HIV: Towards a sustainable remission?

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Sidaction
ENSEMBLE CONTRE LE SIDA

35 years of HIV Science
A good example of translational research

A new era since cART in 1996….

Isolation of HIV
HIV sequencing
AIDS
AZT
Viral load PCR
HAART
Generic ARVs
Tetherin
HIV controllers
Circumcision
RV144 Vaccine Trial
Berlin Patient
SAMHD1
HPTN 052
Post-treatment controllers
Temprano/Start

1981 1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015

1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014

CD4 receptor
PMTCT (AZT)
Co-receptors
APOBEC3G
TRIM5α
Microbial Translocation -> Immune Activation
iPrEX
CAPRISA 004
PreP

Legend:

HIV biology & pathogenesis
Treatment
Prevention

“Which kind of “HIV Cure” are we looking for?

HIV Reservoirs on cART….

Cure

Elimination of all latently infected cells

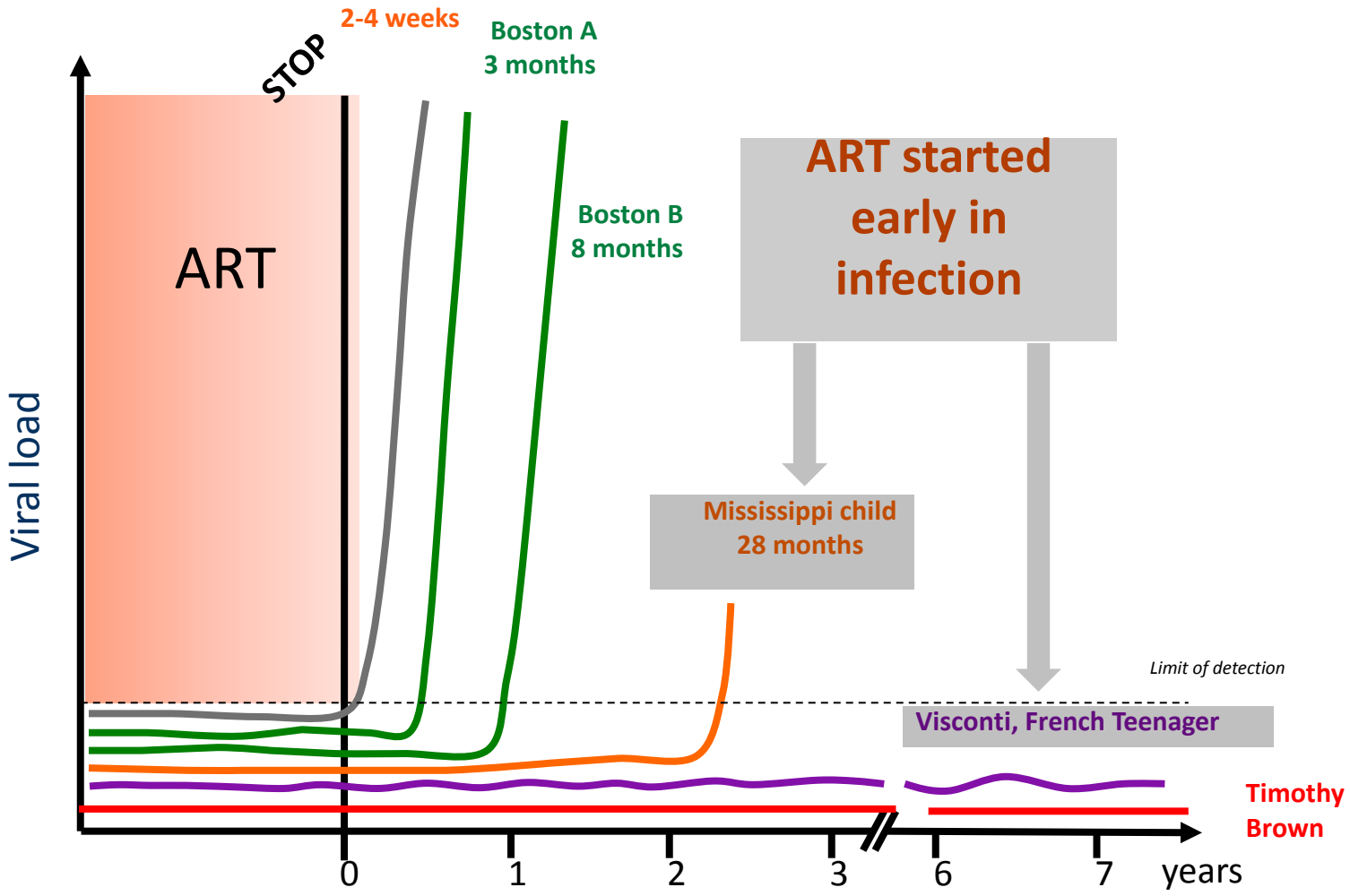
Berlin Patient?

Sustainable Remission

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

Proof of concept…

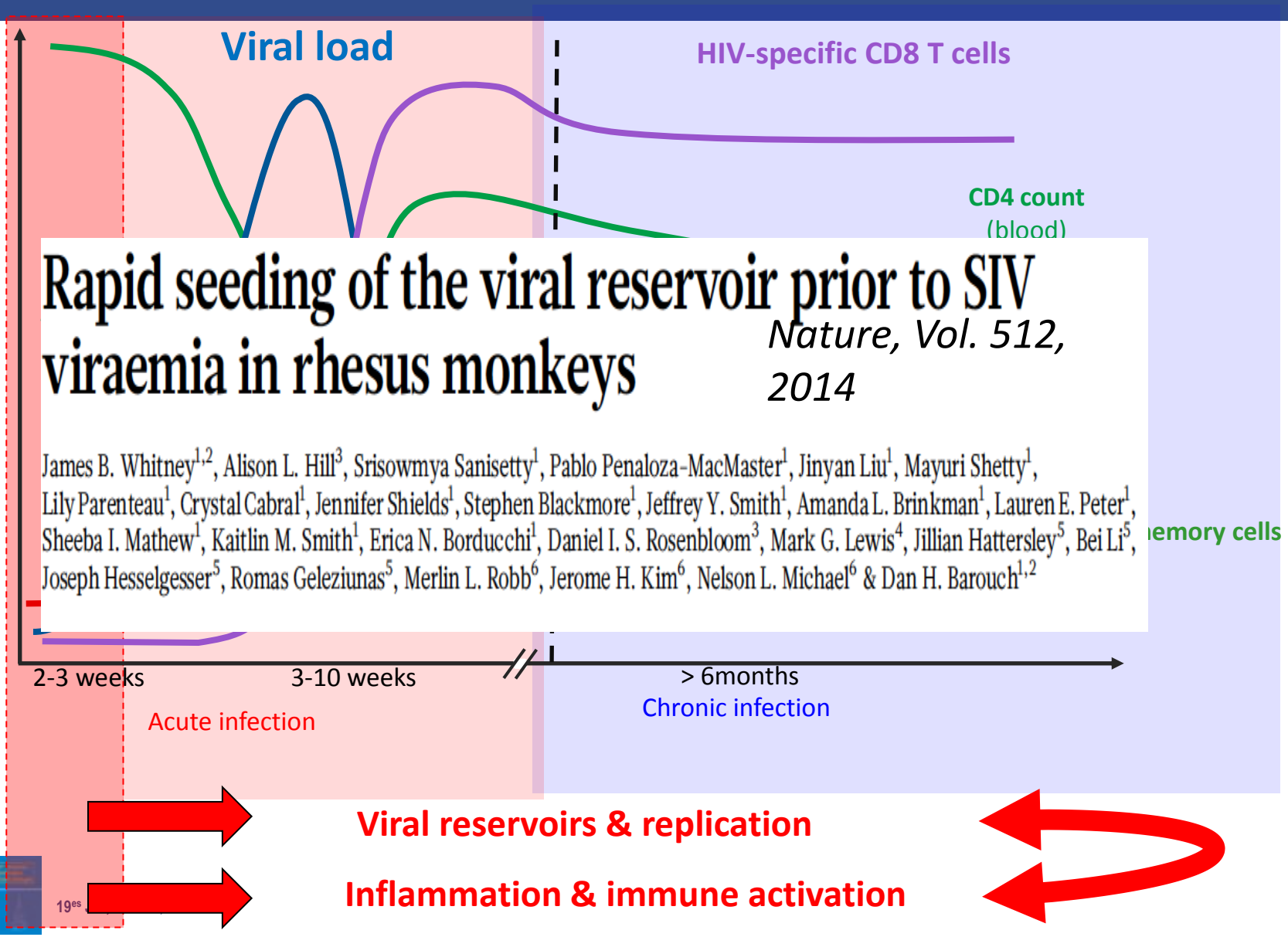
HIV remission is rare but possible



Deeks S, Lewin SR et al., Nature Med 2016

Challenges…..

HIV Reservoirs and immune activation…



Viral reservoirs & replication

Inflammation & immune activation

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);*

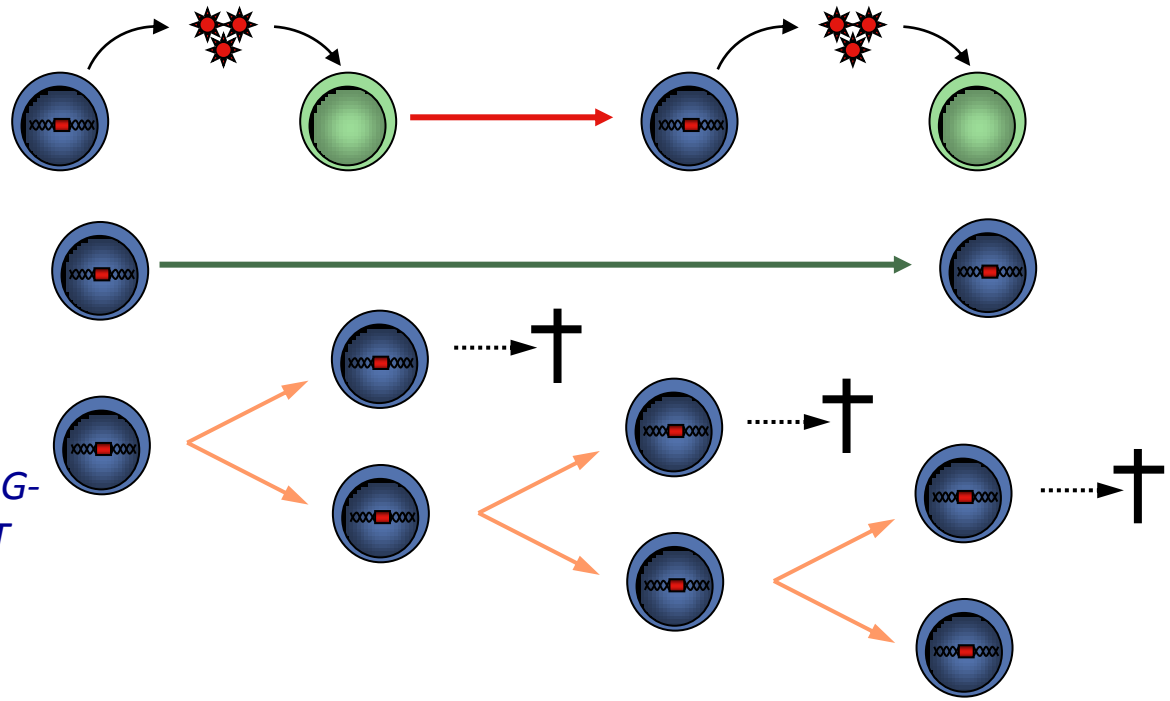
✓**Other reservoir cells**: *naiveT cells, memory stem T cells, T follicular helper cells (EC), meyloid cells, astrocytes, hematopoietic progenitor cells, etc…*

✓**Anatomic reservoirs**: *GI & genital tract, lymphoid tissu, CNS…*

Residual viral replication

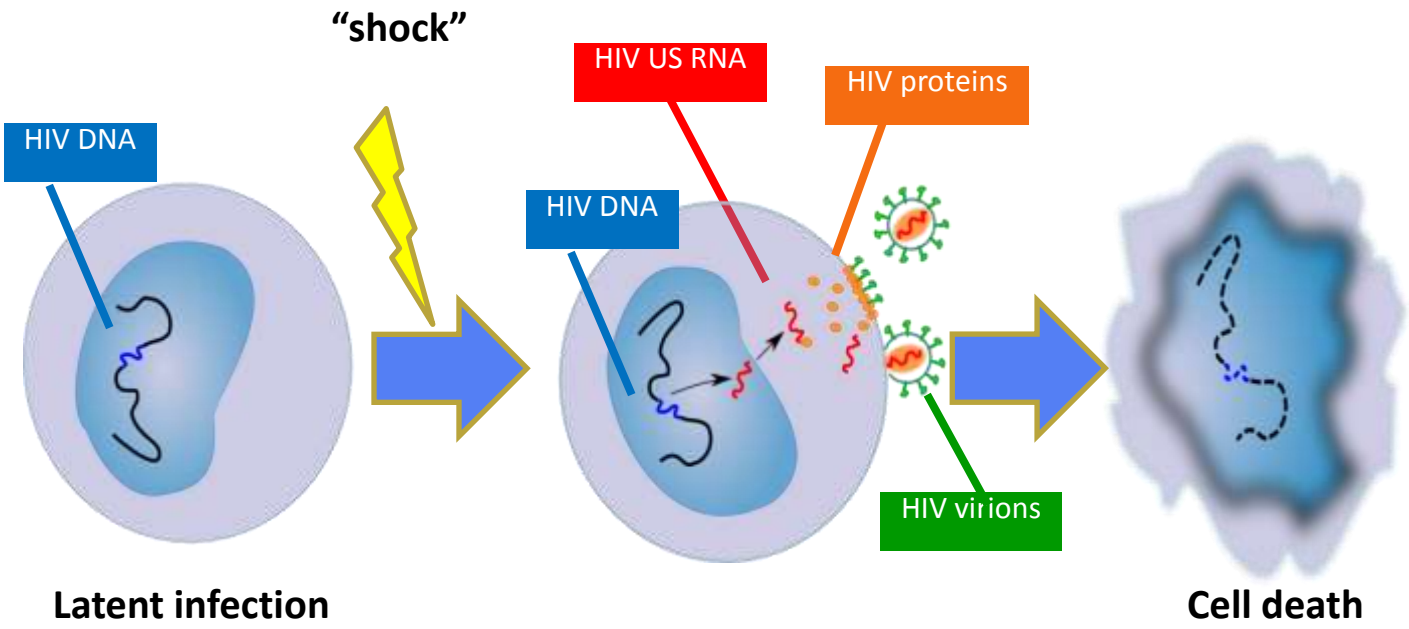
T cell survival

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?

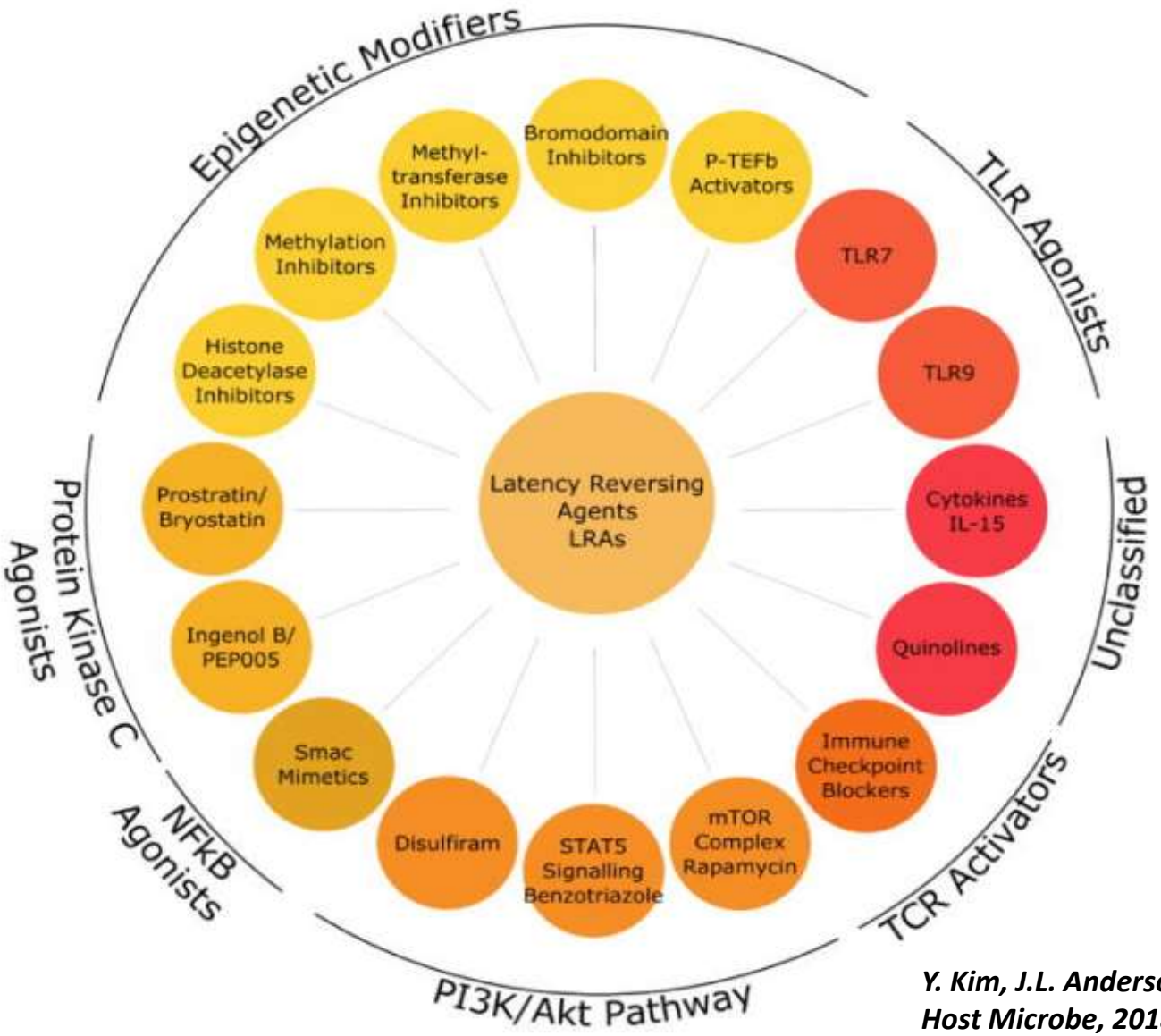
Activating latent infection: the “shock”



Latency reactivating agents (LRA)
eg., modify chromatin

LRA accelerating cell death
eg., disulfiram, TLR agonists

Distinct classes of Latency Reversing Agents (LRAs)



Y. Kim, J.L. Anderson, and S.Lewin. Cell Host Microbe, 2018, 23 (1): 14-26

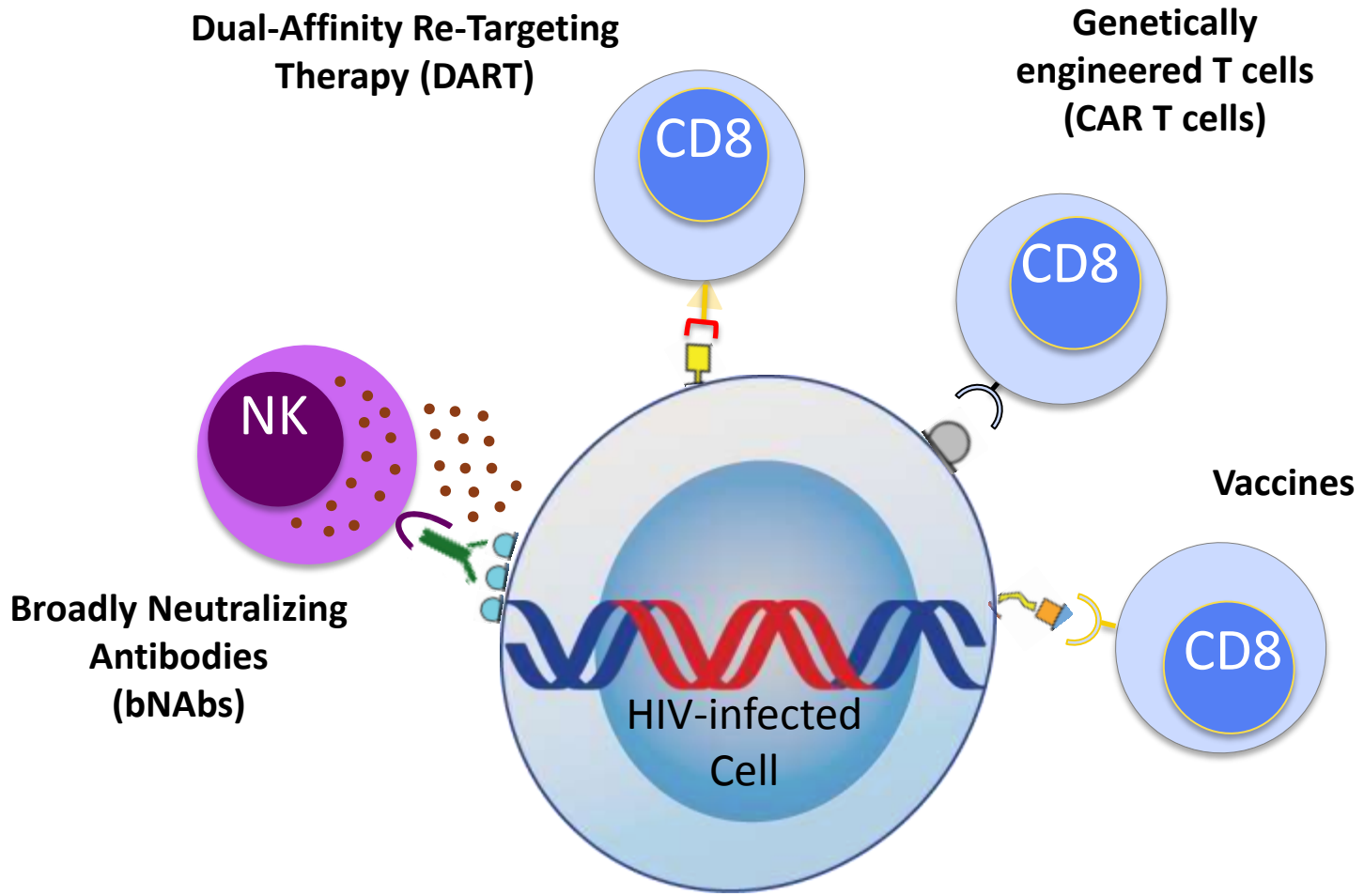
LRAs may activate latency in vivo but none eliminate latently infected cells

Latency reversing agent	Site of action	HIV latency	US HIV RNA	Plasma RNA	HIV DNA
Vorinostat	HDACi	Single dose[1] Intermittent[2] Continuous[3]	↑	↔	↔
Panobinostat	HDACi	Intermittent dose[4]	↑	+/-	↔
Romidepsin	HDACi	Weekly dose[5]	↑↑	↑↑	↔
Disulfiram	AKT activation	High dose 2g/day[6]	↑	↑	↔
Bryostatin	PKC agonist	Low dose 10-20ug/m^2	↔	↔	↔

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

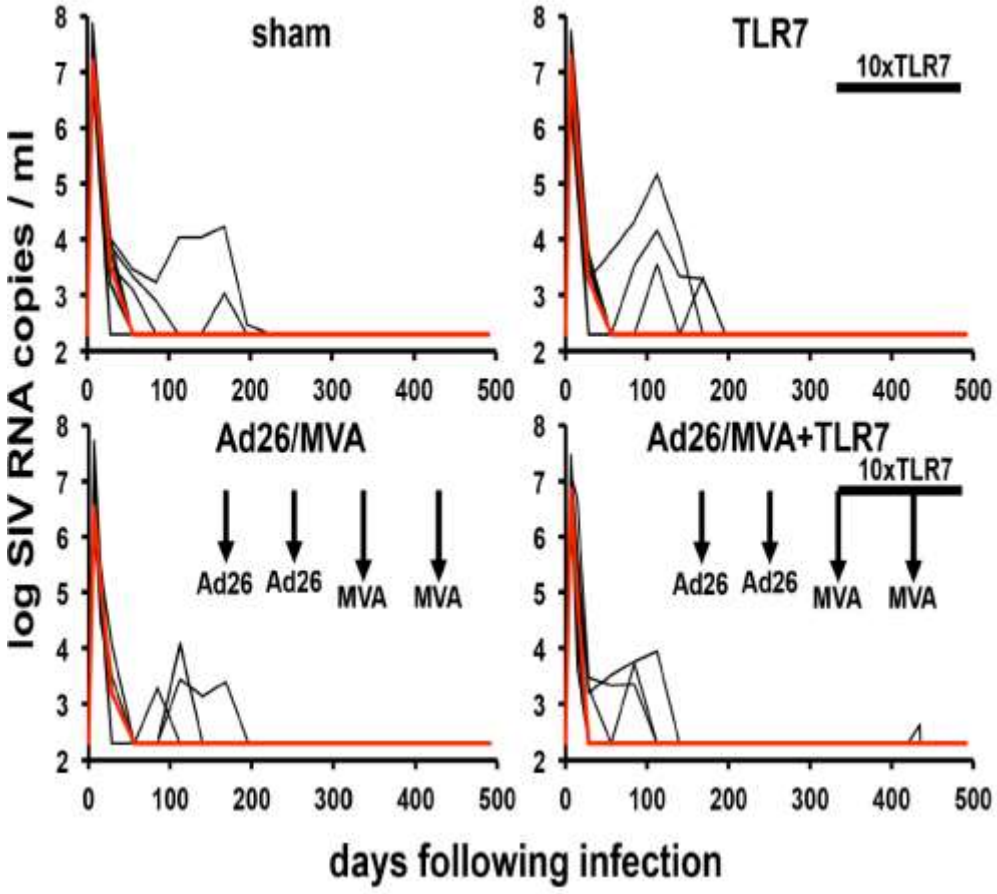
1 Archin et al., *Nature* 2012; 2 Archin et al., *J Infect Dis* 2014; 3Elliott J et al., *Plos Pathogens* 2014; 4Rasmussen et al., *Lancet HIV* 2014; 5Sogaard et al., *Plos Pathogens* 2015; 6Elliott J et al., *Lancet HIV* 2015; 7Gutierrez et al., AIDS 2016

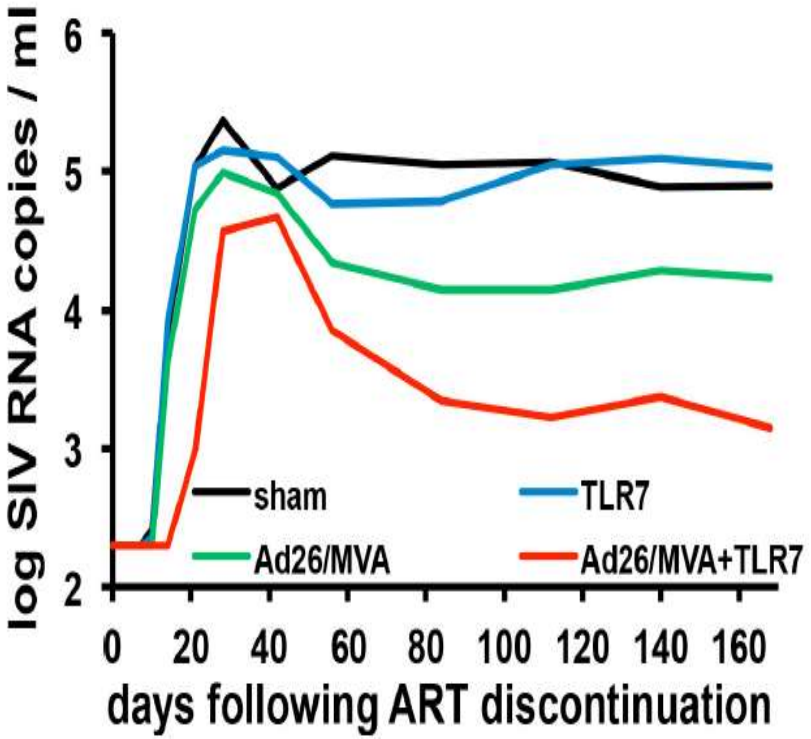
Killing HIV-infected Cells



Jintanat Ananworanich,Joep Lange Memorial Lecture, IAS 2017, Paris

HIV vaccination + TLR7 (adjuvant or latency reversal) leads to SIV control off ART

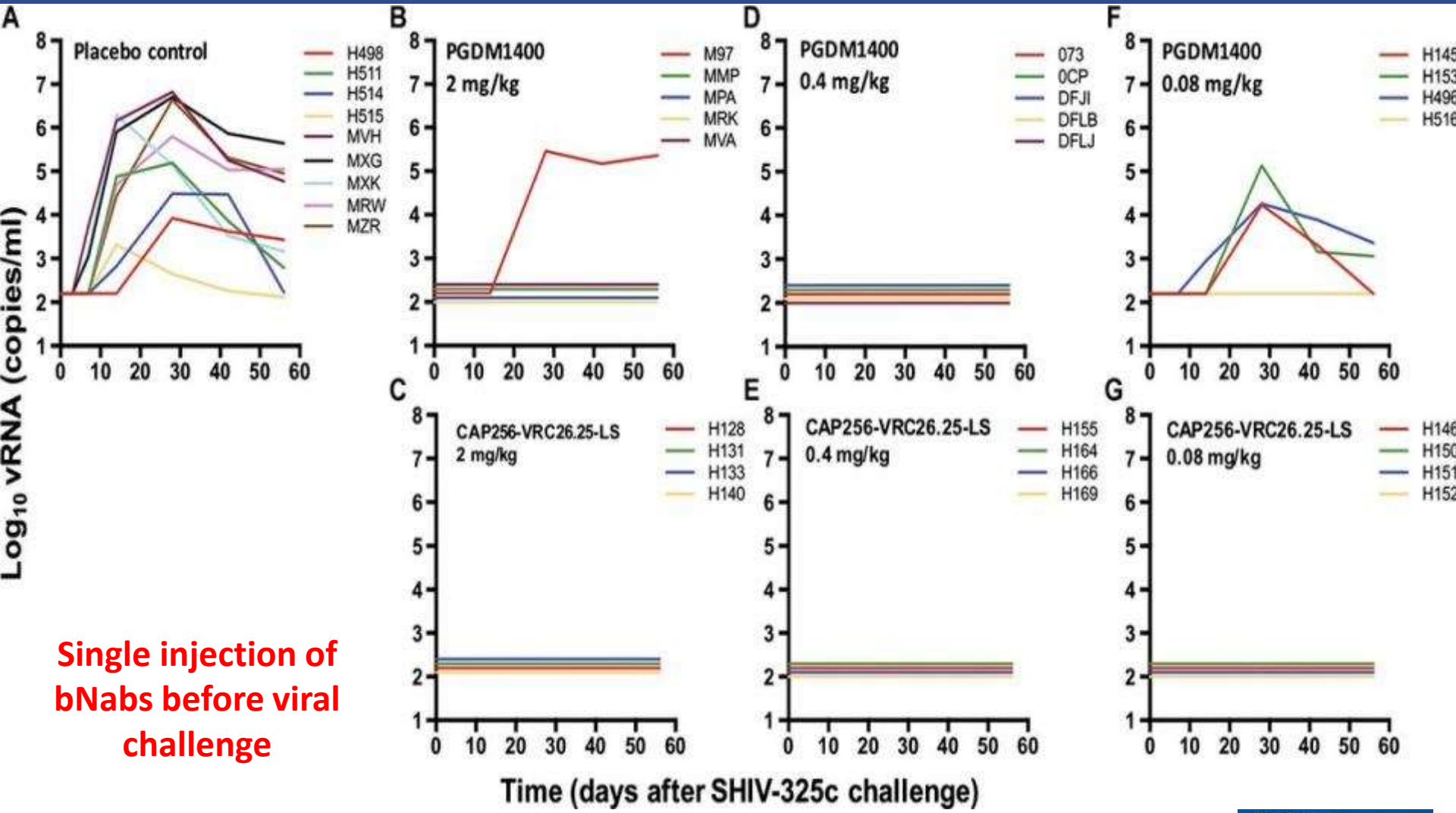




TLR7 agonist (Gilead) and Adenovirus (Ad26) + Modified Vaccine Ankara (MVA, Janssen)

Borducchi et al., Nature 2016

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

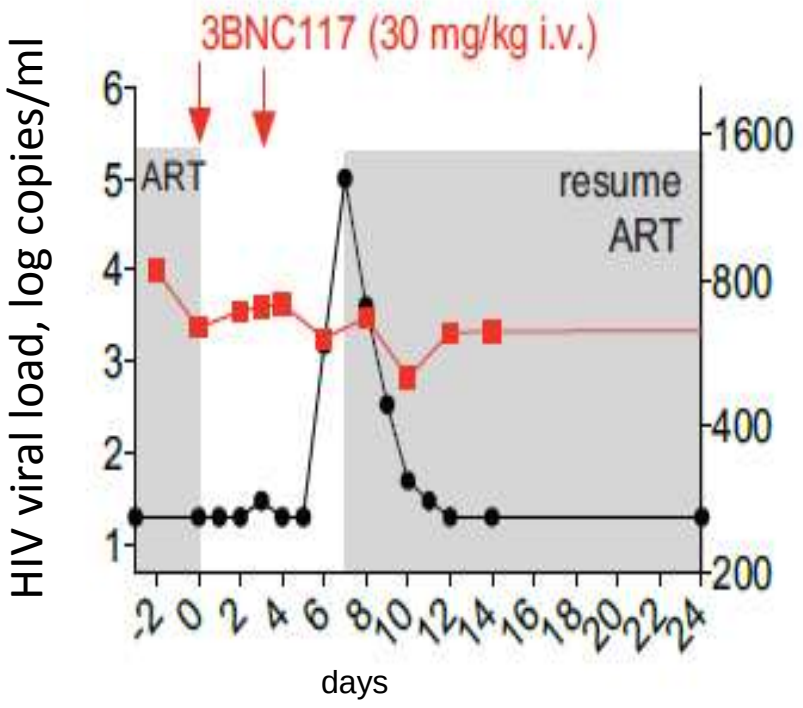


Single injection of bNabs before viral challenge

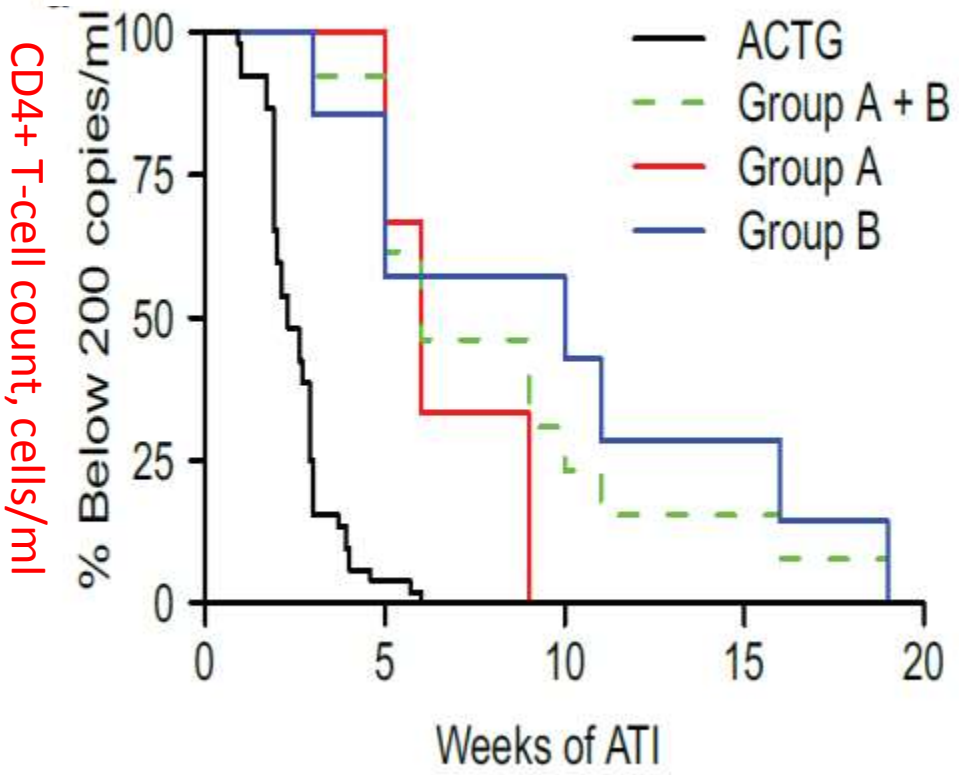
Boris Julg et al.,
Sci Transl Med 2017;9:eaal1321

Science Translational Medicine
AAAS

Broadly neutralising antibodies eliminate infected cells and prolong time to rebound off ART



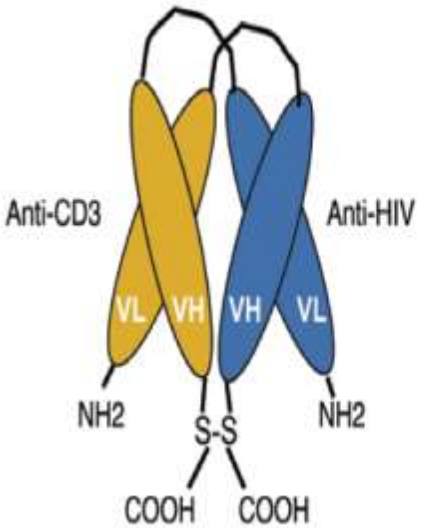
HIV-infected individuals on ART
Antiretroviral treatment interruption 2 days after first infusion

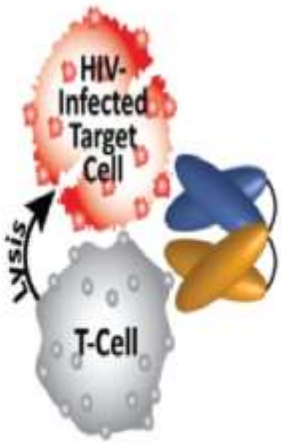


ACTG = historical controls;
Group A = 3BNC1017x2 infusions;
Group B = 3BNC1017 x 4 infusions

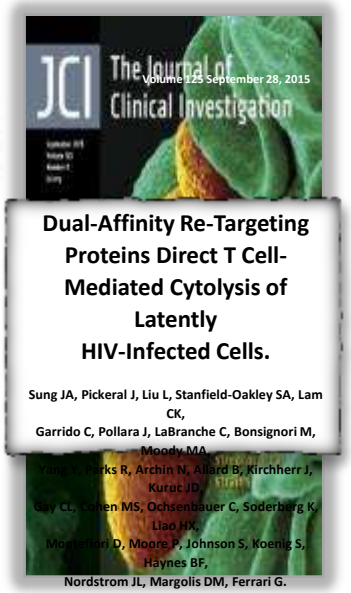
Scheid et al., Nature 2016; Bar et al., N Engl J Med 2016

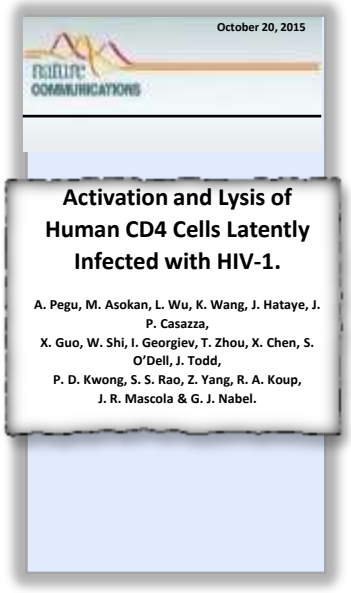
Bi-specific Abs: “shock and kill”

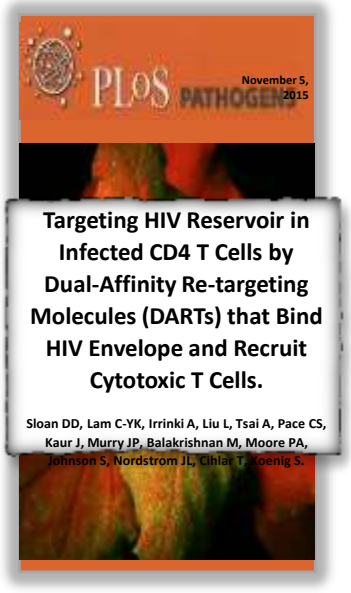




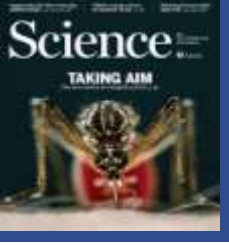
Sung et al., J Clin Inv 2015; Pegu et al., Nat Comms 2015





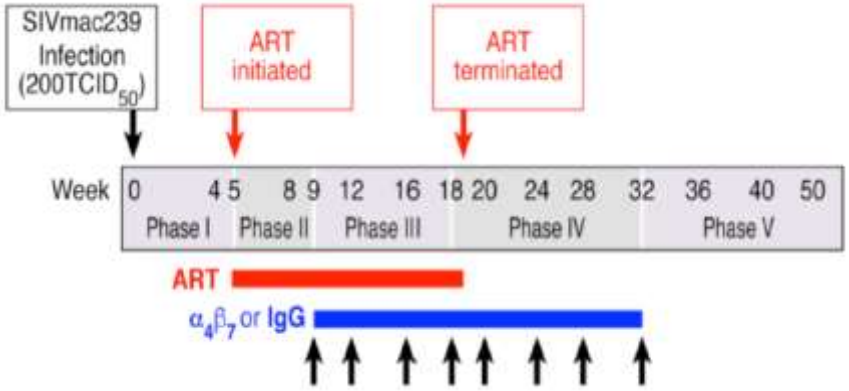


- BITEs and DARTs mediate killing of HIV-infected cells in vitro
- Little in vivo data for treatment of HIV, even in animal models, but ongoing studies
- Products exist and have entered clinical trials for cancer

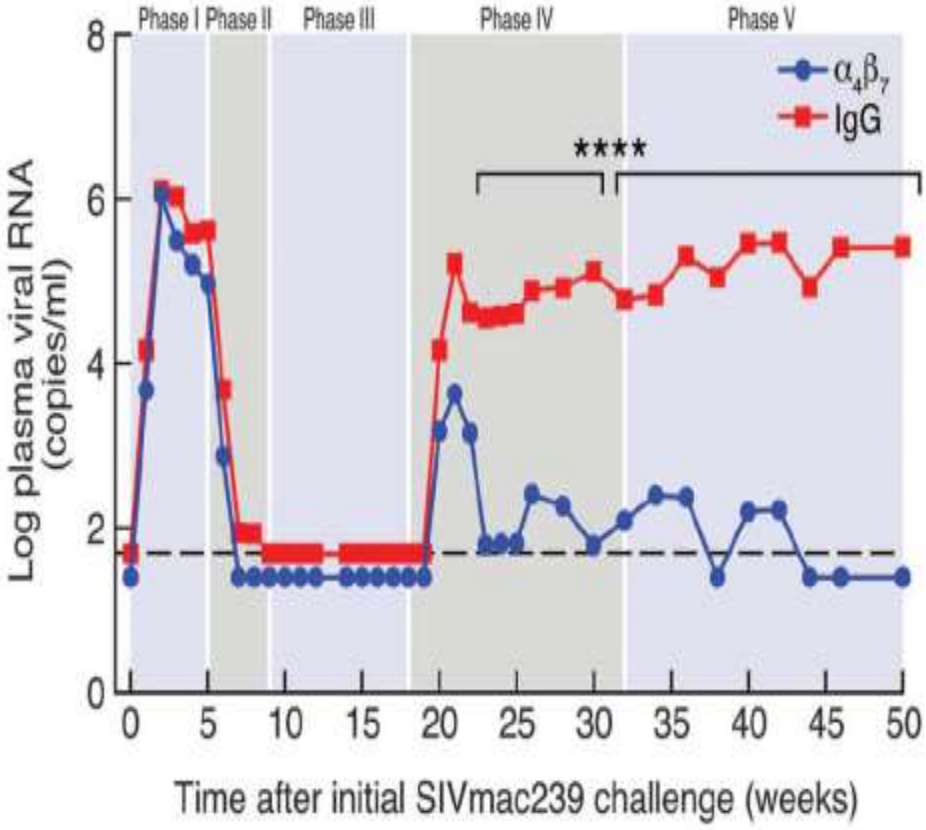


Targeting cell trafficking to the gut? Sustained virus control following α4β7 blockade

- α4β7 is an integrin and enables migration of CD4+ T-cells to GI tract
  - α4β7 is a co-receptor for HIV infection
  - α4β7 expression predicts HIV outcome
  - α4β7 antibody (vedalizumab) is licensed for IBD



Byareddy et al., Science 2016



Vedaluzimab now in clinical trials in HIV-infected individuals on ART

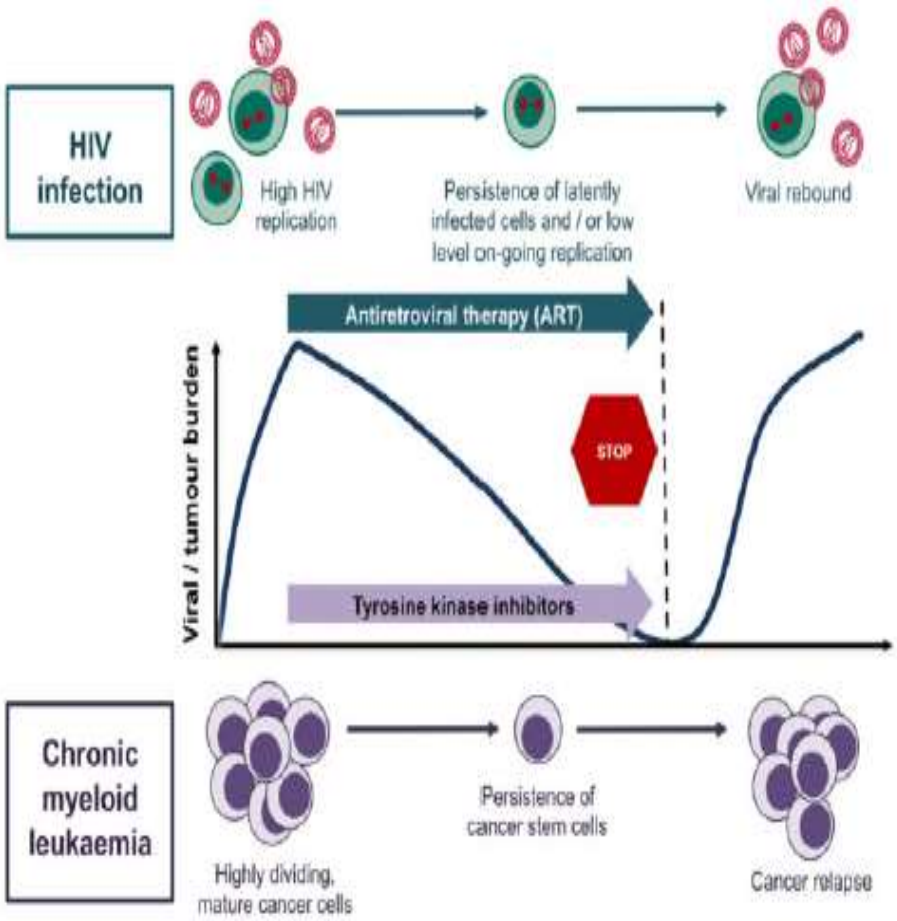
HIV Persistence and cancer

Similar challenges…

Chronic Inflammation

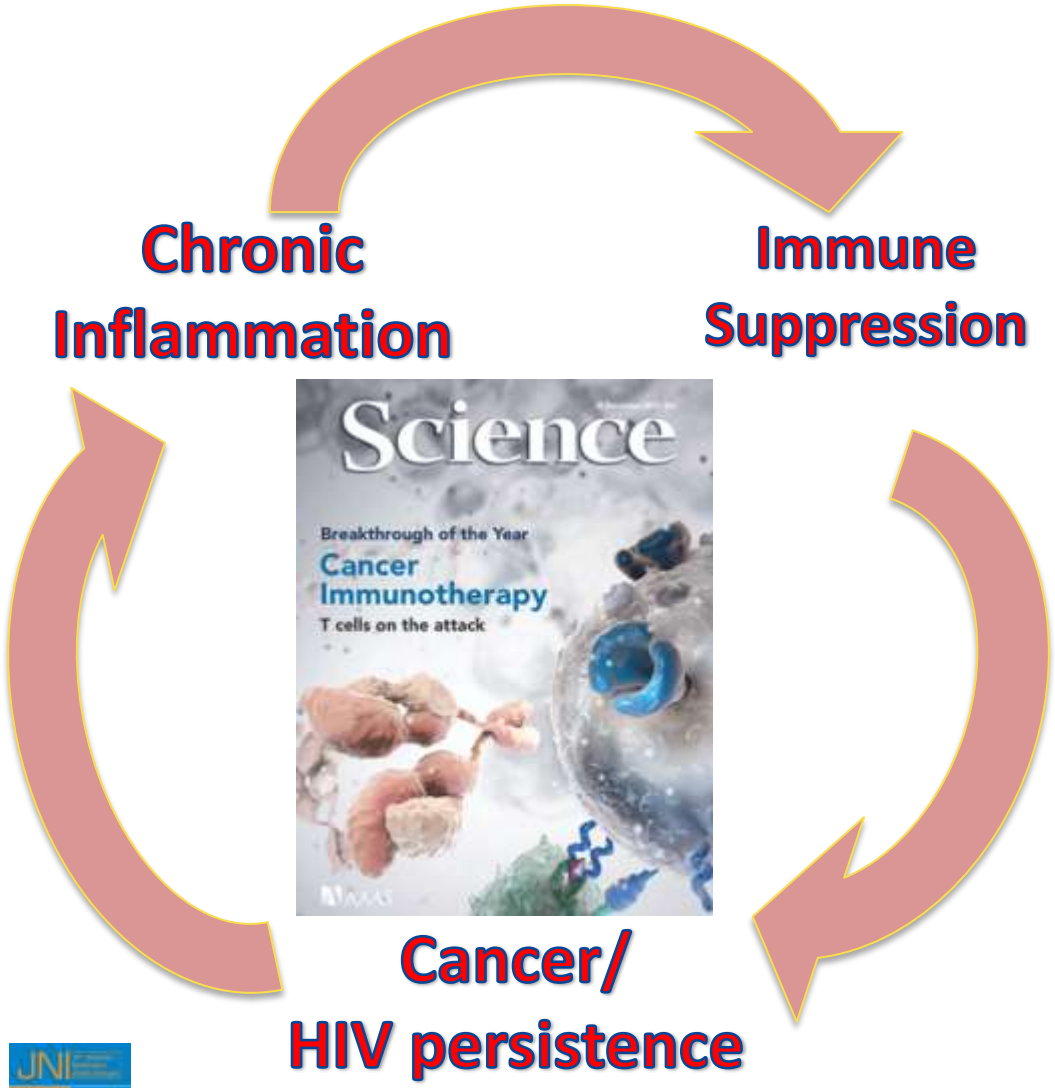
Immune Suppression

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…)***

Clinical trials of ICB in HIV infection

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

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

Letter to the editor, JP.Spano, B. Autran et al. Annals of Oncology, Dec. 2017.

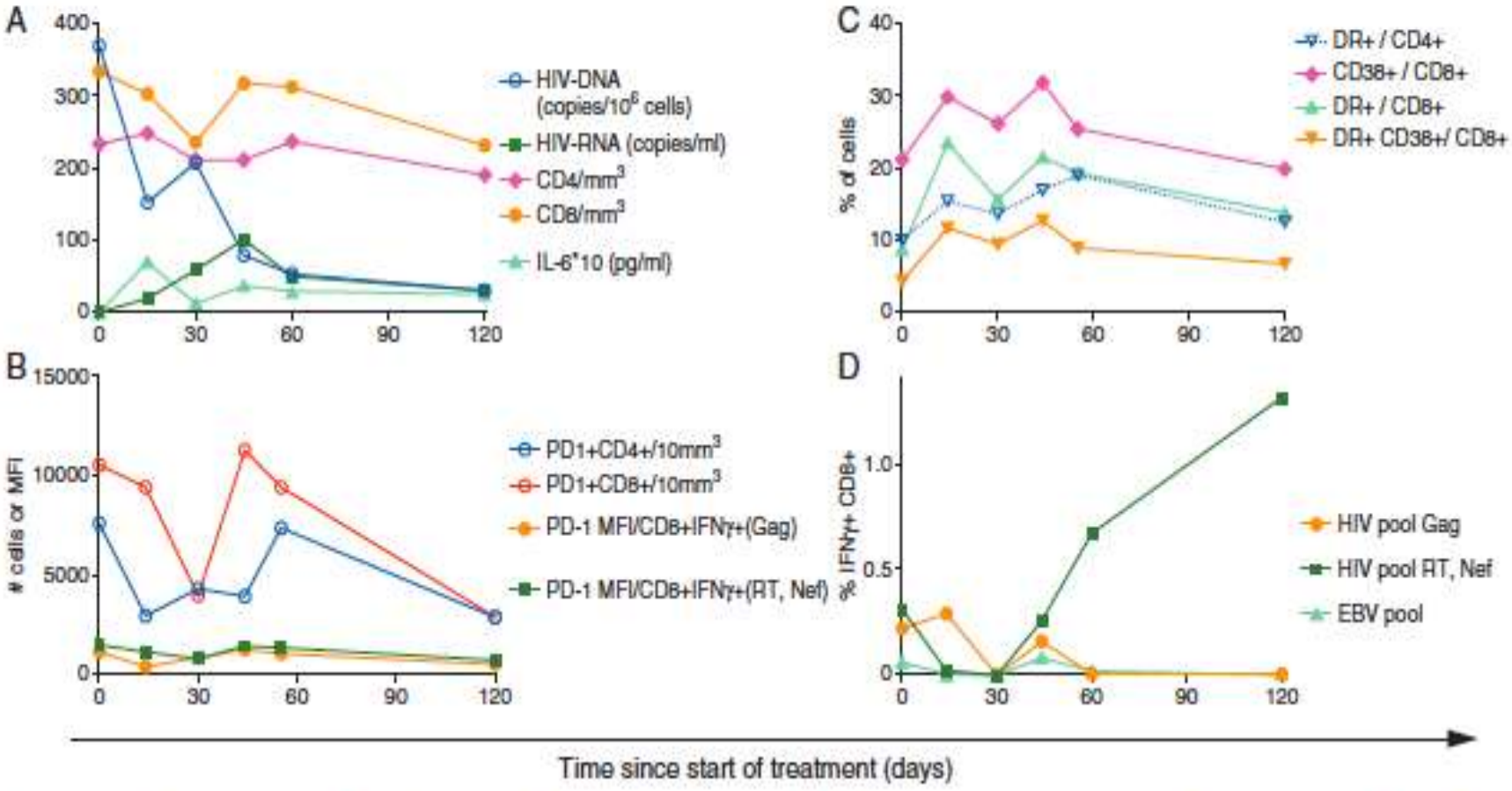
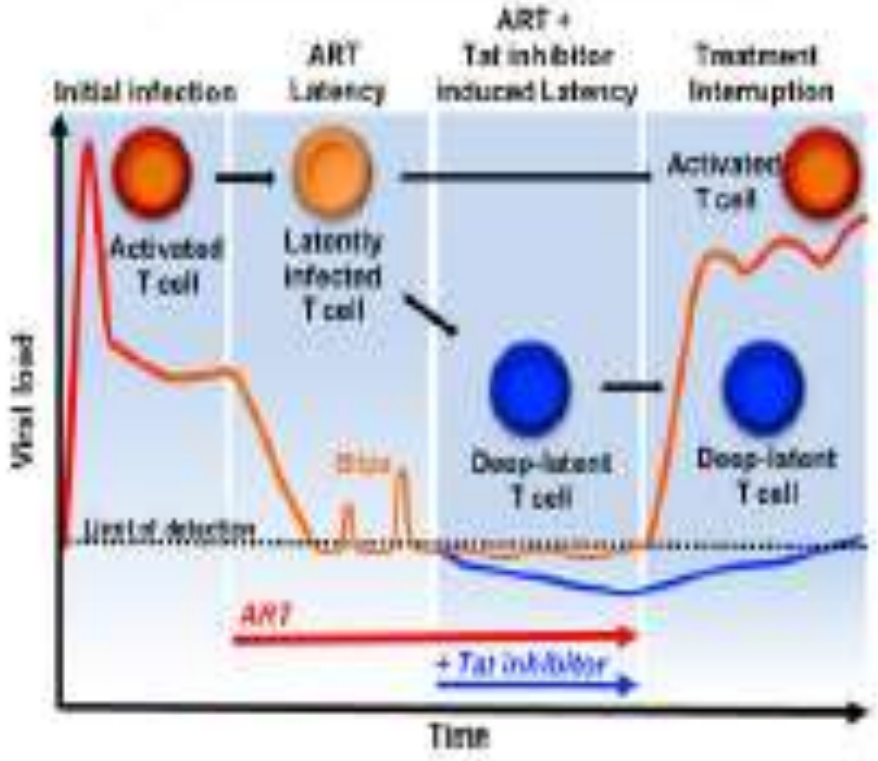
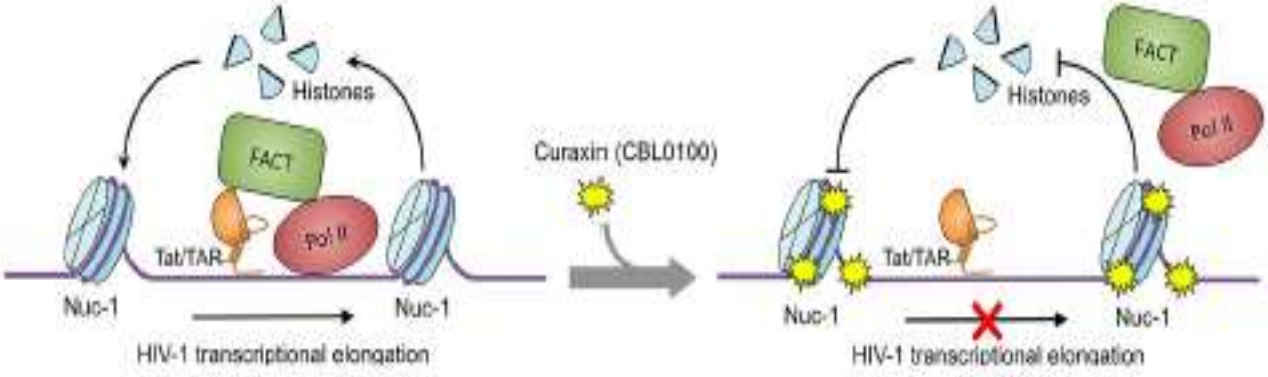


Figure 1. Immunovirological modulations under anti-PD-1 therapy in an HIV-infected patient treated for lung cancer. (A) CD4 cell count, interleukin (IL)-6 plasma levels, HIV-1 plasma viral load measured with ultrasensitive technique (USVL), and total HIV-DNA (DNA copies/million cells) through time. (B) 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/mm^3, 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



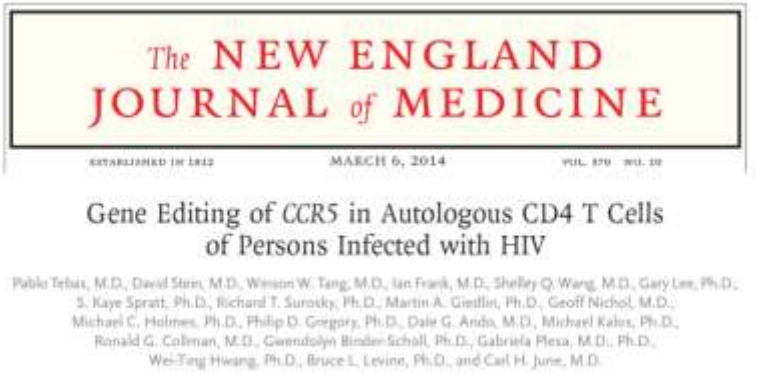
Tat inhibitor like dCA (didehydrocorstatin)



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

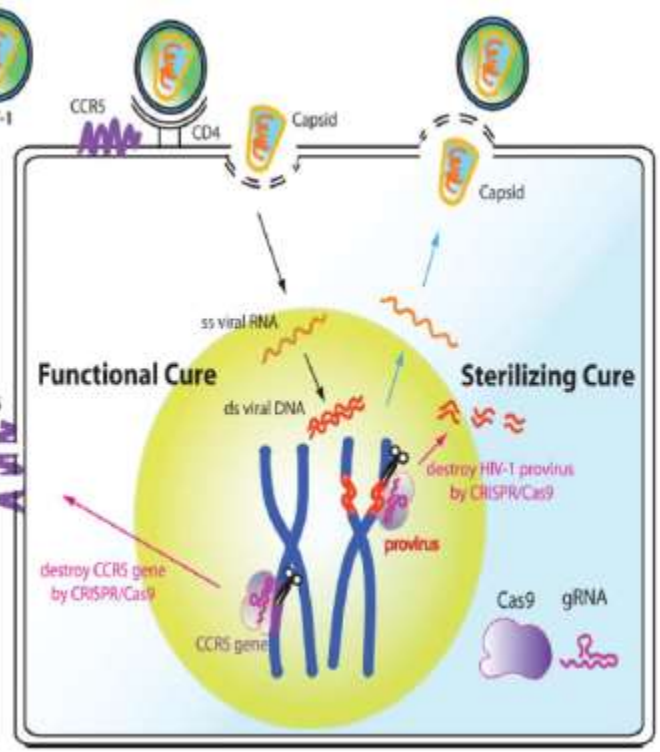
Gene/cell therapy?

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.)*



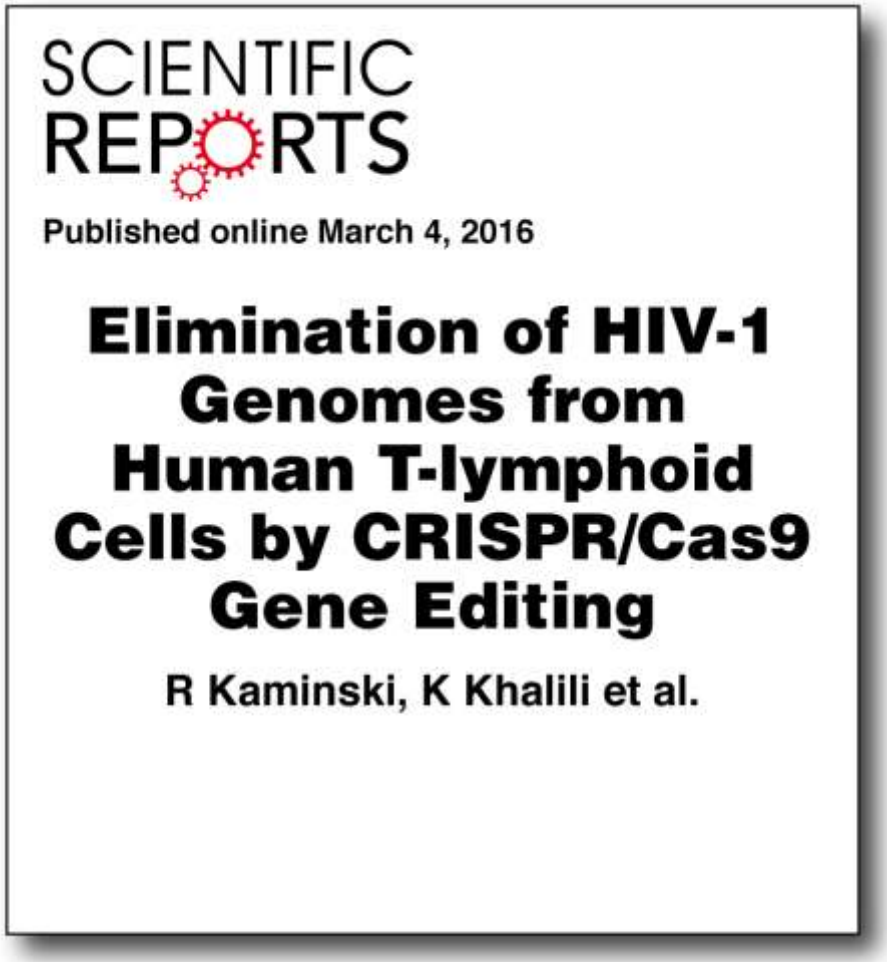
What are the best strategies?

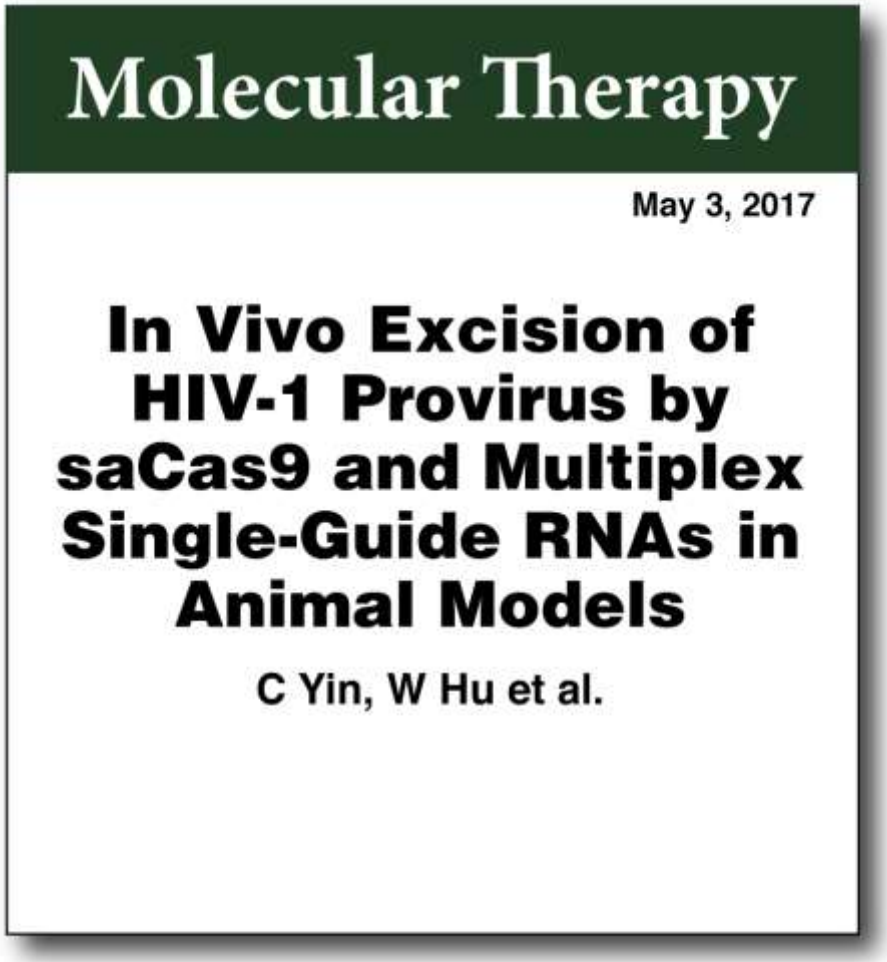
- **Gene editing using CRISPR-Cas9 (modified CCR5, siRNA, CARs, TCRs…)?**
- **Which Cell (T cells or human stem cells, autologous vs. allogeneic) to engineer?**
- **HSC engraftment concerns?**
- **Animal models and best patients for clinical studies?**
- **Safe, effective, affordable and scalable approach?**



Hua et al. PNAS 2015; Liao et al. Cell Cycle 2015

Excising HIV Provirus with Gene Editing





Where are we going?

HIV Cure strategies currently in human studies

MINIMIZE RESERVOIR

Limit reservoir with early treatment

Antiretroviral therapy

Broadly neutralizing antibodies

SHOCK

Reactivating latently infected cells

Inhibit histone deacetylase

Inhibit bromodomain extraterminal

Activate toll-like receptors

Activate protein kinase C

BLOCK and LOCK

Latency Promoting Agent (LPA)

Curaxin100 (CBLO100): inhibitor of transcriptional elongation.

dCA (tat inhibitor didehydroxycorsatin)

KILL

Viral clearance by the immune system

bNabs

therapeutic vaccines

anti-PD1 or PD1-L

HIV RESISTANT CELLS or DESTROY HIV

Transfusing cells with modified CCR5 gene

Gene-editing therapy using CRISPR-Cas9

Bone marrow or cord blood transplantation

URGENT NEED for novel biomarkers predictive of efficacy!

Personalized cure therapy?

Affordable and scalable strategies (<$1400)…

Advisory Board to Implement a Global Multidisciplinary, Integrated and Coodinated Scientific Agenda…

Funding
2012-2016: Investment x 3

New concepts,
new generation

Int. scientific
collaborations

Interaction between
Basic + **Clinical**
Science

Cooperation
public + **privates**
sectors

Social and
Economical
Science

Community
engagement

Cross-talk with other
scientific disciplines

Platforms of **Information & Data exchanges**

towards an HIV cure
people focused
science driven

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And many others…

To all the patients, researchers and health professionals who participate to HIV cure research…