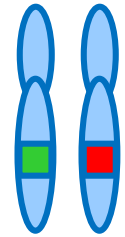
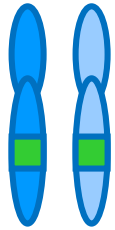
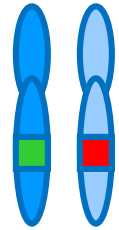
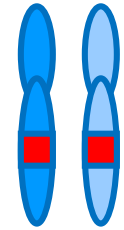
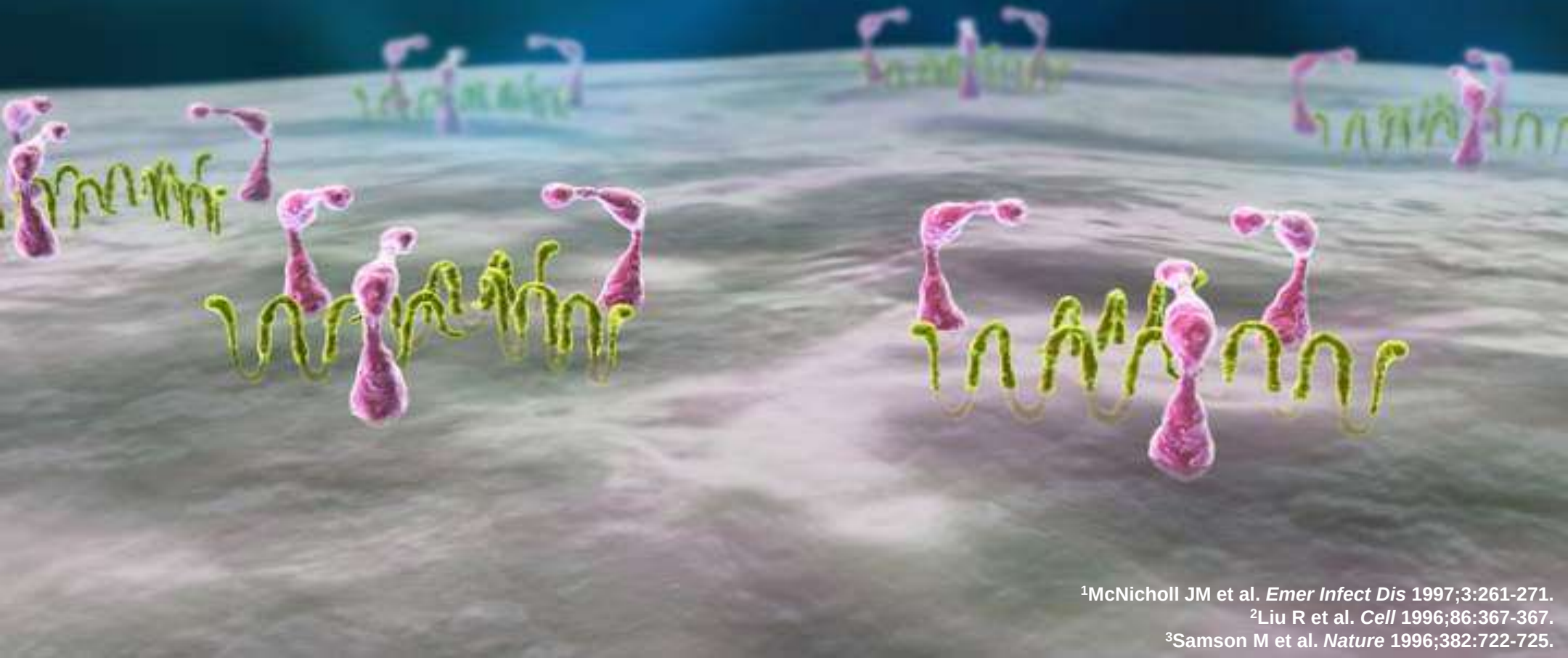
Deleción delta 32

CCR5 *wild type* →  **← CCR5 Δ32**

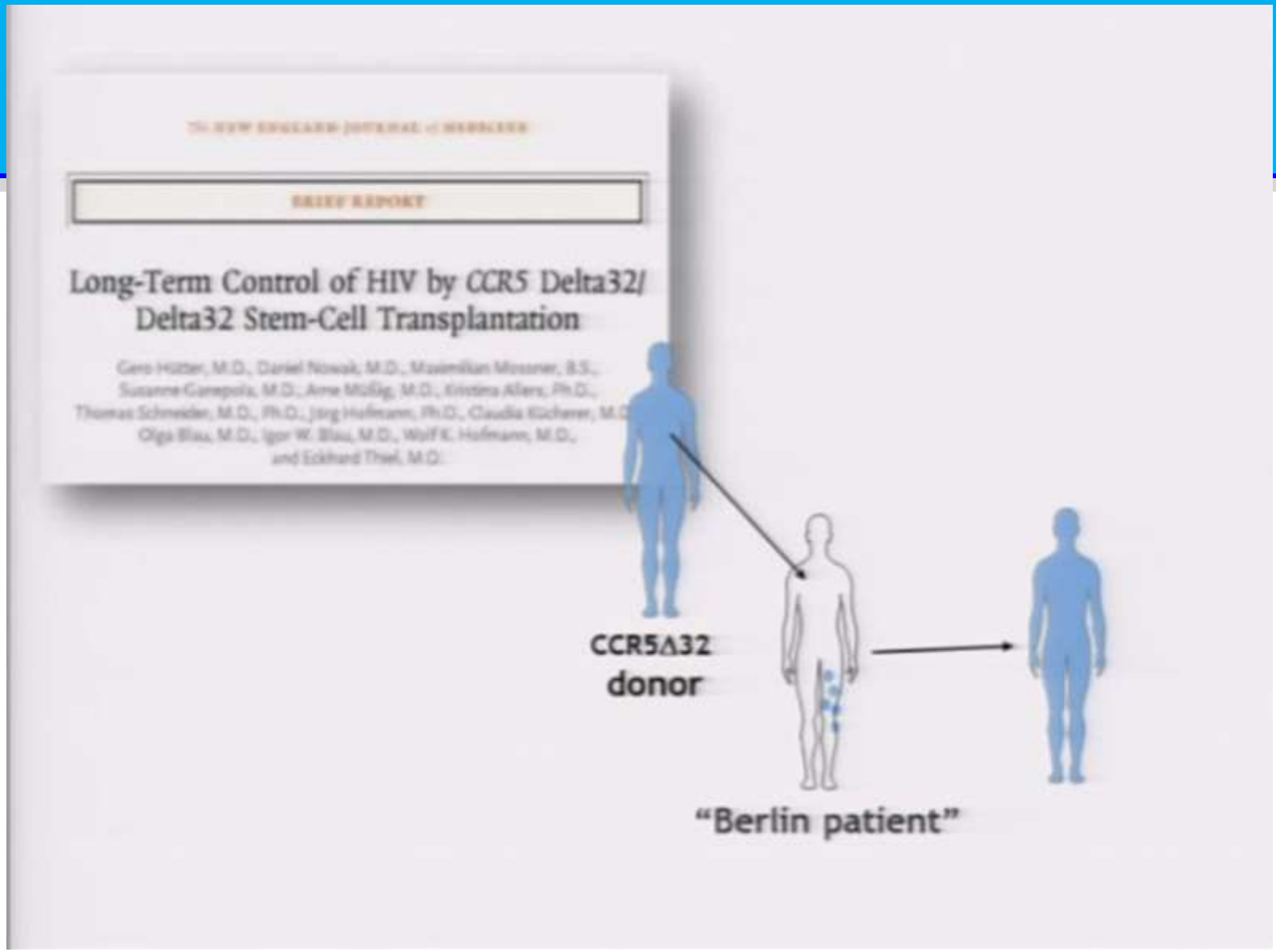
Normal	Heterozygotes	Homozygotes
		
wt/wt	**wt/Δ32**	**Δ32/Δ32**
2 normal copies	1 copy of Δ32	2 copies of Δ32
Standard disease progression	**Delayed disease progression**	**“Resistant” to HIV infection**

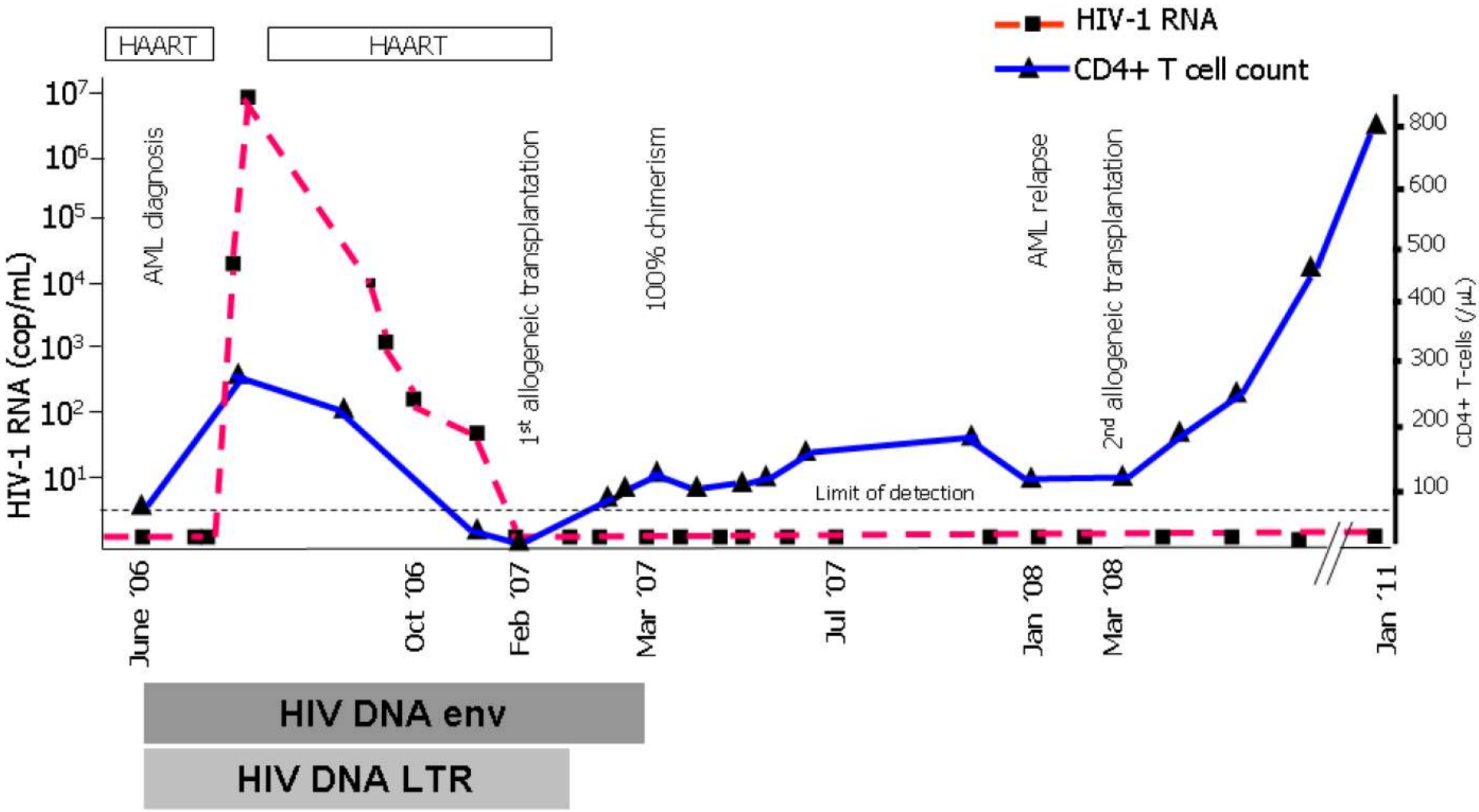
Pacientes homozigotos para CCR5 Δ32

- Representan ~1% de la población caucásica[1]
- No tienen la molécula CCR5 en la superficie del linfocito T[2,3]
- Son “inmunes” a la infección por virus R5[2,3]
  - Susceptibles al virus X4 pero con baja eficacia
- Su función inmune es normal[2,3]



[1]McNicholl JM et al. *Emer Infect Dis* 1997;3:261-271.
[2]Liu R et al. *Cell* 1996;86:367-367.
[3]Samson M et al. *Nature* 1996;382:722-725.


BRIEF REPORT
Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation
CCR5Δ32
donor
"Berlin patient"



Hutter G, Ganepola S. Scientific Word Journal 2011

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantatio

NEJM, 2010

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D.

Infection with the hu
ence of a CD4 recepto
(CCR5). Homozygosi

CLINICAL TRIALS AND OBSERVATIONS

Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation

Bood, 2010

Kristina Allers,[1] Gero Hütter,[2] Jörg Hofmann,[3] Christoph Loddenkemper,[4] Kathrin Rieger,[2] Eckhard Thiel,[2] and Thomas Schneider[1]

[1]Department of Gastroenterology, Infectious Diseases, and Rheumatology, Medical Clinic I, Campus Benjamin Franklin, Charité-University Medicine Berlin, Berlin, Germany; [2]Department of Hematology, Oncology, and Transfusion Medicine, Medical Clinic III, Campus Benjamin Franklin, Charité-University Medicine Berlin, Berlin, Germany; [3]Institute of Medical Virology, Helmut-Ruska-Haus, Campus Mitte, Charité-University Medicine Berlin, Berlin, Germany; and [4]Institute of Pathology/Research Center ImmunoSciences (RCIS), Campus Benjamin Franklin, Charité-University Medicine Berlin, Berlin, Germany

HIV entry into CD4⁺ cells requires interaction with a cellular receptor, generally either CCR5 or CXCR4. We have previously reported the case of an HIV-infected patient in whom viral replication remained absent despite discontinuation of antiretroviral therapy after transplantation with CCR5Δ32/Δ32 stem cells. However, it was expected that the long-lived viral reservoir would lead to HIV rebound and disease progression during the process of immune reconstitution. In the present study, we demonstrate successful reconstitution of CD4⁺ T cells at the systemic level as well as in the gut mucosal immune system after CCR5Δ32/Δ32 stem cell transplantation, while the patient remains without any sign of HIV infection. This was observed although recovered CD4⁺ T cells contain a high proportion of activated memory CD4⁺ T cells, ie, the preferential targets of HIV, and are susceptible to productive infection w tropic HIV. Furthermore, duri cess of immune reconstitutio evidence for the replacemer lived host tissue cells with donor-derived cells, indicating that the size of the viral reservoir has been reduced over time. In conclusion, our results strongly suggest that cure of HIV has been achieved in this patient. (*Blood*. 2011;117(10):2791-2799)

Is the patient functionally cured?

The patient has been off antiretroviral medication for 4 years and there are no measurable signs of viral replication. Interestingly, the patient displayed a partial serodeconversion concerning his anti-HIV antibodies, indicating that there is no relevant virus replication left. Therefore, the possibility that the patient will suffer or die from his HIV infection is very unlikely and there is nothing else to conclude that transplantation of CCR5-delta32 stem cells has led to a functional cure.

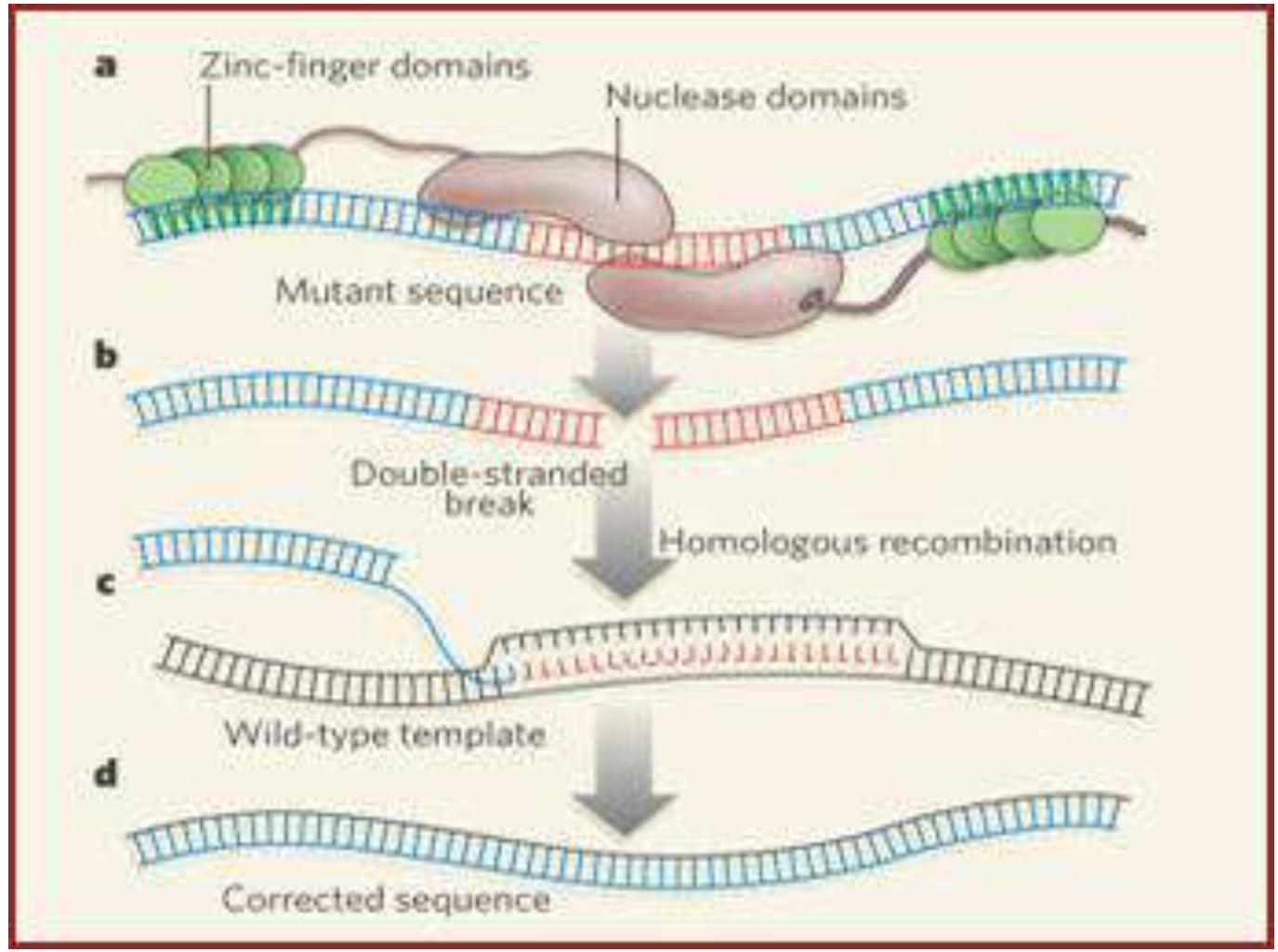
Is the patient sterilizing cured?

The principal idea of complete eradication of a pathogen out of the human body goes back to the Paul Ehrlichs concept of a "*therapia sterilisans magna*"[20]. In the case of HIV-1, a retrovirus that becomes

Hutter G, Ganepola S. Scientific Word Journal 2011

¿Se puede modificar artificialmente el correceptor?

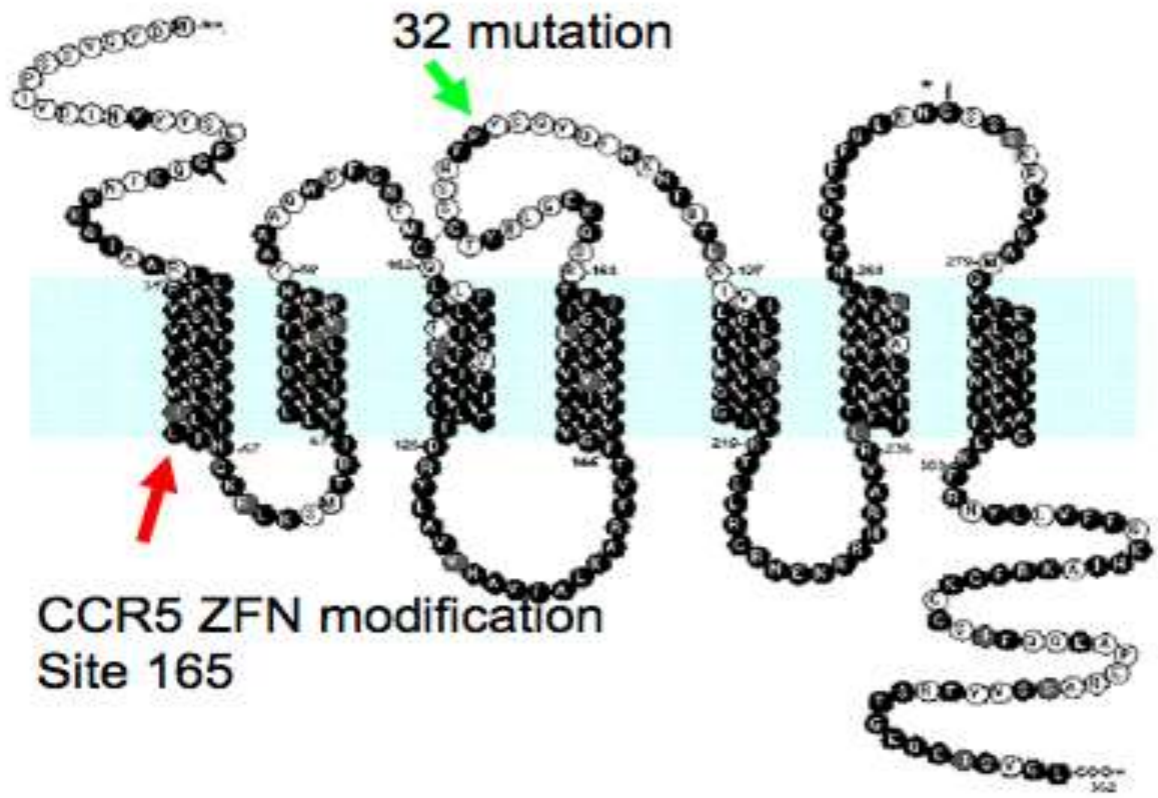
Las nucleasas en dedos de cinc ("zinc finger")



Successful and persistent engraftment of ZFN-M-R5-D autologous CD4 T Cells (SB-728-T) in aviremic HIV-infected subjects on HAART

Lalezari J et al. 18th CROI, abstract 46, 2011.

Targeting the *CCR5* Locus with ZFNs



ZFN pairs targeted to region upstream of the Δ32 mutation

Sangamo SB-728-0902 Summary

- **SB-728-T can be manufactured at doses of 10-30 billion cells from a single apheresis with a CCR5 disruption frequency of ~25%**
- **SB-728-T treatment is well-tolerated**
  - Minor reversible infusion-related symptoms
- **Improved and sustained increase in total CD4+T-cell counts seen in 5/6 subjects**
- **Normalization of CD4:CD8 ratios seen in 3/5 subjects**
- **ZFN-modified T-cells engraft, expand, and persist in peripheral blood**
  - ZFN-modified CD4+ T-cells detected at frequencies up to 7-fold higher (median 2.9) than predicted input on day 14
  - Expansion of ZFN-modified T cells in PBMC may be due to cell proliferation and/or altered distribution
- **ZFN-modified T-cells engraft and persist in rectal mucosa**
  - Engraftment and persistence of ZFN-modified T cells in rectal mucosa demonstrated normal homing to this important tissue

¿Ha habido más casos como en paciente Berlín?

Cómo erradicar la infección VIH / sida

- **Reducir al mínimo los nuevos contagios**
- **Curar a los infectados**
  - **Erradicar el virus**

¿Podremos erradicar la infección VIH?

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

The Beginning of the End of AIDS?

Diane Havlir, M.D., and Chris Beyrer, M.D., M.P.H.

We are at a moment of extraordinary optimism in the response to the human immunodeficiency virus (HIV). A series of scientific breakthroughs, including several trials showing the partial efficacy of oral and topical chemoprophylaxis[1-4] and the first evidence of efficacy for an HIV vaccine candidate,[5] have the potential to markedly expand the available preventive tools. There is evidence of the first cure of an HIV-infected person. And most important, the finding that early initiation of antiretroviral therapy can both improve individual patient outcomes and reduce the risk of HIV transmission to sexual partners by 96%[6] has led many to assert what had so long seemed impossible: that control of the HIV pandemic may be achievable.

What will it take to achieve what U.S. Secretary of State Hillary Rodham Clinton called, in a 2011 address, an "AIDS-free generation"? Expanded access to and coverage of high-quality prevention and treatment services tailored to affected populations are critical to keeping people living with HIV healthy and to dramatically reducing the number of new HIV infections.[7] This goal requires an ambitious implementation-science agenda that improves efficiency and effectiveness and incorporates strategies for overcoming the stigma and discrimination that continue to limit the uptake and utilization of services. Research efforts on HIV vaccines will also probably be key, and the field has been reinvigorated, after a series of unsuccessful trials, by the findings of the RV144 trial involving Thai adults, which showed that the vaccine provided modest protection against HIV acquisition in selected populations.[8] Research focused on curing HIV disease is yielding fascinating insights into how HIV persists in the face of current therapy, and such research must be earnestly pursued. A combination approach to prevention that includes HIV treatment can generate tremendous gains in the short term by curtailing new HIV infections, but ending the AIDS epidemic will probably require a vaccine, a cure, or both.

The scientific opportunities and optimism at this moment in HIV research are not matched, however, by the available resources. Global resources have been de-

COMMENT

The 'Berlin Patient,' Timothy Brown, has been cured of HIV since 2007. His story has renewed interest in cure research.

Towards a cure for HIV

Steven G. Deeks and **Françoise Barré-Sinoussi** present an international research agenda to seek out a cure for AIDS.

One of the greatest achievements of modern medicine has been the development of combination antiretroviral (ARV) therapy for HIV. Today, fewer than half of the world's people who need treatment have access to therapy. A substantial and sustained increase in funding will be required to effectively treat the global population (see 'Cost of managing HIV'). And this life-saving therapy has limitations — medicines have side effects and must be taken daily, and HIV can develop resistance. Clearly, a new approach to tackling HIV is needed.

In 2007, an HIV-infected man in Berlin received a transplant of haematopoietic stem cells from a naturally HIV-resistant donor, and then he stopped HIV therapy[1]. He has now been free of readily detectable virus in the absence of therapy for more than five years. In other words, he is cured. His experience suggests that HIV infection might one day be curable.

One of the key priorities of the International AIDS Society (IAS) is to promote and facilitate the search for a safe, affordable and scalable cure. The multidisciplinary IAS Scientific Working Group on HIV Cure has developed a broad and ambitious set of priorities for cure research (see 'Priorities for HIV cure research'). Some of these research questions have been pursued for decades, but the focus has been mainly on improving therapy or developing vaccines. Unique perspectives on these old questions will almost certainly be needed for cure research to succeed.

Cure research is not completely new. Several high-profile approaches were attempted soon after the development of combination therapy[2]. But these attempts failed, and the field shifted towards optimizing therapy so that it could be taken indefinitely. Since ▸

❍ NATURE.COM
Read more about the HIV/AIDS pandemic:
go.nature.com/oyhlk

Hacia la curación del VIH

towards an HIV cure
people focused
science driven

Estrategias para la curación

- **Optimizar el TARV**
  - Tratamiento temprano
- **Células diana resistentes al VIH**
  - Terapia génica
- **Eliminar pool celular con infección latente**
  - Estimular la replicación

Estrategias para la curación

- **Optimizar el TARV**
  - Tratamiento temprano
- **Células diana resistentes al VIH**
  - Terapia génica
- **Eliminar pool celular con infección latente**
  - Estimular la replicación

Las nucleasas en dedos de cinc ("zinc finger")

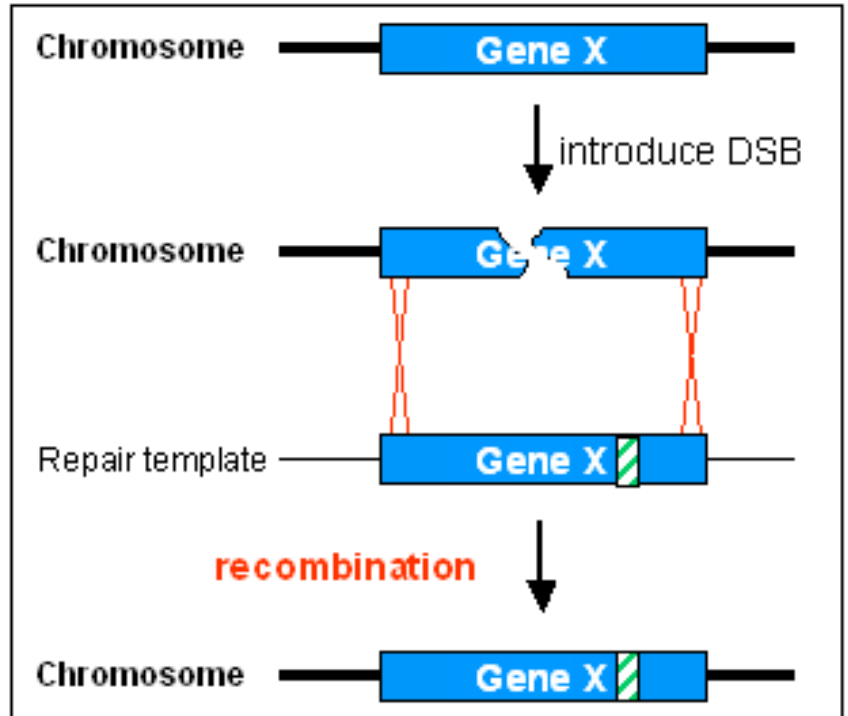


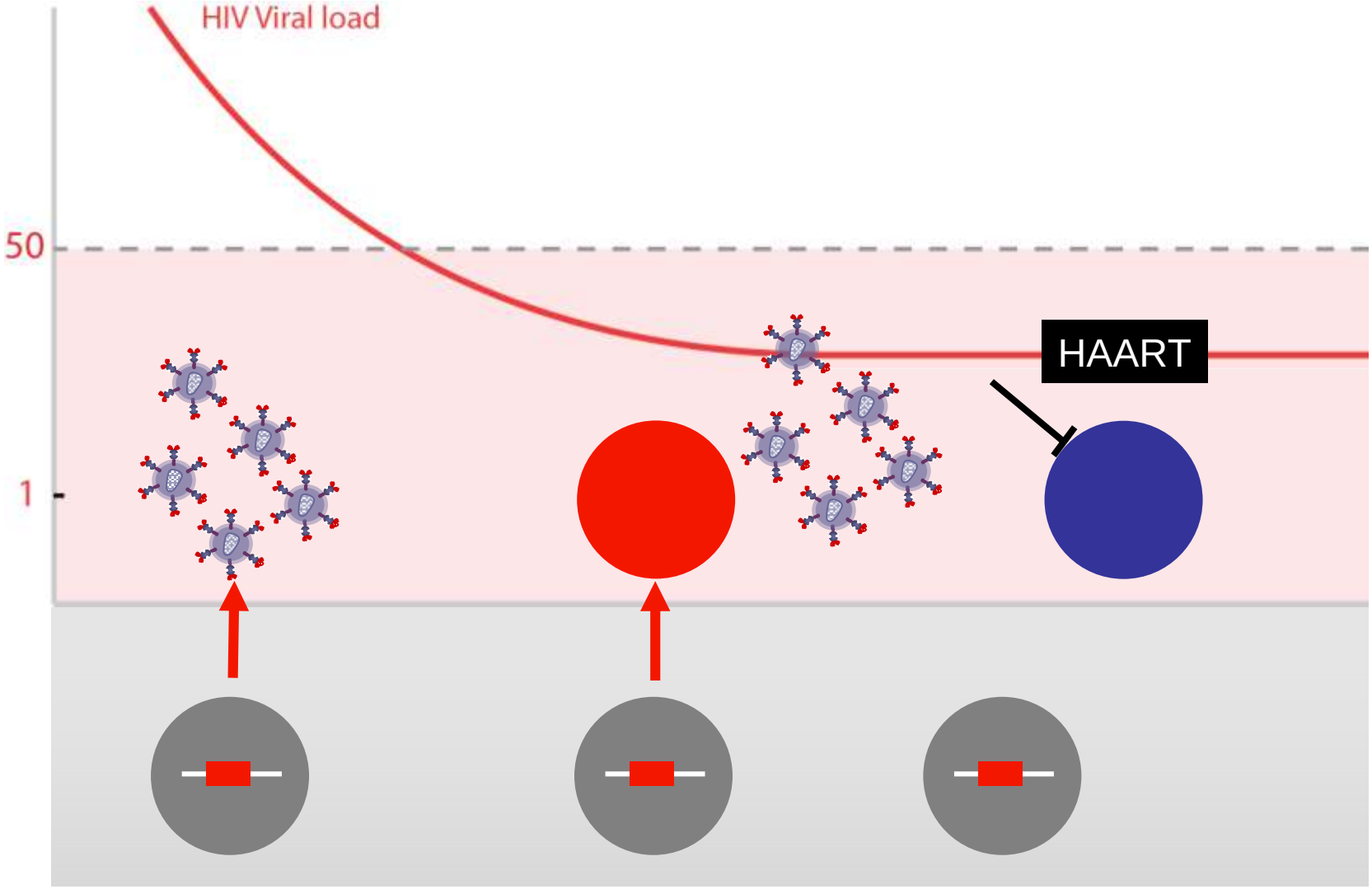
Figure 1: DSB-enhanced gene targeting

http://www.zincfingers.org/scientific-background.htm

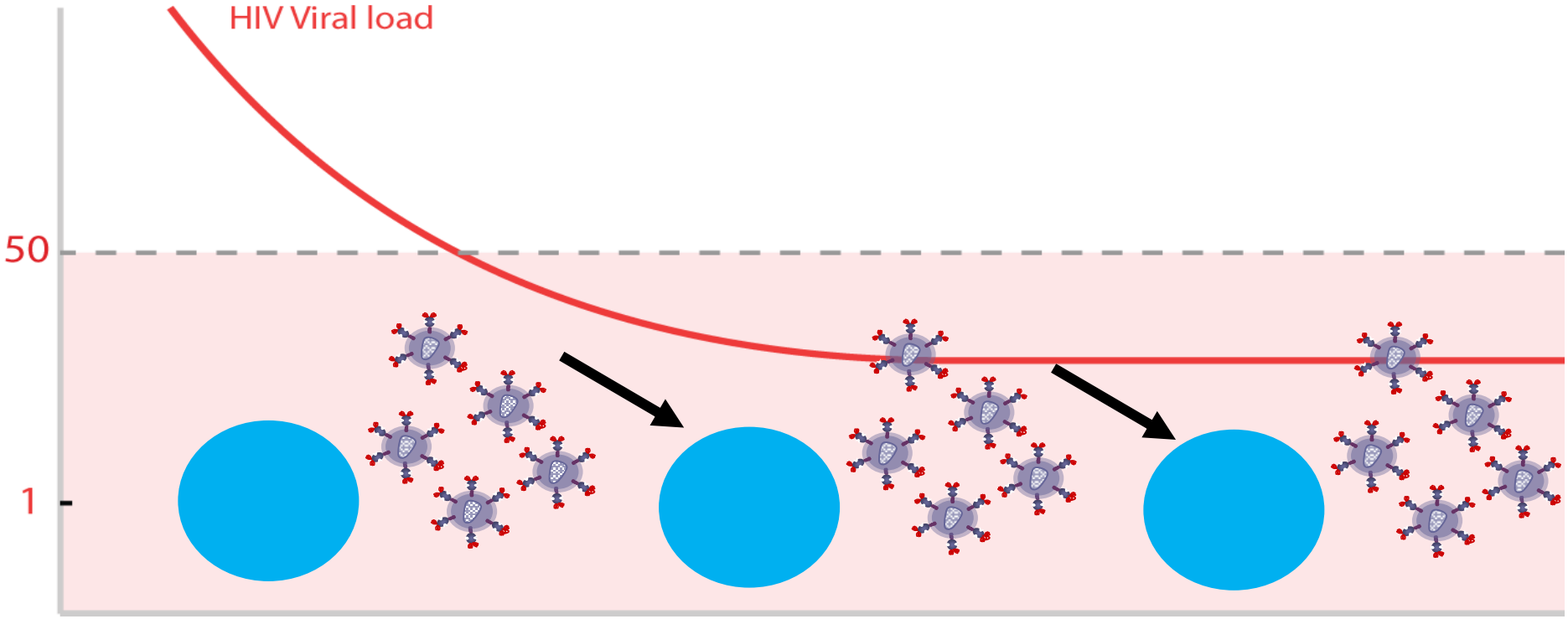
Estrategias para la curación

- **Optimizar el TARV**
  - Tratamiento temprano
- **Células diana resistentes al VIH**
  - Terapia génica
- **Eliminar pool celular con infección latente**
  - Estimular la replicación

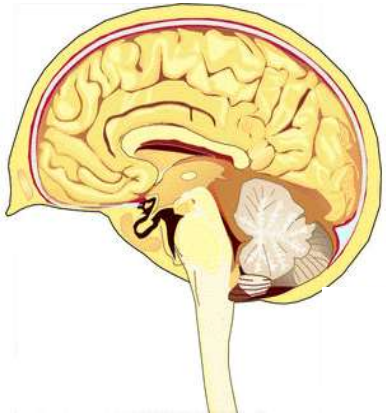
Células con infección latente

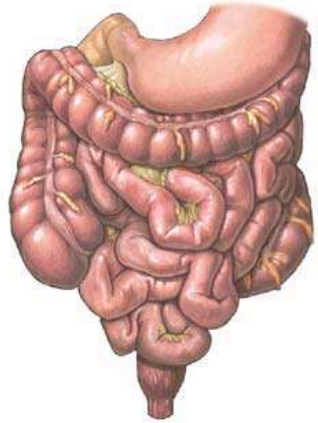


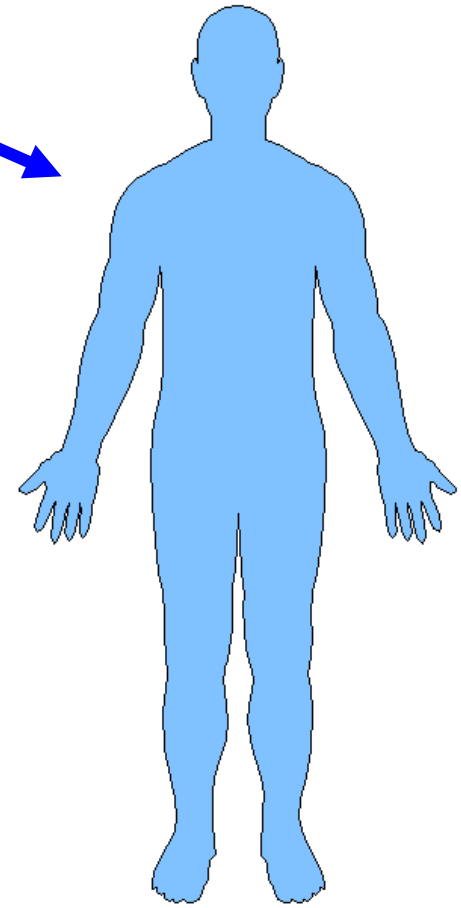
Replicación viral residual



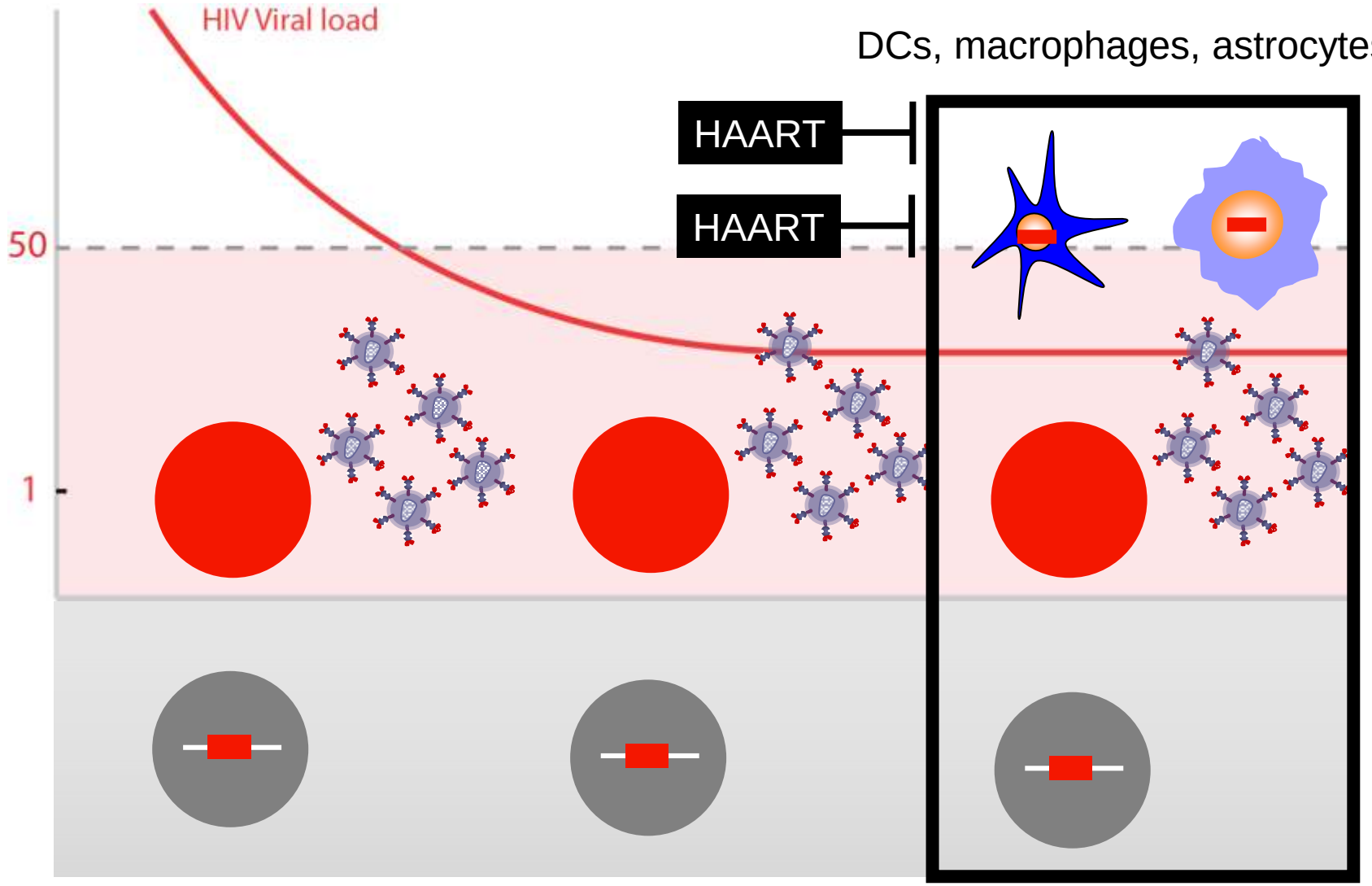
Reservorios anatómicos





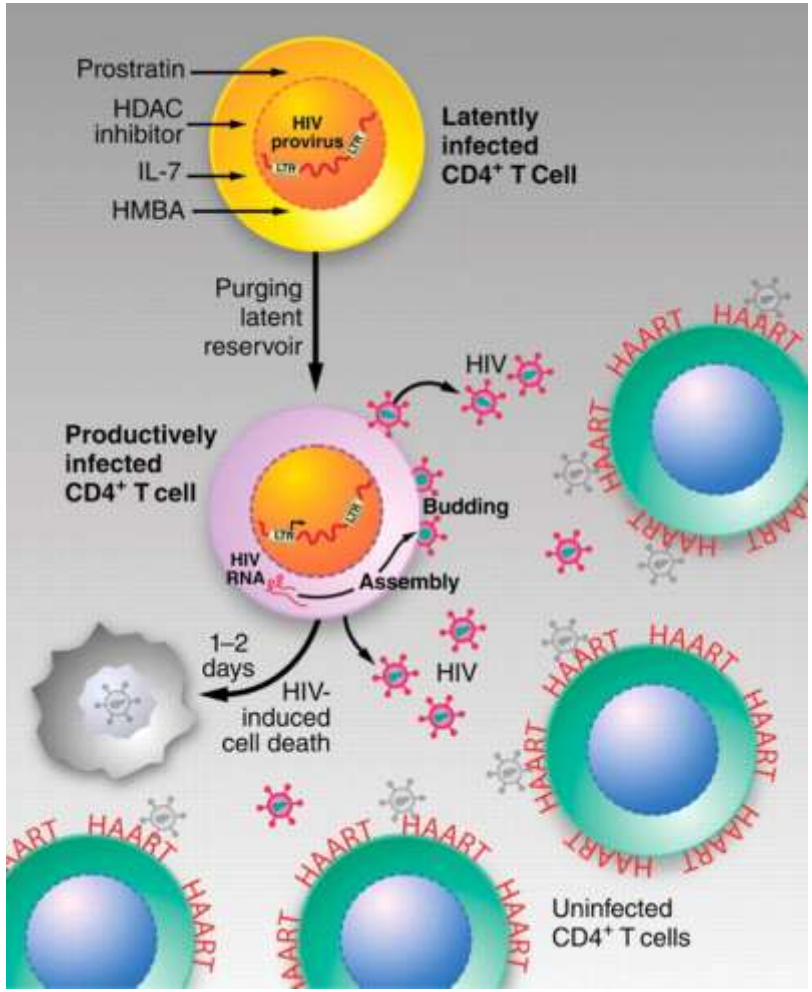


Reservorios anatómicos



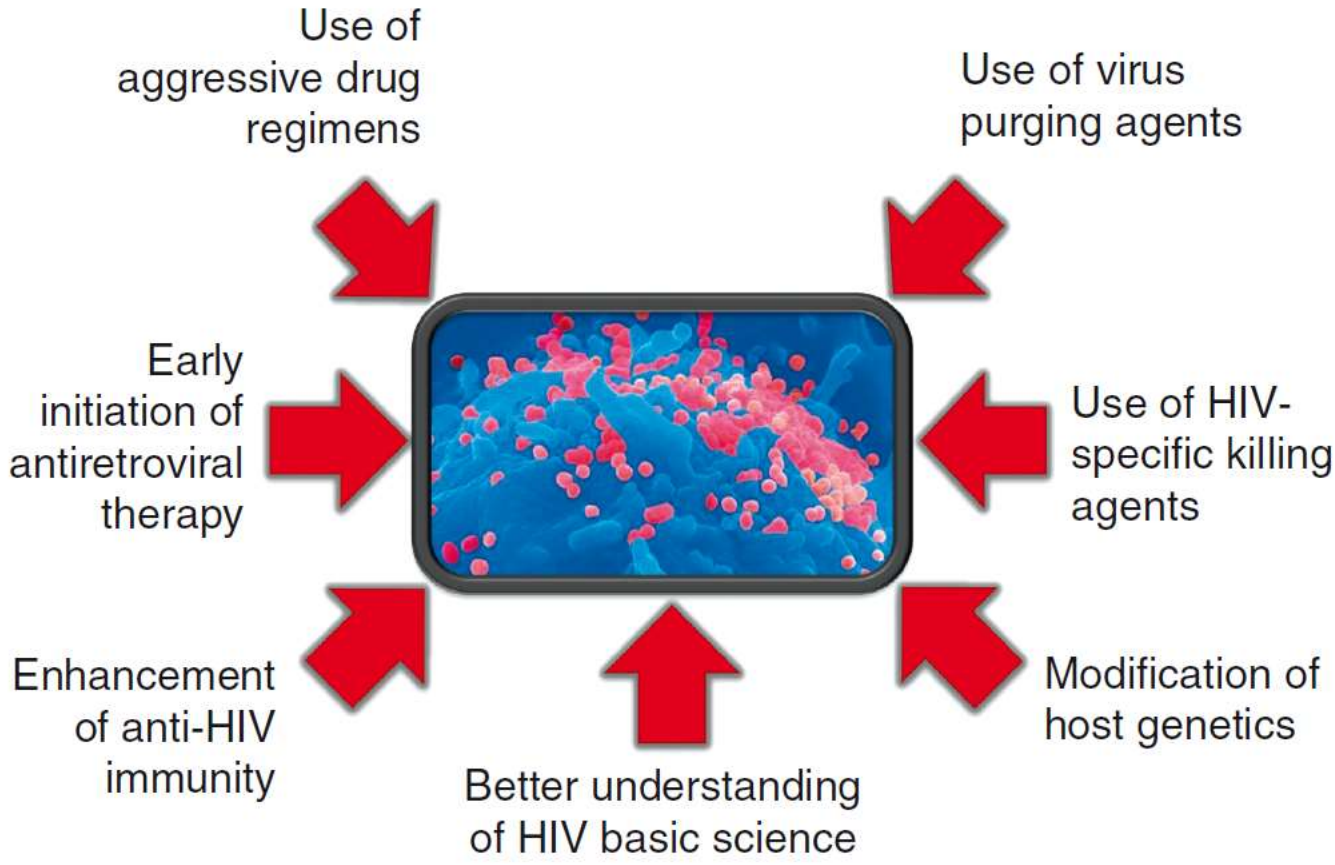
Células con infección latente: escasas y difíciles de detectar

Purgar los reservorios



- IL-7
- HDAC inhibition
  - Valproic acid
- Prostratin
- HMBA

Estrategias para erradicar el virus en los pacientes con TAR



Chun TW & Fauci AS. AIDS 2012

Qué tipo de curación queremos

Curación	Remisión
Modelo enfermedad infecciosa	Modelo oncológico
Eliminación total del VIH	Vida saludable sin TARV
HIV RNA < 1 cop/ml	HIV RNA < 50 cop/ml
Esterilizante	Curación funcional

Infección VIH ¿Podremos curarla?

"... hay que ser muy imaginativos y tener la valentía de atreverse a hacer realidad lo imaginado".

(Sobre una idea de Jonas Salk)

…y gracias por vuestra atención