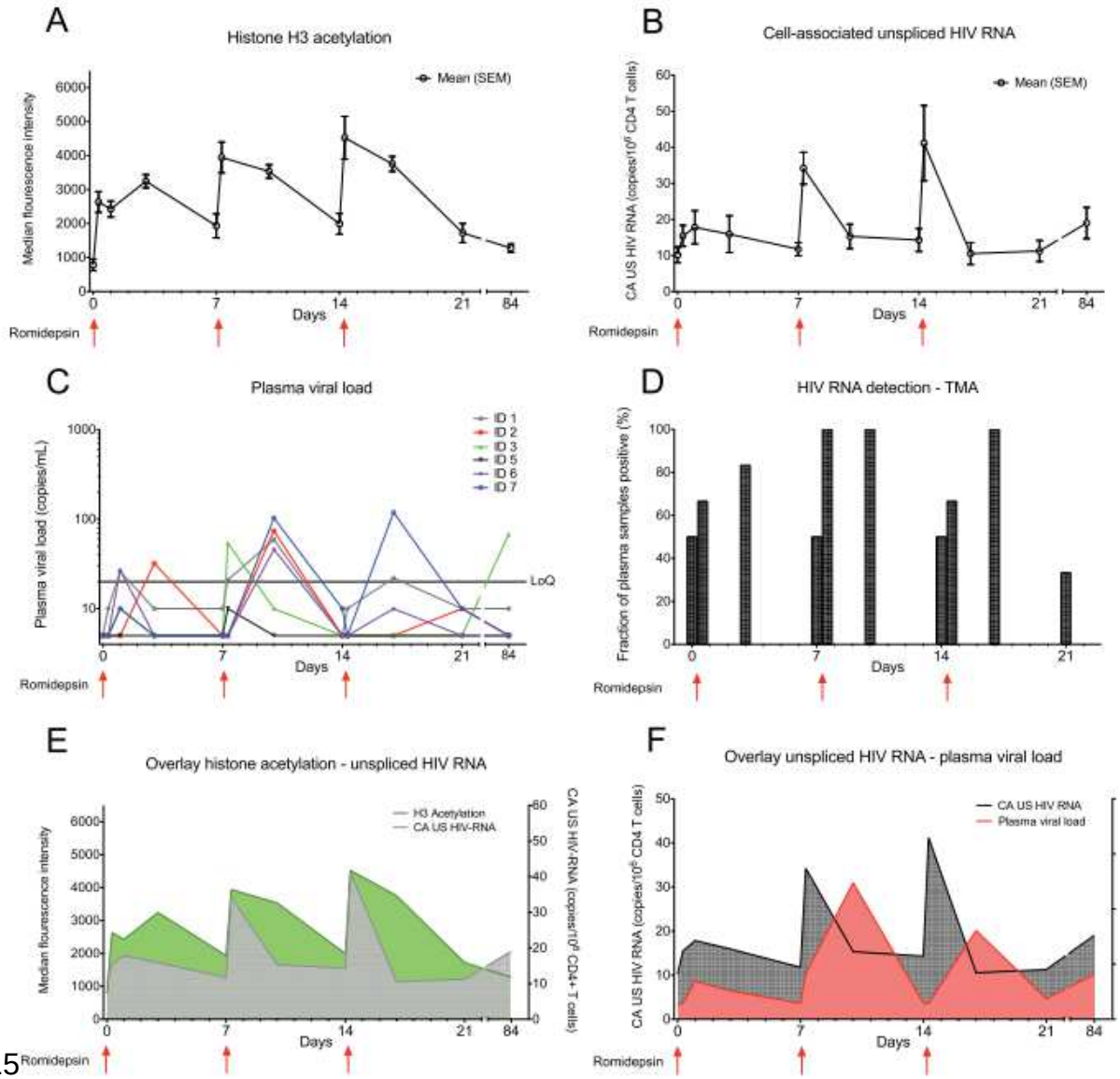
6 patients sous ART

1 perfusion de 4h par semaine 3 semaines

1/3 dose utilisée en cancérologie

Aucun effet secondaire > Grade 1

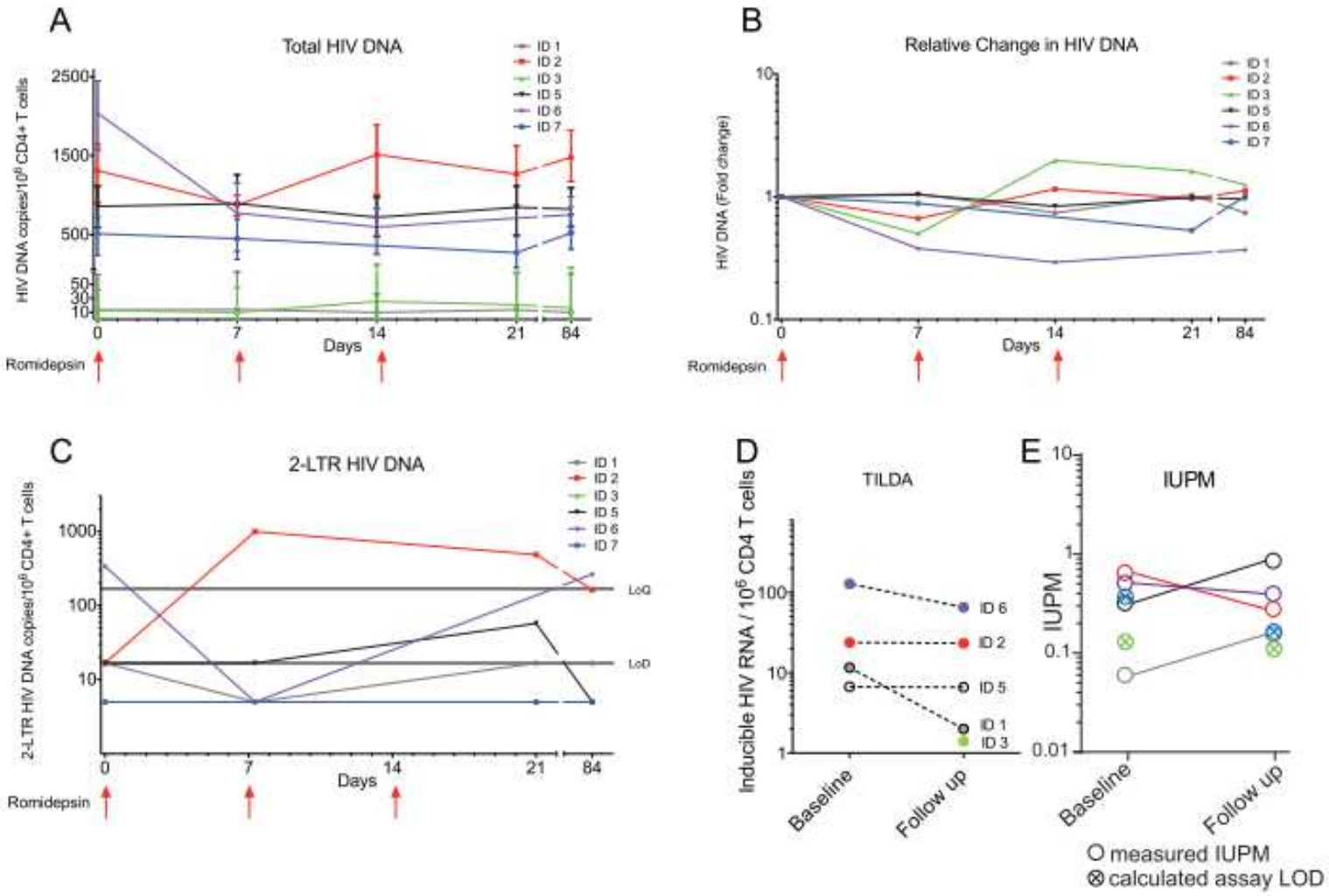
Mobilisation documentée du réservoir latent



Sogaard et al. Plos Path 2015

Une molécule prometteuse? la romidepsine

Mais pas de réduction
de la taille du réservoir…

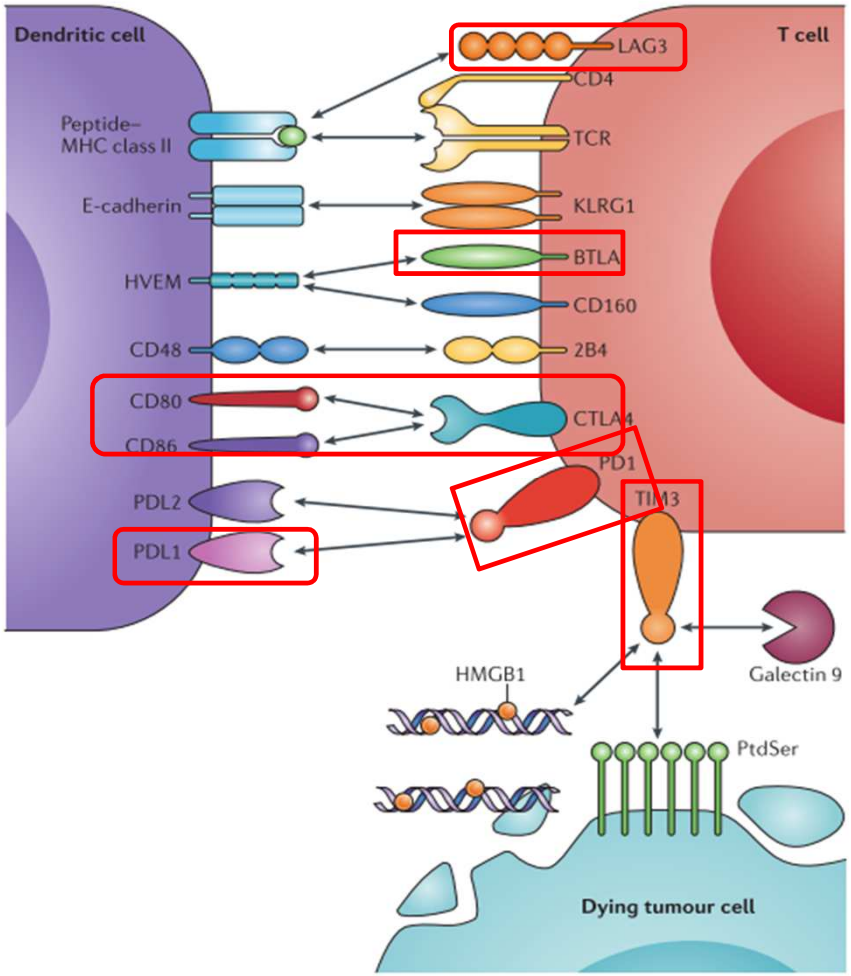


Sogaard et al. Plos Path 2015

Est-ce que ça marche ?

- Les iHDACs sont capables de mobiliser le réservoir du VIH sans le diminuer
- Utilisation de molécules de cancérologie
  - Doses plus faibles mais efficacité à démontrer in vitro
  - Intérêt de combiner les molécules ensembles (Reuse et al. Plos One, Darcis et al. Plos Path 2015)
- Les iHDACs pourraient réduire la réponse TCD8 anti-VIH (Jones et al. Plos Path 2014)
- Si pas de réponse immune spécifique efficace anti-VIH : échec (Shan et al Immunity 2013)
- modèle trop simpliste ?
- Intérêt d'ajouter des effecteurs : Ac « broadly neutralizing » médiant ADCC (Bruel et al. Nat Com 2016)

The « world » of the immune check points which control the T cell immune response

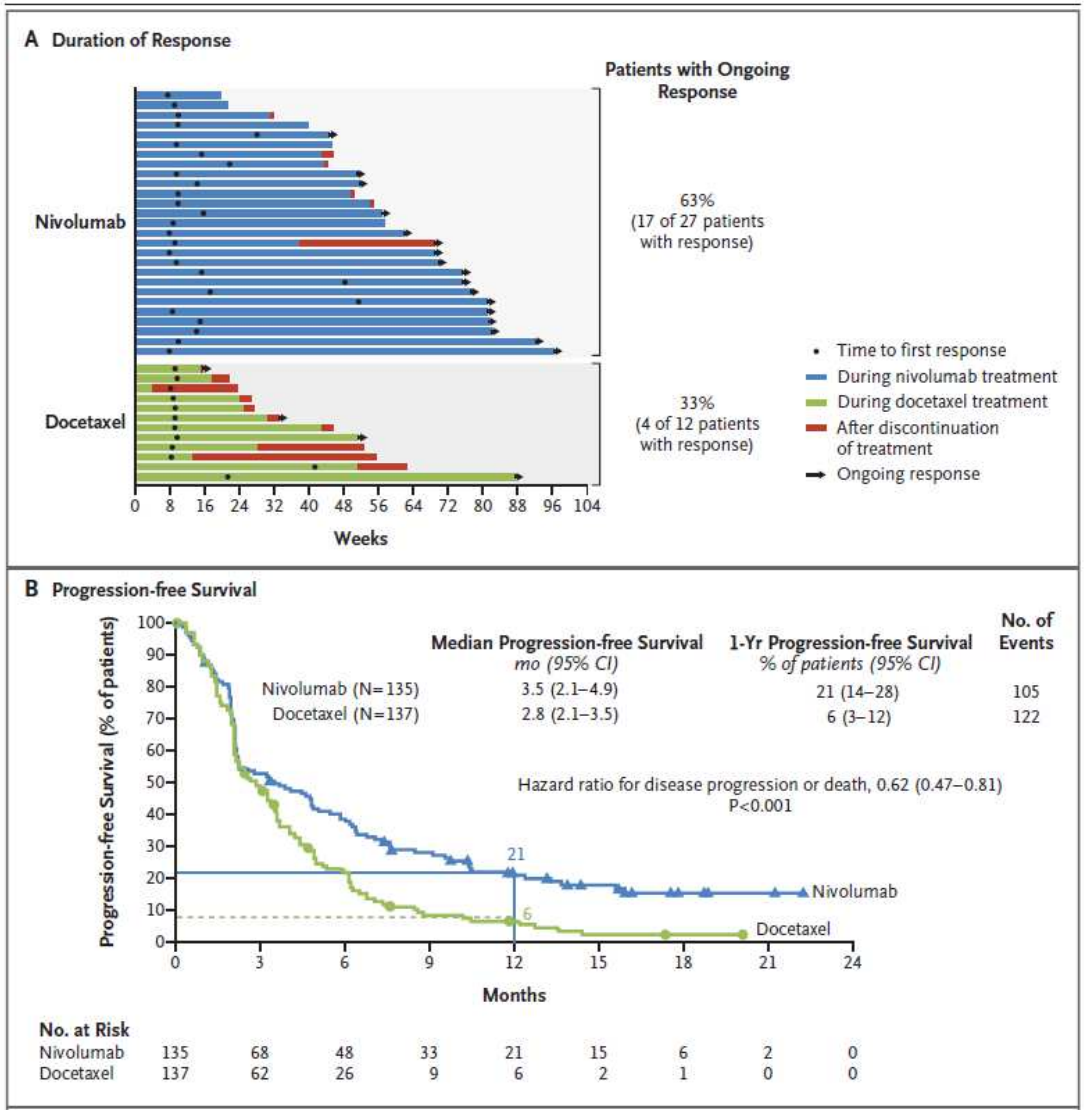


In clinical development

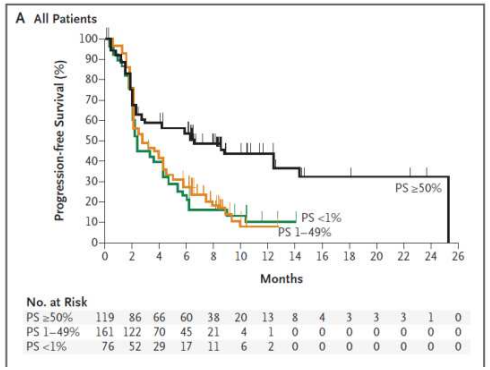
- Describe in murine models of chronic infections (LCMV) (Wherry et al, Immunity 2007)
- Inducible after T cell activation
- Describe for most of them in human on virus-specific and tumor-specific T cells
- Different levels of expression according to the status of differenciation and activation of the T cell

Nguyen et al. Nature Rev Immunol 2015

Nivolumab and lung cancer



- Phase III
- 272 patients
- Nivolumab versus docetaxel
- No impact of PD-L1 expression (≠ pembrolizumab)
- AE ≥ grade 3
  - 7% Nivo
  - 55% docetaxel



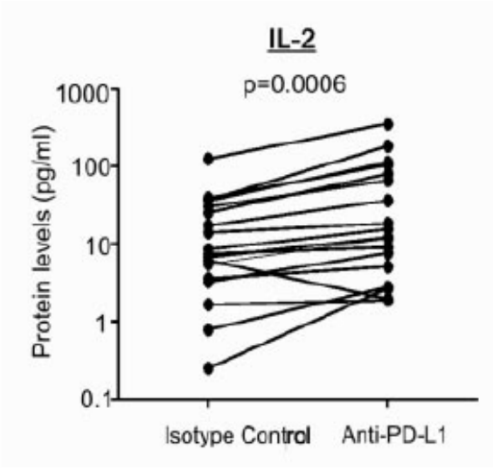
Brahmer et al; Garon et al, NEJM 2015

Immune activation is associated with exhaustion of the immune system: role of the PD-1 / PD-L1 axis

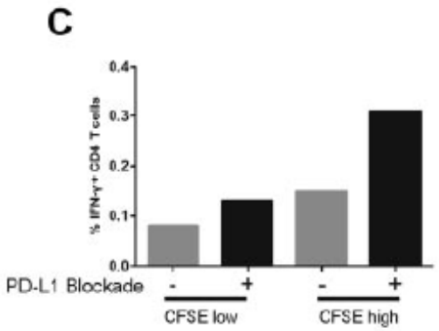
- PD-1 expression on CD8+ and CD4+ T cells correlates with disease progression
- Functional improvement of CD4 T and CD8 T cells if PD-1/PD-L1 blockade

Velu et al. Retrovirology 2015, Porichis et al. Blood 2011, Chomont et al. Nat Med 2009

PD-1 blockade in CD4 in HIV infection

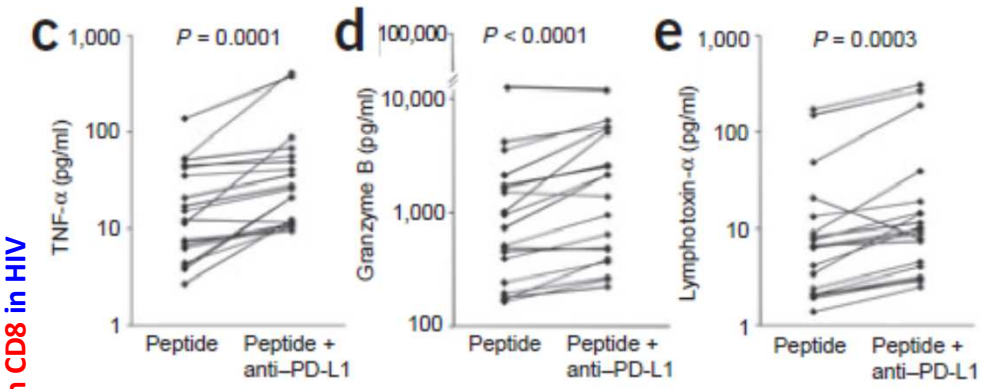


Increase of IL-2 production



Increase of HIV-specific CD4 T cell proliferation

PD-1 blockade in CD8 in HIV infection



Increase of cytotoxicity

PD-1 blockade in vivo: the monkey model

Letter

Nature **458**, 206-210 (12 March 2009) | doi:10.1038/nature07662; Receive
November 2008; Published online 10 December 2008

Enhancing SIV-specific immunity *in vivo* by PD-1 blockade

Vijayakumar Velu[1,2,6], Kehmia Titanji[1,2,6], Baogong Zhu[3,4], Sajid Husain[1,2], Annette Pladevega[1,2], Lilin Lai[1,2], Thomas H. Vanderford[5], Lakshmi Chennareddi[1,2], Guido Silvestri[5], Gordon J. Freeman[3,4], Rafi Ahmed[1] & Rama Rao Amara[1,2]

- 14 Indian macaques
- 4 doses humanized anti-PD-1 day 0,3,7,10 (n=9)
- Ig control (n=5)
- safety OK
- Increase of SIV-specific CD8 T cell responses with polyfunctionality (IFNg, IL-2, TNFa), and cytotoxicity (perforine, granzyme)
- Increase of the production of SIV-specific antibodies
- Decrease of the plasmatic viral load
- Increase of the survival

Letter

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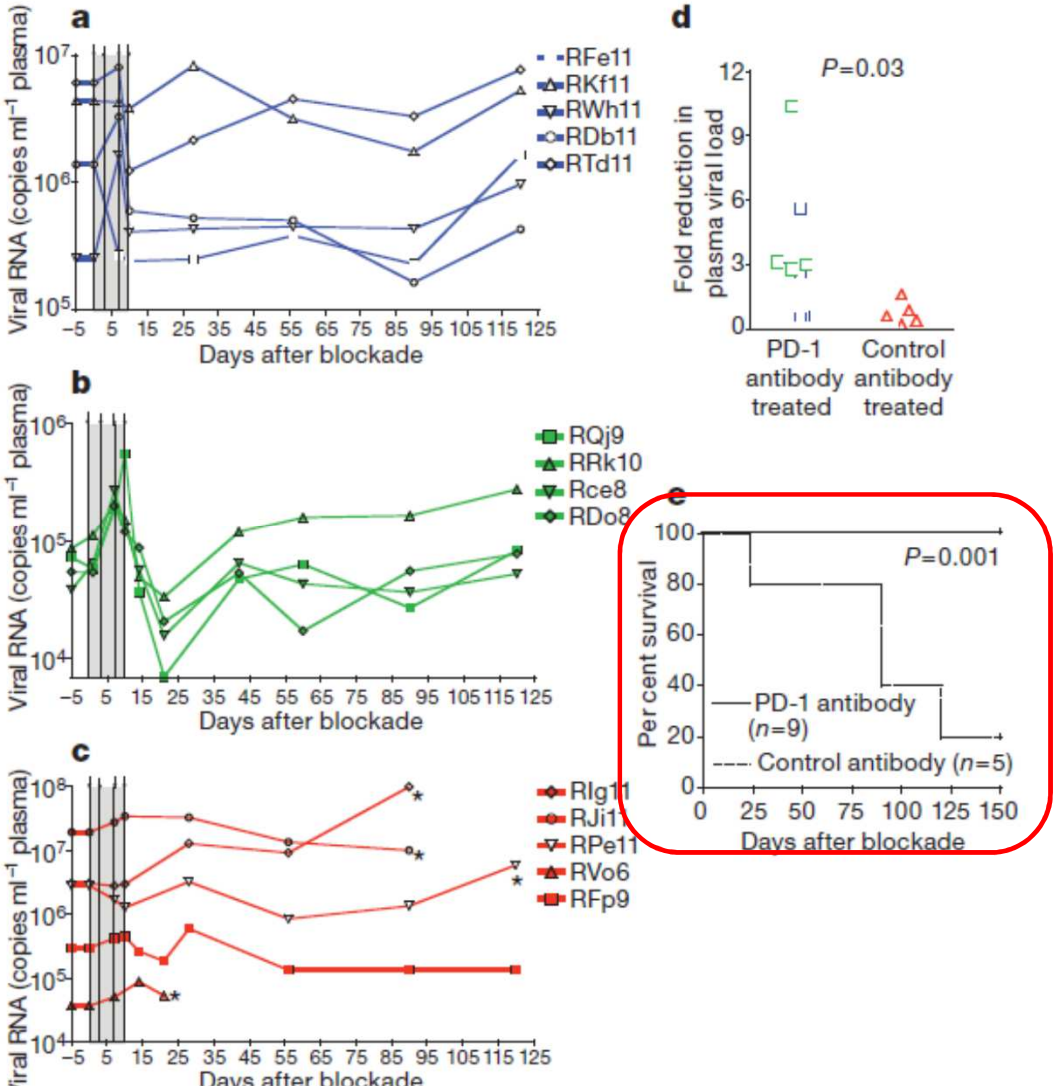
PD-1 blockade in vivo: the monkey model



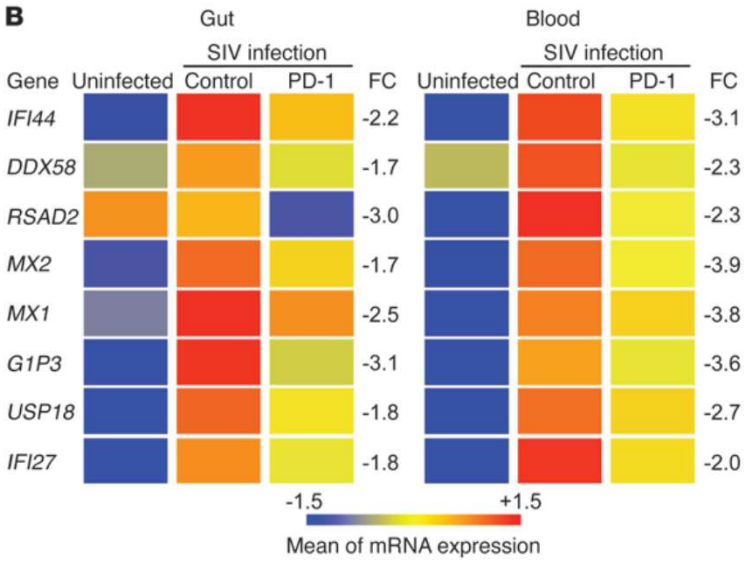
PD-1 blockade in vivo: the monkey model

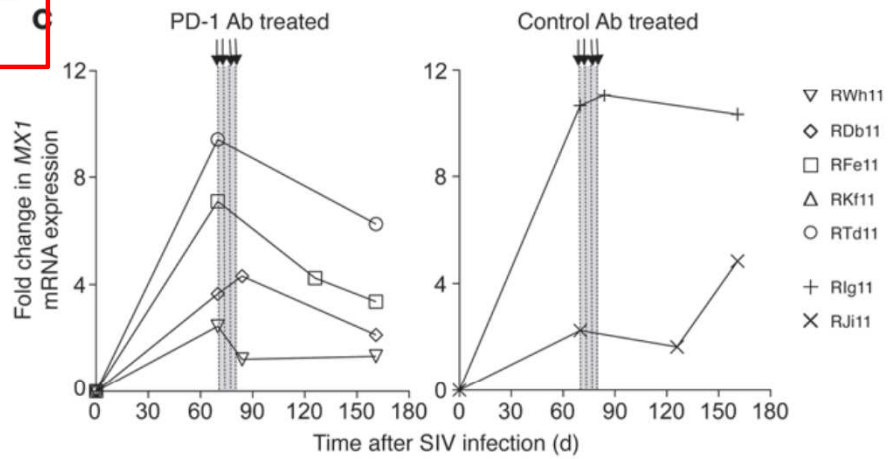
Published in Volume 122, Issue 5 (May 1, 2012)
J Clin Invest. 2012;122(5):1712–1716. doi:10.1172/JCI60612.

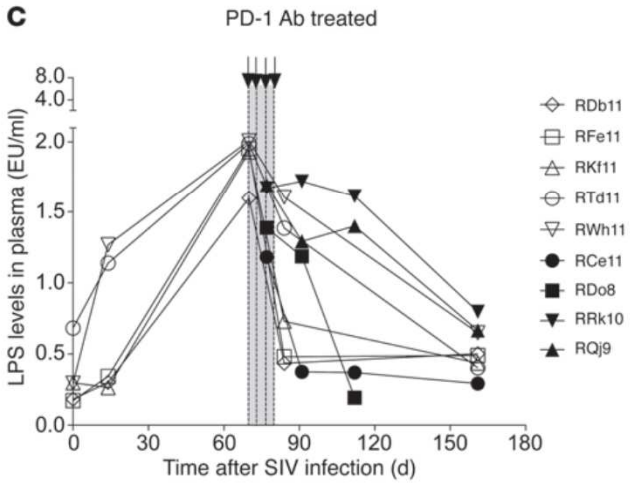
Brief Report

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

Ravi Dyavar Shetty[1], Vijayakumar Velu[1], Kehmia Titanji[1], Steven E. Bosinger[1], Gordon J. Freeman[2], Guido Silvestri[1,3] and Rama Rao Amara[1,4]

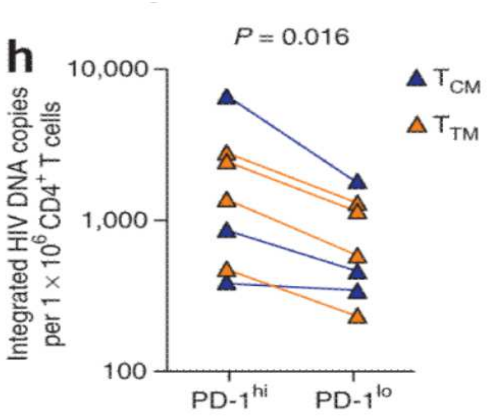




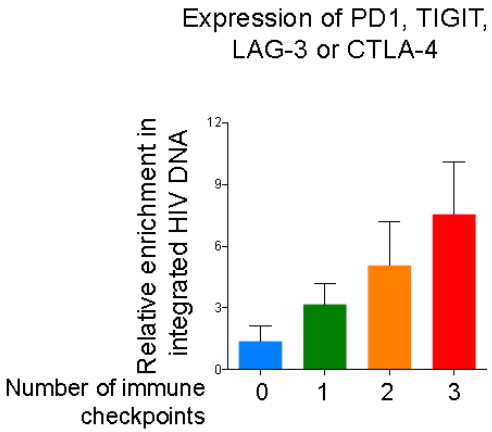


Perspectives for anti-PD1

- Reduction of the HIV lymphocyte reservoir?



Latent HIV is enriched in T-cells expressing PD-1 and other immune checkpoint markers



Boost of cytotoxicity (CD8 T cells)
Question of ADCC?
IgG4 or IgG1?
Bispecific Abs

Fromentin/Chomont (unpublished)

Trials in HIV infection

- NCT02028403
- **Safety and Immune Response of BMS-936559 in HIV-Infected People Taking Combination Antiretroviral Therapy**
- Safety, Pharmacokinetics and Immunotherapeutic Activity of an Anti-PD-L1 Antibody (BMS-936559) in HIV-1 Infected Participants on Suppressive cART: A Phase I, Double-Blind, Placebo-Controlled, Ascending Single Dose Study
- **Sponsor:** National Institute of Allergy and Infectious Diseases (NIAID)
- **Start: June 2014**
- 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)
- **Start: July 2015**
- **Sponsor:** National Cancer Institute (NCI)
- Recruiting

Développement de nouvelles stratégies d'immunothérapies : thérapies cellulaires

TAG Treatment Action Group

Research Toward a Cure May 12, 2016

Table 1. Current Clinical Trials

Trial	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase	Estimated Study Completion Date
ADOPTIVE IMMUNOTHERAPY				
Early ART in combination with autologous HIV-specific cytotoxic T lymphocyte (CTL) infusion	NCT02231281	Yongtao Sun, MD, PhD, Tangdu Hospital, the Fourth Military Medical University	Phase III	December 2016
Reconstitution of HIV-specific immunity against HIV	NCT02563509	Guangzhou 8th People's Hospital	Phase I/II	December 2016
HXTC: HIV 1 antigen expanded specific T cell therapy	NCT02208167	University of North Carolina, Chapel Hill	Phase I	September 2018

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

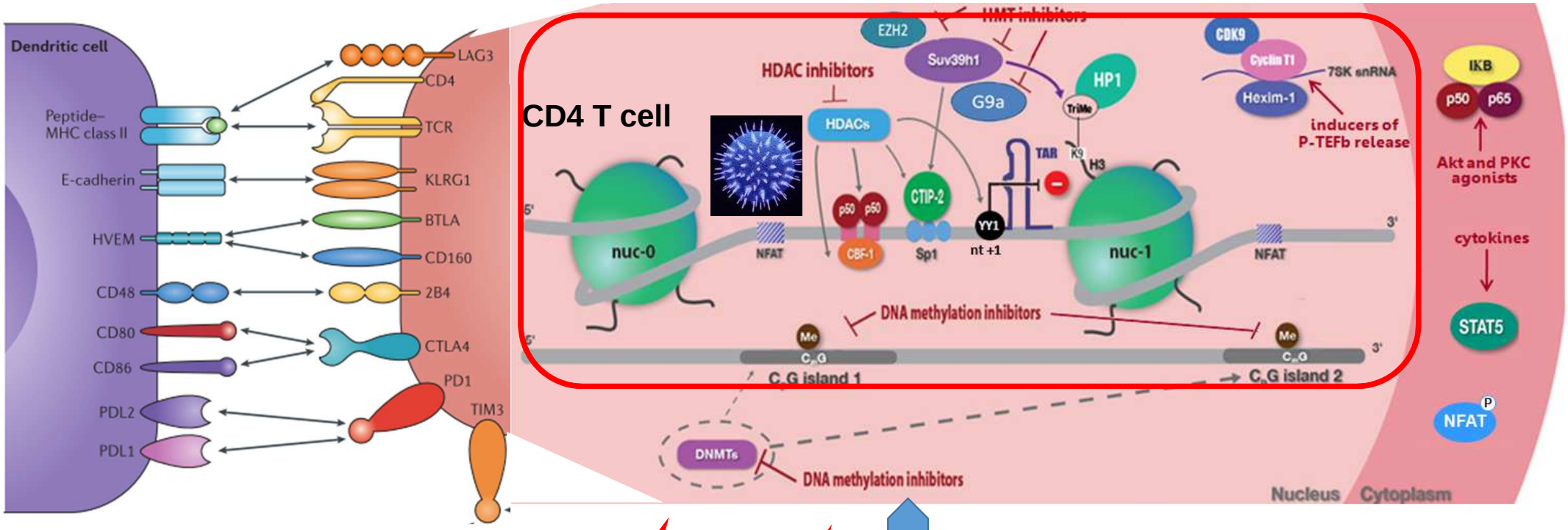
Daniela Benati,[1] Moran Galperin,[1] Olivier Lambotte,[2,3,4,5] Stéphanie Gras,[6,7] Annick Lim,[8] Madhura Mukhopadhyay,[1] Alexandre Nouël,[1] Kristy-Anne Campbell,[6] Brigitte Lemercier,[8] Mathieu Claireaux,[1] Samia Hendou,[9] Pierre Lechat,[10] Pierre de Truchis,[11] Faroudy Boufassa,[9] Jamie Rossjohn,[6,7,12] Jean-François Delfraissy,[2,3,4] Fernando Arenzana-Seisdedos,[1,13] and Lisa A. Chakrabarti[1,13]

First published April 25, 2016 - More info

ANRS

Is it the time to think about HIV cure as a cancer cure ?

Many targets and weapons…



Anti-PD1….

CCR5

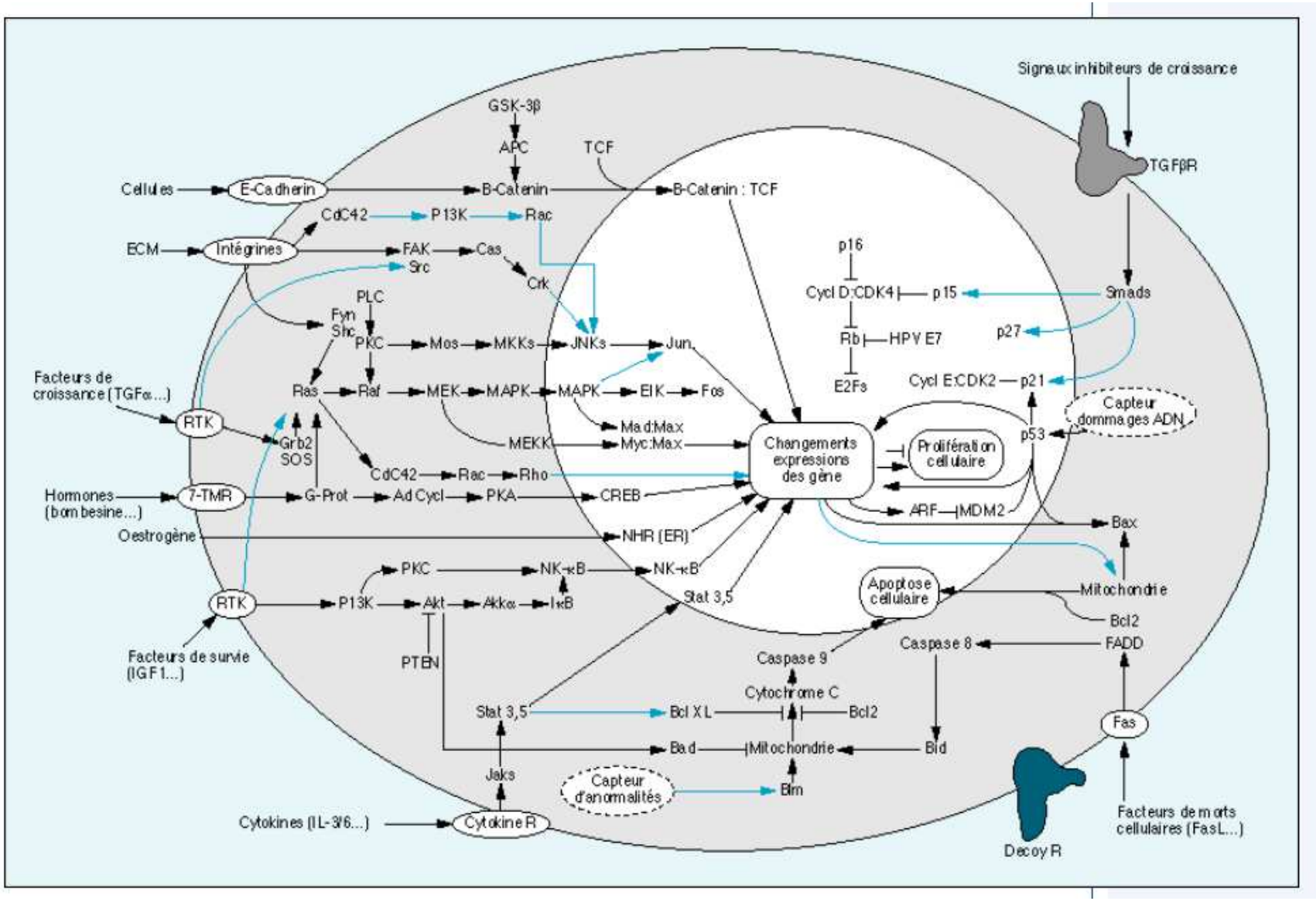
CD8 T

NK

B cell

bNabs

Van Lint *et al. Retrovirology* 2013
Nguyen et al. *Nature Rev Immunol* 2015



Voies de signalisation cellulaires décrites impliquées dans l'oncogenèse

Beaucoup de cibles…

LTCD4 réservoir

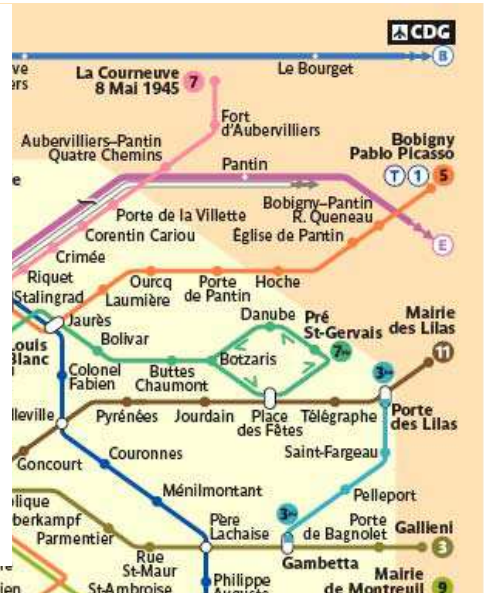
Cellule cancéreuse

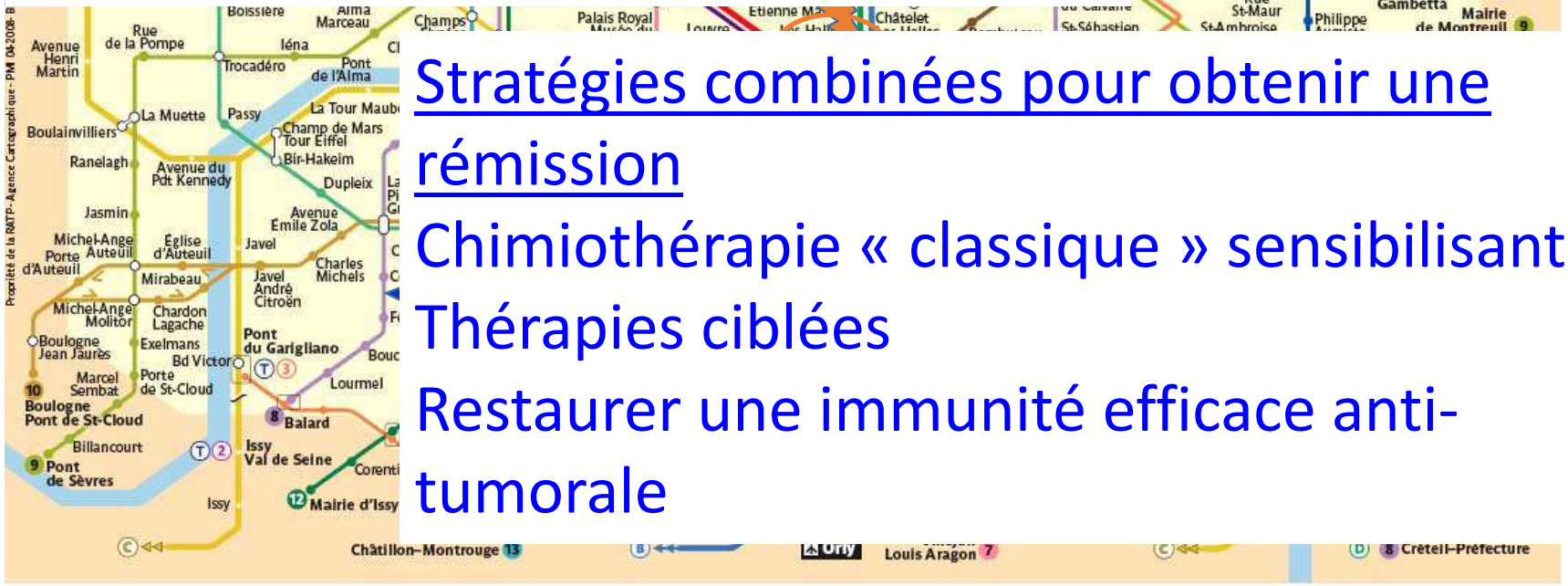
Stratégies combinées pour obtenir une rémission

ARV

Cibler la latence

Restaurer une immunité efficace anti-virale





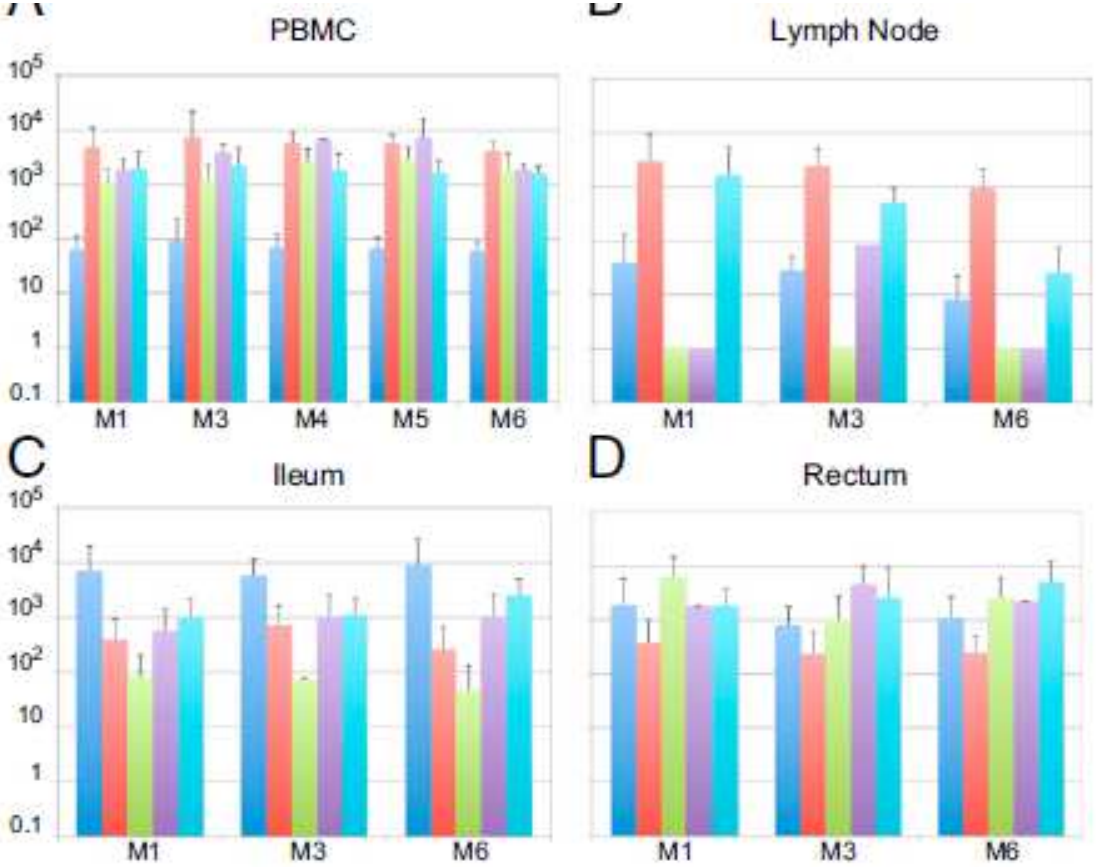
Stratégies combinées pour obtenir une rémission

Chimiothérapie « classique » sensibilisante

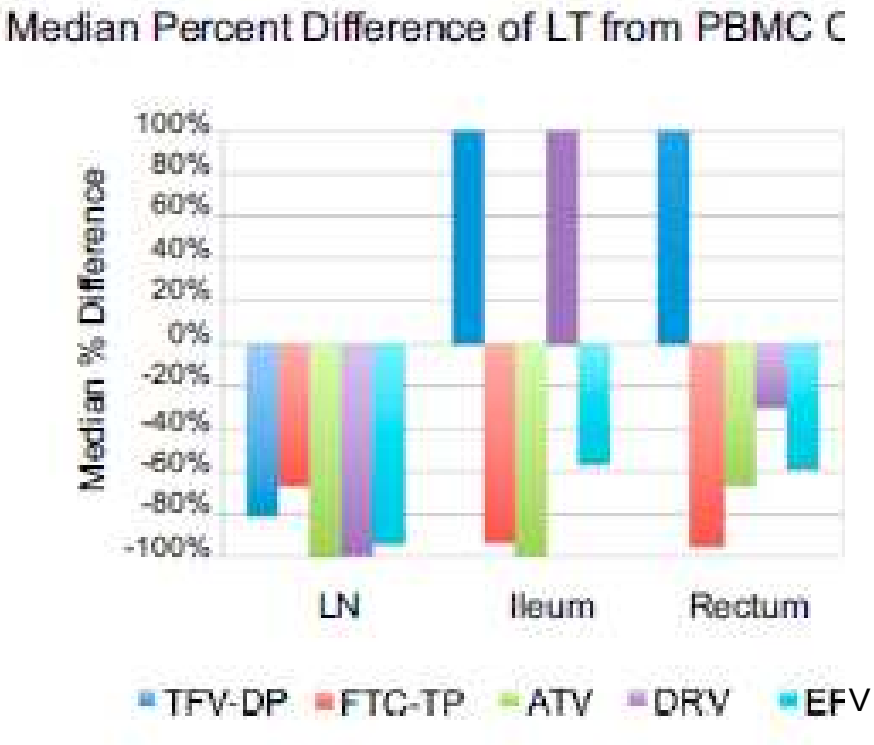
Thérapies ciblées

Restaurer une immunité efficace anti-tumorale

Thanks to JC Soria, DITEP Gustave Roussy France



Diffusion très insuffisante des ARV dans les ganglions



Fletcher C et al. PNAS 2014

PD-1 expression is associated with the size of the HIV reservoir in 2 independent cohorts of virally suppressed subjects