XIV Jornada de Actualización en infección por VIH

Revisión CROI
Conference on Retroviruses and Opportunistic Infections

AVANCES EN LA CURA DEL VIH

Pepe Alcamí
Instituto de Salud Carlos III
Coordinador de la Red de Investigación en SIDA

Con el Patrocinio científico de : GeSIDA Grupo de Estudio del SIDA-SEIMC

Con la Colaboración de : ViiV Healthcare

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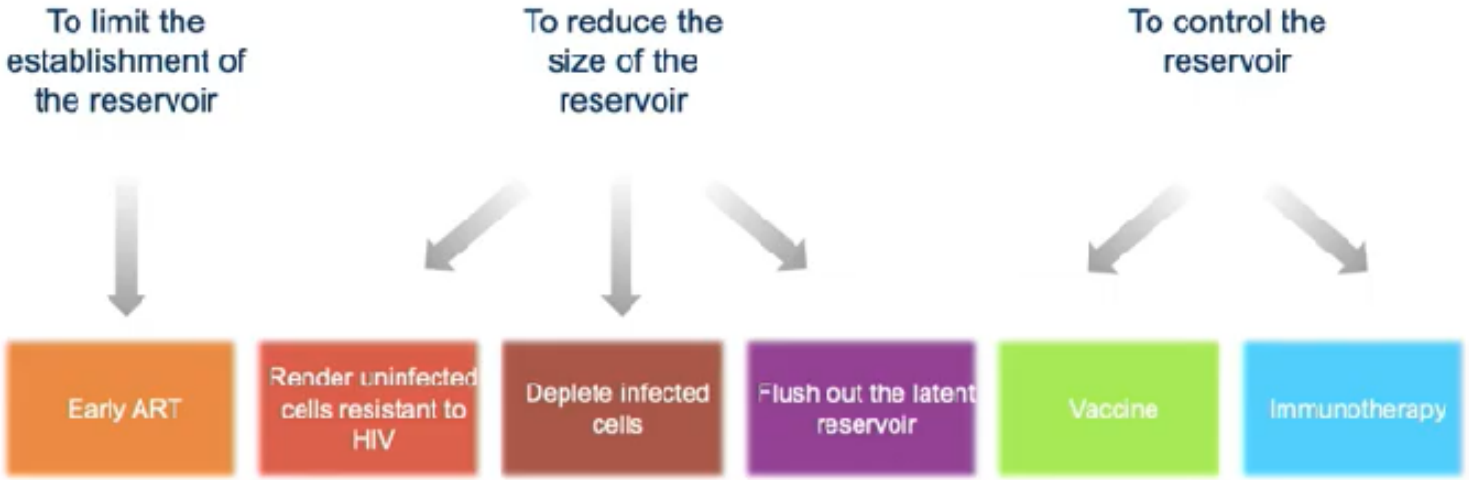
AVANCES EN LA CURA DEL VIH

ADVANCES IN HIV CURE
Nicolas Chomont, *Univers*

- Why do we need a cure?
- What are viral reservoirs?
- How to measure reservoirs?
- What are the strategies to cure HIV?



Chomont N. Advances in HIV Cure. CROI 2020 #W-01

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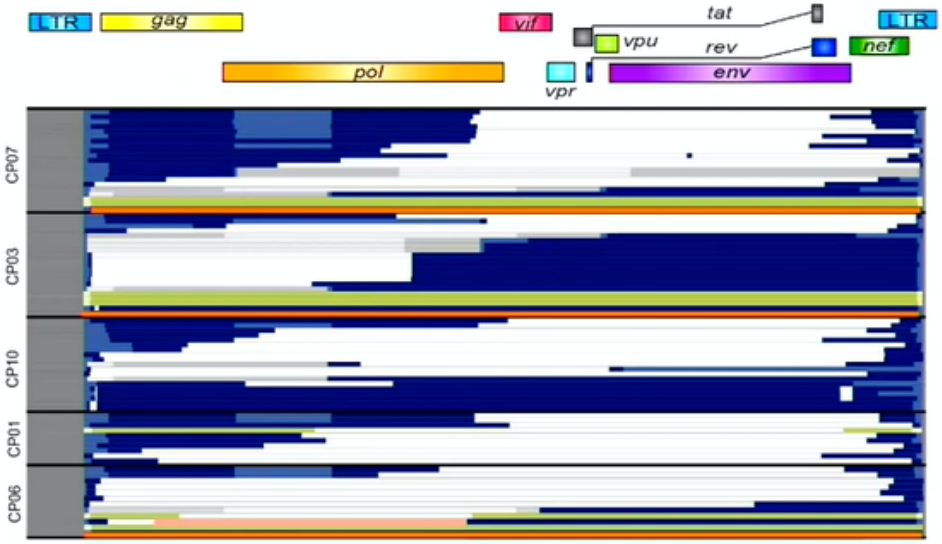
AVANCES EN LA CURA DEL VIH

CONCEPTS IN RESERVOIR MEASUREMENTS

Janet M. Siliciano, *The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

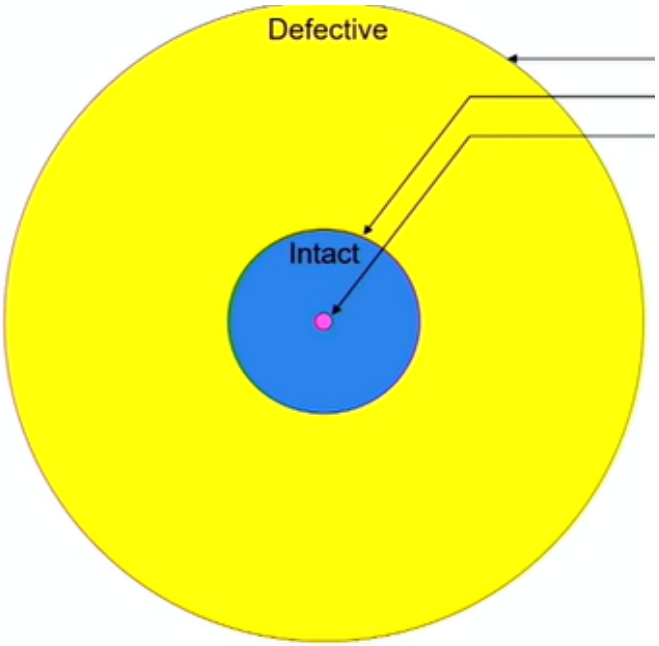
Cuantificación de virus completos

Most HIV proviruses are defective



Ho et al, **Cell**, 2013
Bruner et al, **Nature Med** 2016

Discovery of intact non-induced proviruses



Assay	Frequency (per 10^6)
gag PCR	1000 – 10,000
nFLS	100
QVOA	1

Siliciano J. Concepts in reservoir measurement. CROI 2020 #W-02

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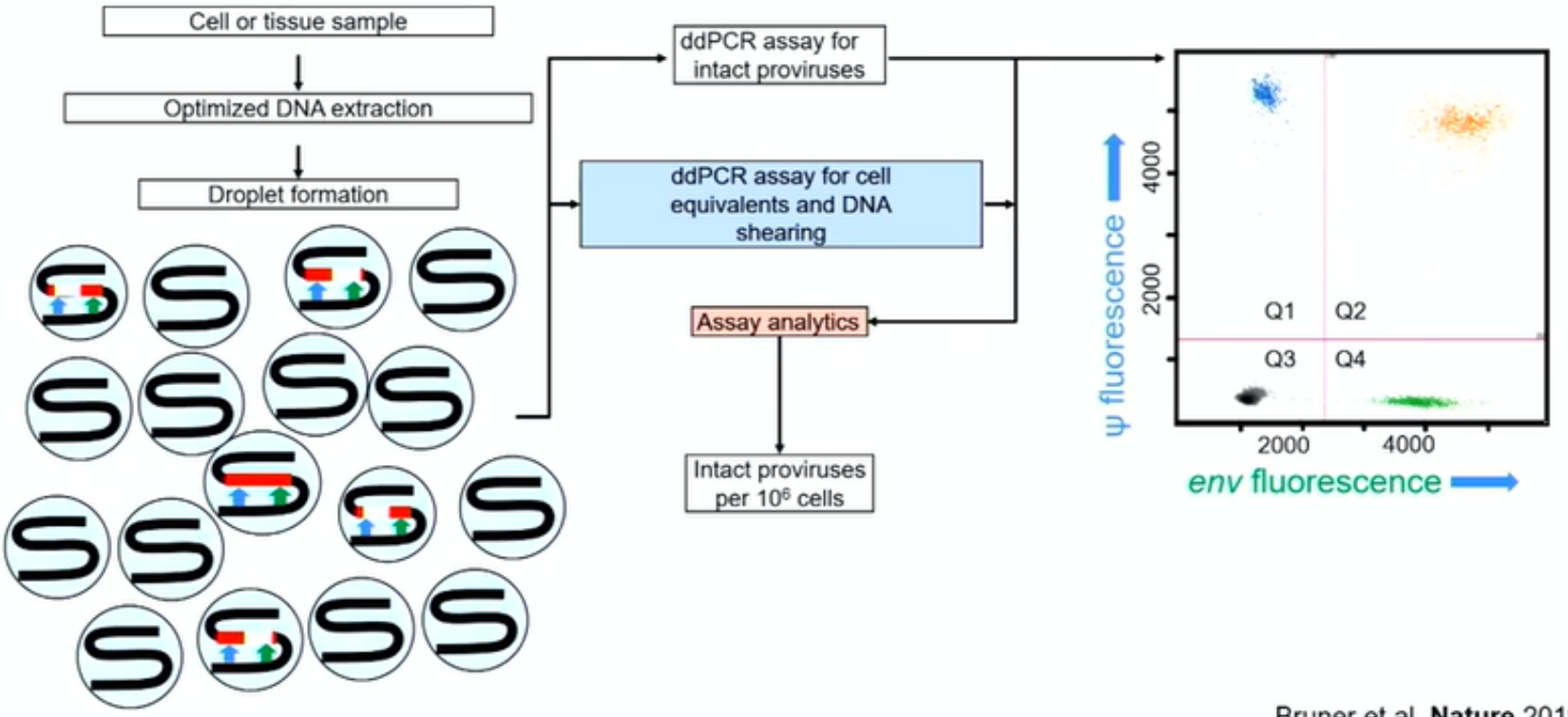
AVANCES EN LA CURA DEL VIH

CONCEPTS IN RESERVOIR MEASUREMENTS

Janet M. Siliciano, *The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Intact proviral DNA assay



Bruner et al, **Nature** 2019

Siliciano J. Concepts in reservoir measurement. CROI 2020 #W-02

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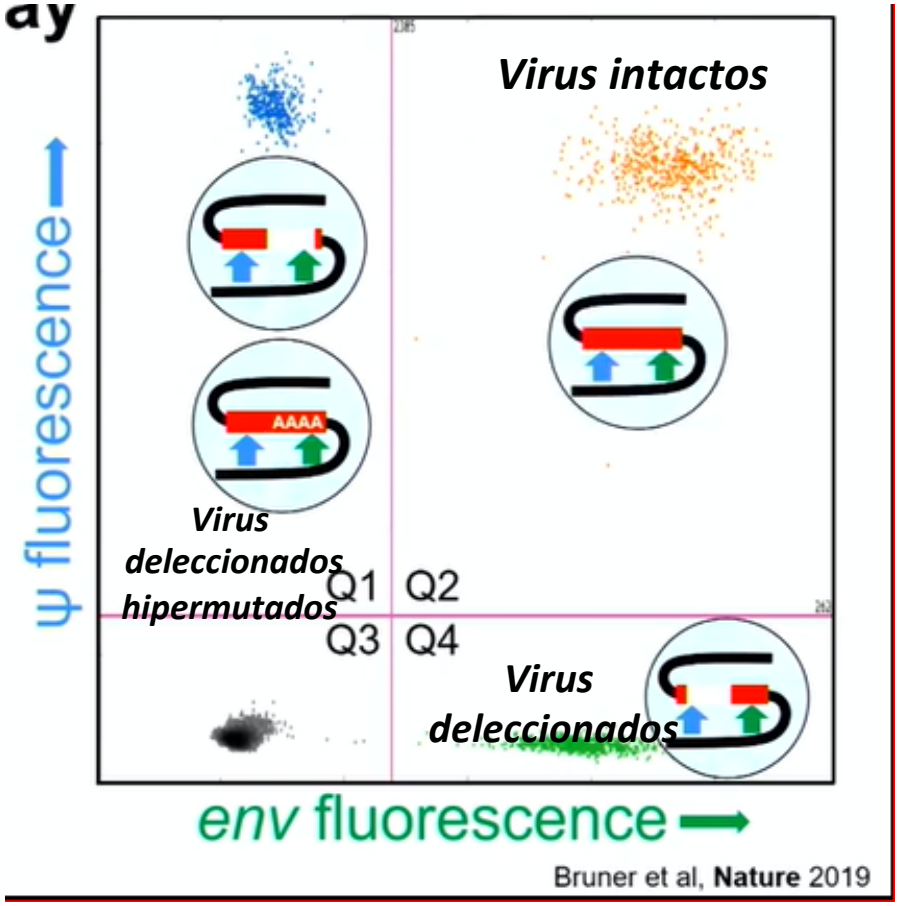
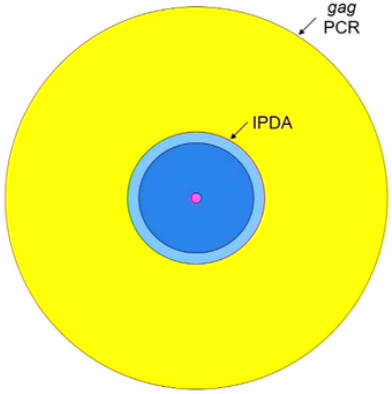
Intact Proviral DNA Assay (IPDA)

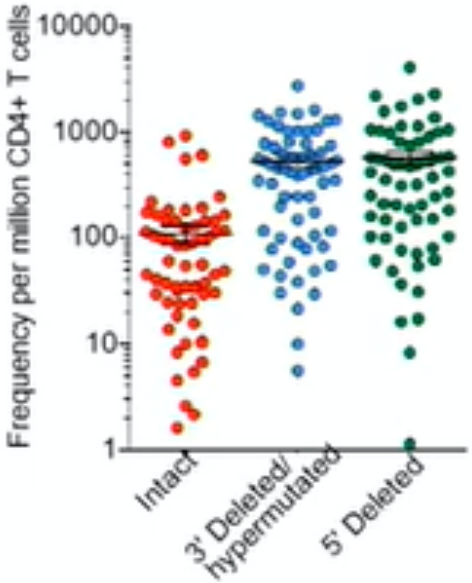


CONCEPTS IN RESERVOIR MEASUREMENTS

Janet M. Siliciano, *The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

IPDA as a replacement for proviral DNA PCR





Siliciano J. Concepts in reservoir measurement. CROI 2020 #W-02

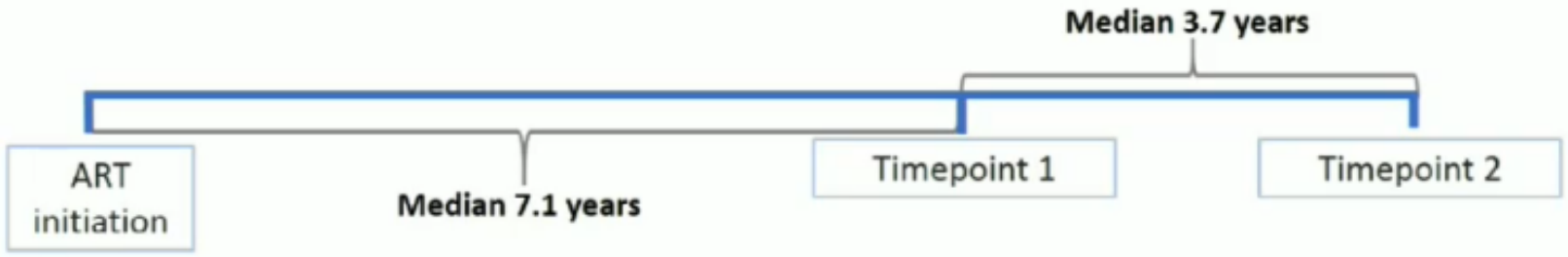
AVANCES EN LA CURA DEL VIH

INTACT PROVIRAL DNA LEVELS DECLINE IN PEOPLE WITH HIV ON ANTIRETROVIRAL THERAPY

Rajesh T. Gandhi, Joshua C. Cyktor, Ronald Bosch, Hanna Mar, Gregory Laird, Albine Martin, Ann Collier, Sharon Riddler, Bernard J. Macatangay, Charles Rinaldo, Joseph J. Eron, Robert Siliciano, Deborah McMahon, John W. Mellors, for the ACTG A5321 team

ACTG HIV Reservoir Cohort (AHRC; ACTG A5321)

- Participants with chronic HIV who initiated ART in ACTG trials and who had well-documented and sustained virologic suppression
- 50 participants from this cohort underwent testing

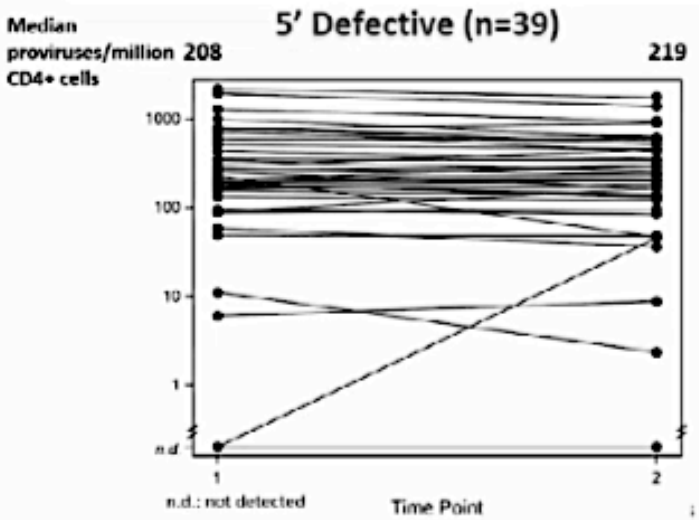


Longitudinal analysis excluded:
N=2: no intact proviruses detected by IPDA at either timepoint;
N=2: exclusionary medications.

RT Gandhi J. CROI 2020 #75

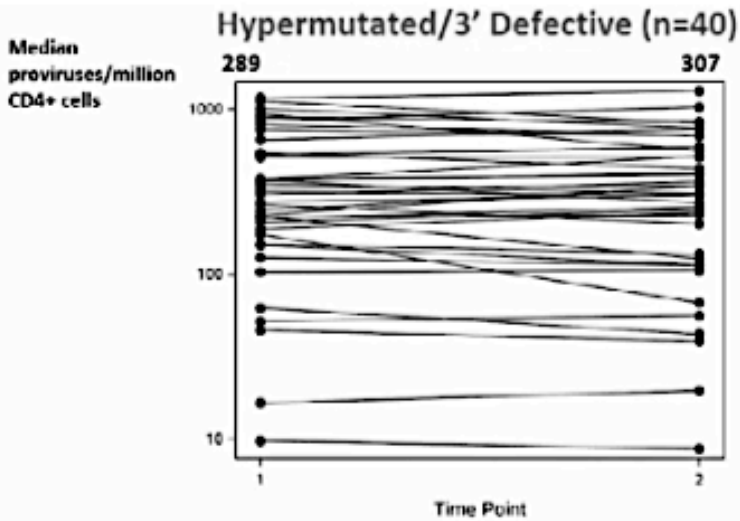
AVANCES EN LA CURA DEL VIH

Defective Proviruses Do Not Decrease In Participants On ART



$T_{1/2}$: 22 y (95% CI 11 y to infinity)

Change (log10) Between Entry and Year 4	Median (-0.014) Decreased 23 (59%) Increased 16 (41%)



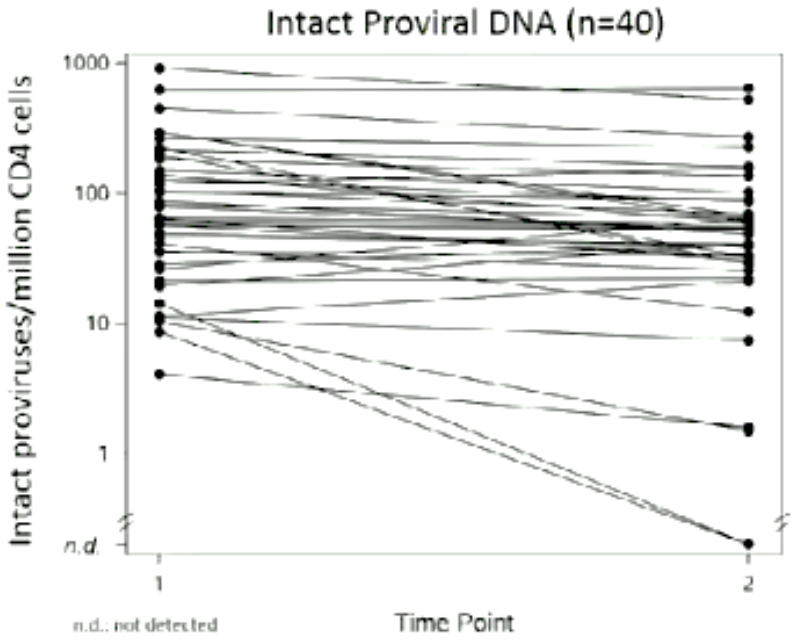
Change (log10) Between Entry and Year 4	Median (0.001) Decreased 20 (50%) Increased 20 (50%)

Total Proviral DNA (Intact + Defective) Median Half-life: 30 yr (95% CI 12 to 61 yr)

RT Gandhi J. CROI 2020 #75

Intact Proviruses Decrease In Participants On ART

- Median intact proviral DNA:
  - Timepoint 1: **65/million CD4 cells**
  - Timepoint 2: **53/million CD4 cells**
- Between timepoint 1 and 2, 83% of participants had decrease in intact proviral DNA levels; 17% had increase
- Median half-life: 7.1 y (95% CI 4.7 to 18 y)
- No evidence that decay differed by age, sex, pre- or on-ART measurements of inflammation, activation



Timepoint 1: median 7.1 yr after ART initiation
Timepoint 2: approximately 4 yr after Timepoint 1

Siliciano J. Concepts in reservoir measurement. CROI 2020 #W-02

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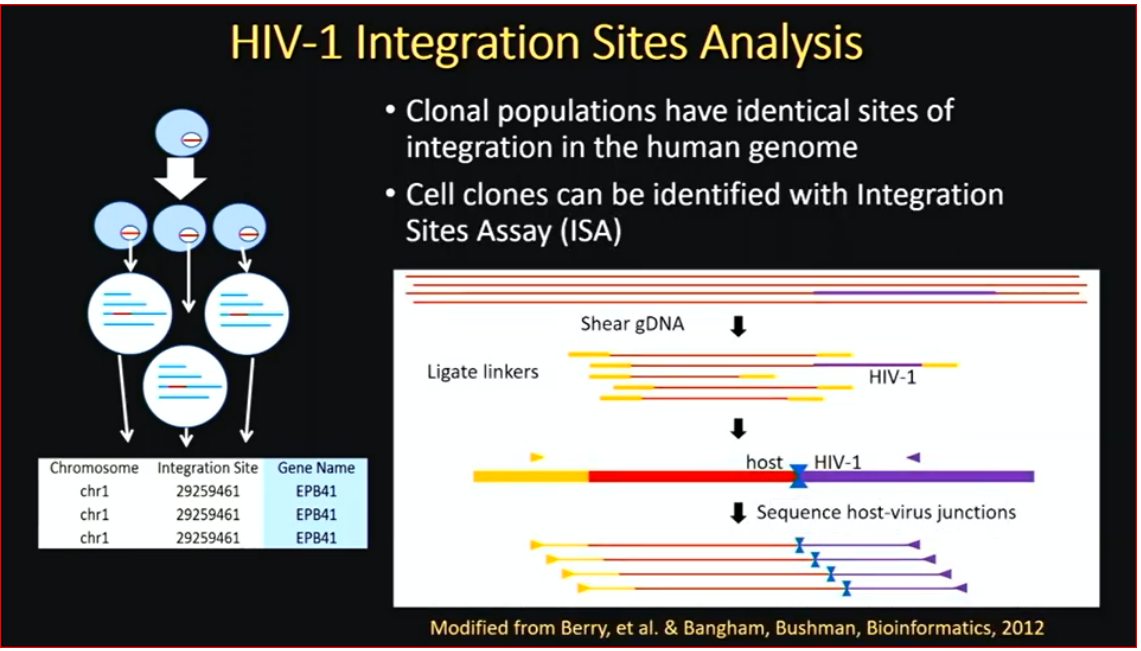
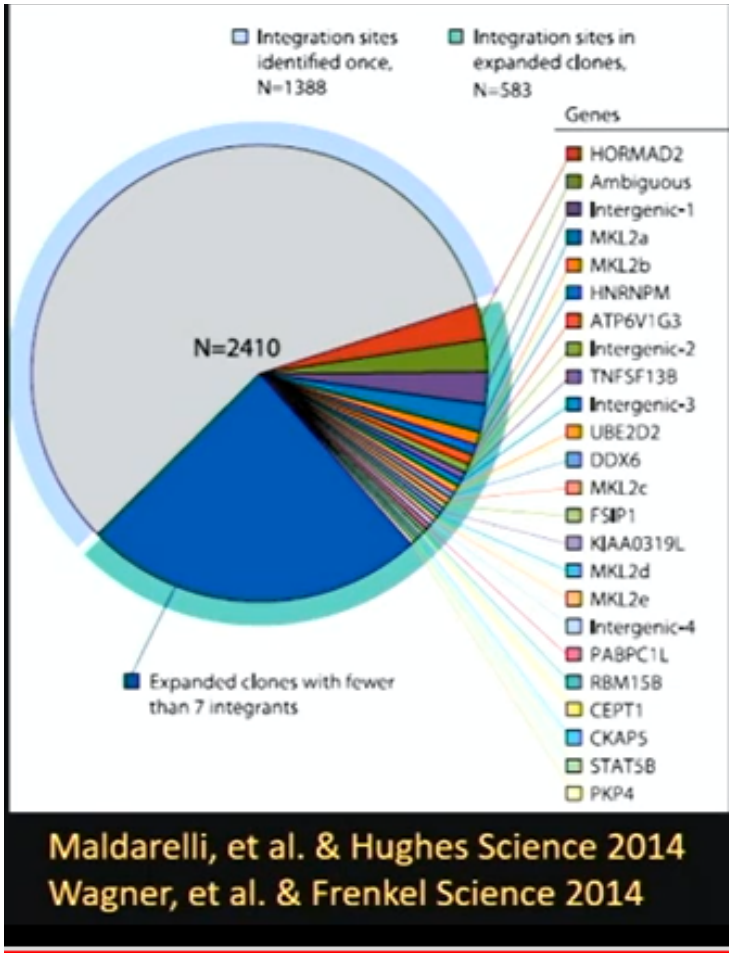
Expansión clonal y determinación de los sitios de integración

CHARTING GENOME-WIDE INTEGRATION
Mary F. Kearney, *National Cancer Institute, Frederick,*





Kearne M. Charting Genome Wide integration. CROI 2020 #W-02

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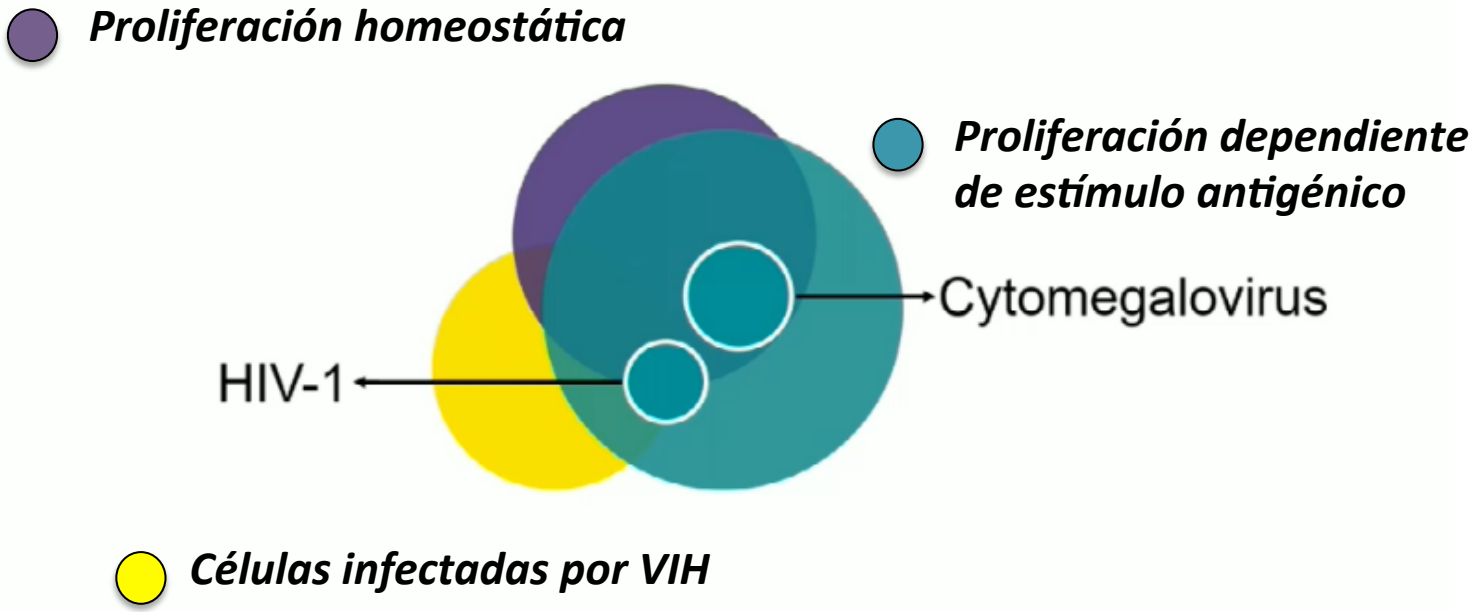
ANTIGEN-DRIVEN CLONAL SELECTION SHAPES THE FATE OF HIV-INFECTED CD4+ T CELLS IN VIVO

Francesco R. Simonetti, Hao Zhang, Garshasb Soroosh, Subul A. Beg, Jiayi Duan, Kyle Rhodehouse, Christopher L. Nobles, Jun Lai, Rebecca Hoh, Steven G. Deeks, Frederic Bushman, Janet Siliciano, Robert Siliciano

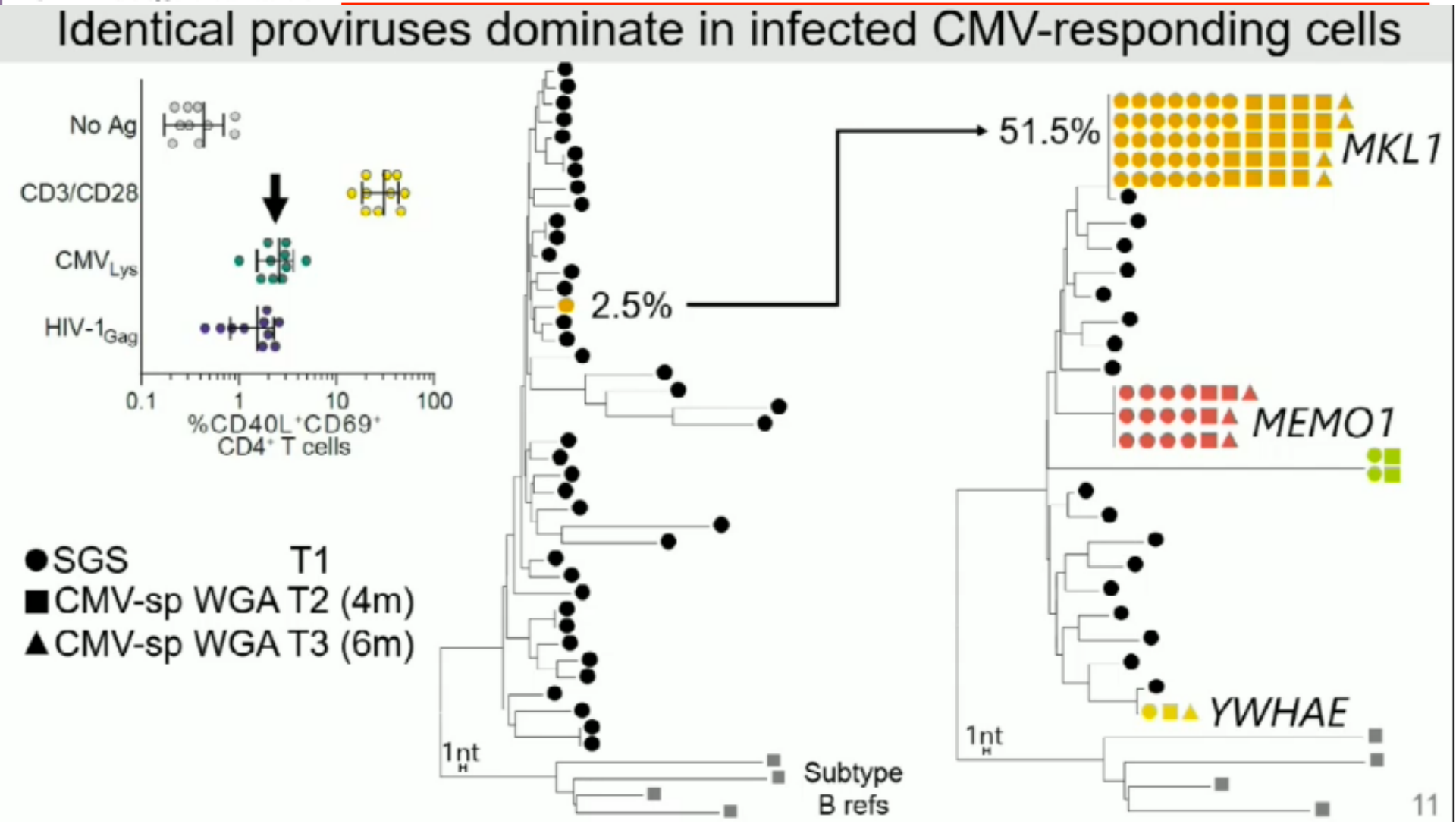
Proliferation of HIV-infected T cells contributes to HIV persistence



4

F Simonetti. CROI 2020 #73

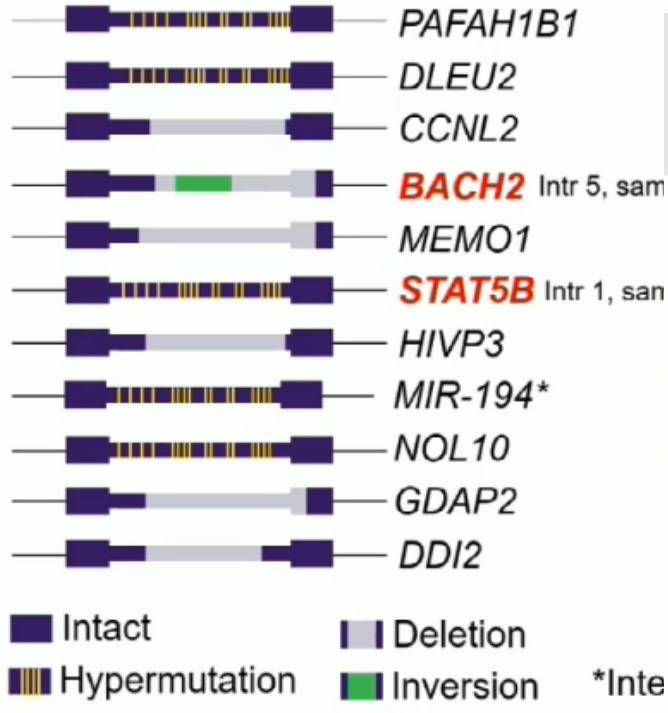
AVANCES EN LA CURA DEL VIH



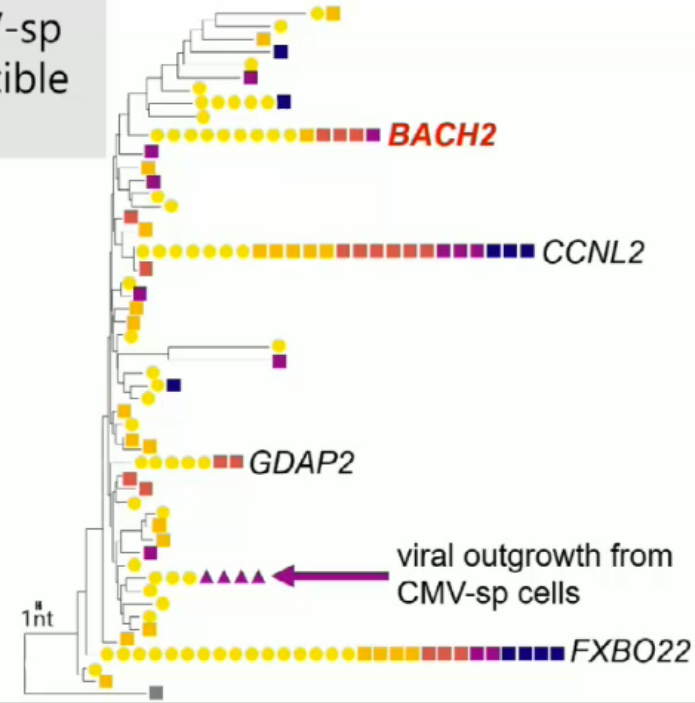
F Simonetti. CROI 2020 #73

AVANCES EN LA CURA DEL VIH

Most proviruses from CMV-responding clones are defective



Identification of a CMV-sp clone carrying an inducible infectious provirus



F Simonetti. CROI 2020 #73

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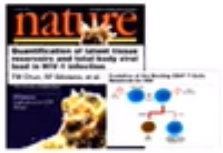
AVANCES EN LA CURA DEL VIH

17 8:30 **HIV CURE FROM BENCH TO BEDSIDE**

Sharon R. Lewin, *University of Melbourne, Melbourne, VIC, Australia*

A short history of HIV cure research: from cure to remission to cure again



HIV latency identified

1997

2009

The Berlin patient

VISCONTI
SPARTAC
CHAMP

Post treatment control (remission)

2010

2013

Case reports of delayed viral rebound

Mississippi baby
Boston patients
San Francisco patient

nature

The London patient

2019

2020

- Latency is far more complex
- Combination approaches will be needed
- The why and who needs a cure for HIV is changing

Lewin S. HIV Cure from bench to bedside. CROI 2020 #17

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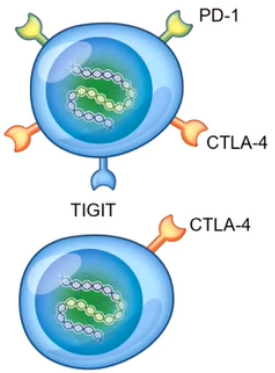
AVANCES EN LA CURA DEL VIH

Immunomodulatory LRAs: immune checkpoint blockers



- Latent virus is enriched in cells that express PD-1 and other immune checkpoint markers (CTLA-4, TIGIT)[1-3]
- In vitro and in vivo anti-PD-1 reverses HIV latency and greater effect with anti-CTLA-4[4,5,6]
- Anti-PD-1 increases HIV/SIV-specific T-cell function and can lead to enhanced viral control in macaques[7]
- Significant challenges in using these agents in PLWH given immune related toxicity [8,9]

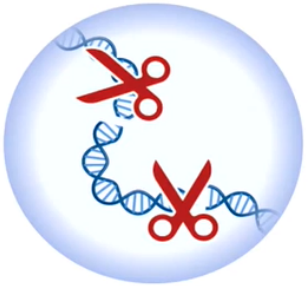
1 Chomont et al., Nat Med 2009; 2 Fromentin et al Plos Path 2016; 3 McGarry et al., Immunity 2017; 4 Fromentin et al., Nature Comms 2019; 5 Uldrick CROI 2019, Seattle, WA; 6 Van der Sluis et al., J Immunol 2020; 7 Velu et al., Nature 2006; 8 Gay et al J Infect Dis 2017; 9 https://actgnetwork.org/; Rasmussen et al CROI 2020 **abs 37**; Lau et al CROI 2020 **abs 334** ; Okoye et al., CROI 2020 **abs 117**

Latency reversing agents (LRA): can 'shock' but not 'kill'

- Need for **more potent** and **less toxic** LRAs
- Need to get the 'kill' into shock and kill: **pro-apoptotic drugs**[1]
- Immune modulating latency reversing agents such as **toll like receptor (TLR) agonists** or **anti-PD1** have dual activity of targeting the virus and immune system[2]

1 Kim, Anderson and Lewin, Cell Host Microbe 2018; 2 Zerbato et al., Curr Op Virol 2019

Gene therapy: targets and strategies



Attack: enhance anti-HIV immune responses

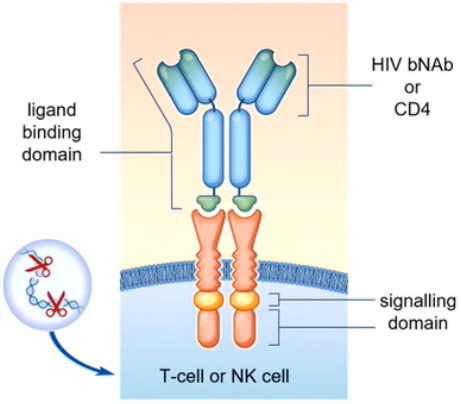
Protect: engineer uninfected cells to be resistant to HIV

Purge: directly eliminate the virus itself

Delivery of gene therapy a major challenge :
ex vivo (gene editing of cells outside the body) or **in vivo** (gene editing in the body)

Slide courtesy of Paula Cannon

Chimeric antigen receptor (CAR)-T cells



- Autologous T-cells or NK cells undergo gene editing to express a CAR to bind and kill cells that express HIV envelope [1-4]
- CAR T-cells for HIV tested in mice, macaque models and in clinical trials in China (x3) and the US (x1)[5]
- Major challenges include toxicity (potentially preventable), delivery to tissue sites and low expression of HIV envelope on ART

1 Deeks et al., Mol Ther 2002; 2 Sung et al., Mol Ther 2018; 3 Herzig et al., Cell 2019; 4 Anthony-Gonda Sci Transl Med 2019; 5 clinical trials.gov

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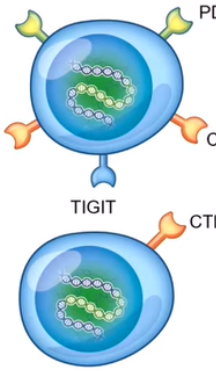
AVANCES EN LA CURA DEL VIH

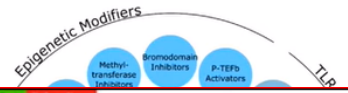
Immunomodulatory LRAs: immune checkpoint blockers



- Latent virus is enriched in cells that express PD-1 and other immune checkpoint markers

1 Chomont et al., Nat Med 2009; 2 Fromentin et al Plos
Uldrick CROI 2019, Seattle, WA; 6 Van der Sluis et
https://actgnetwork.org/; Rasmussen et al CROI 2020 **abs**

Latency reversing agents (LRA): can 'shock' but not 'kill'



- Need for **more potent** and **less toxic** LRAs

eed to get the 'kill' into
hock and kill: **pro-apoptotic**
rugs[1]

mmune modulating latency
eversing agents such as **toll**
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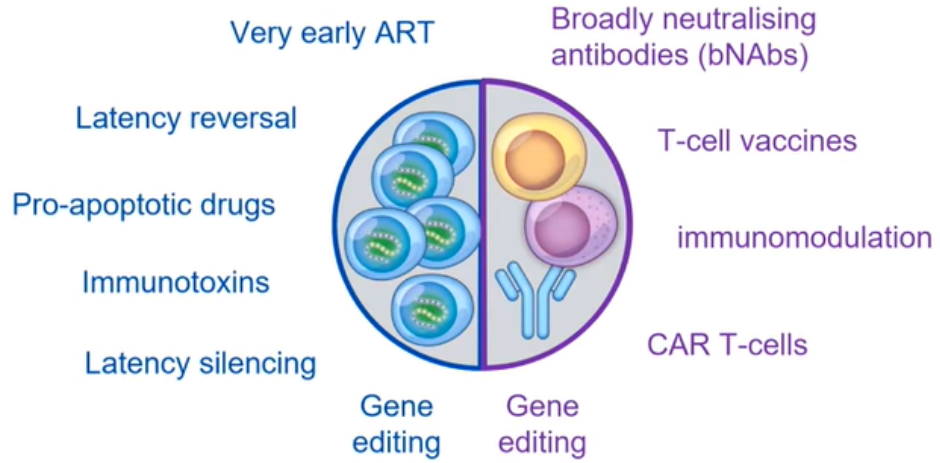
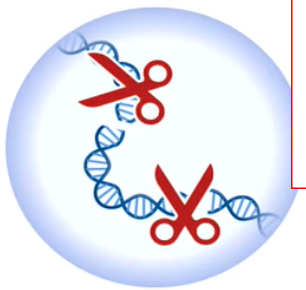
r anti-PD1 have dual activity
f targeting the virus and
mmune system[2]

lost Microbe 2018; 2 Zerbato et al., Curr Op Virol 2019

Combination immunotherapy



Gene therapy: targets



Purge: directly eliminate the virus itself

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Slide courtesy of Paula Cannon

cells

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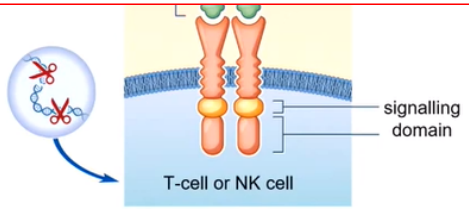

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Lewin S. HIV Cure from bench to bedside. CROI 2020 #17

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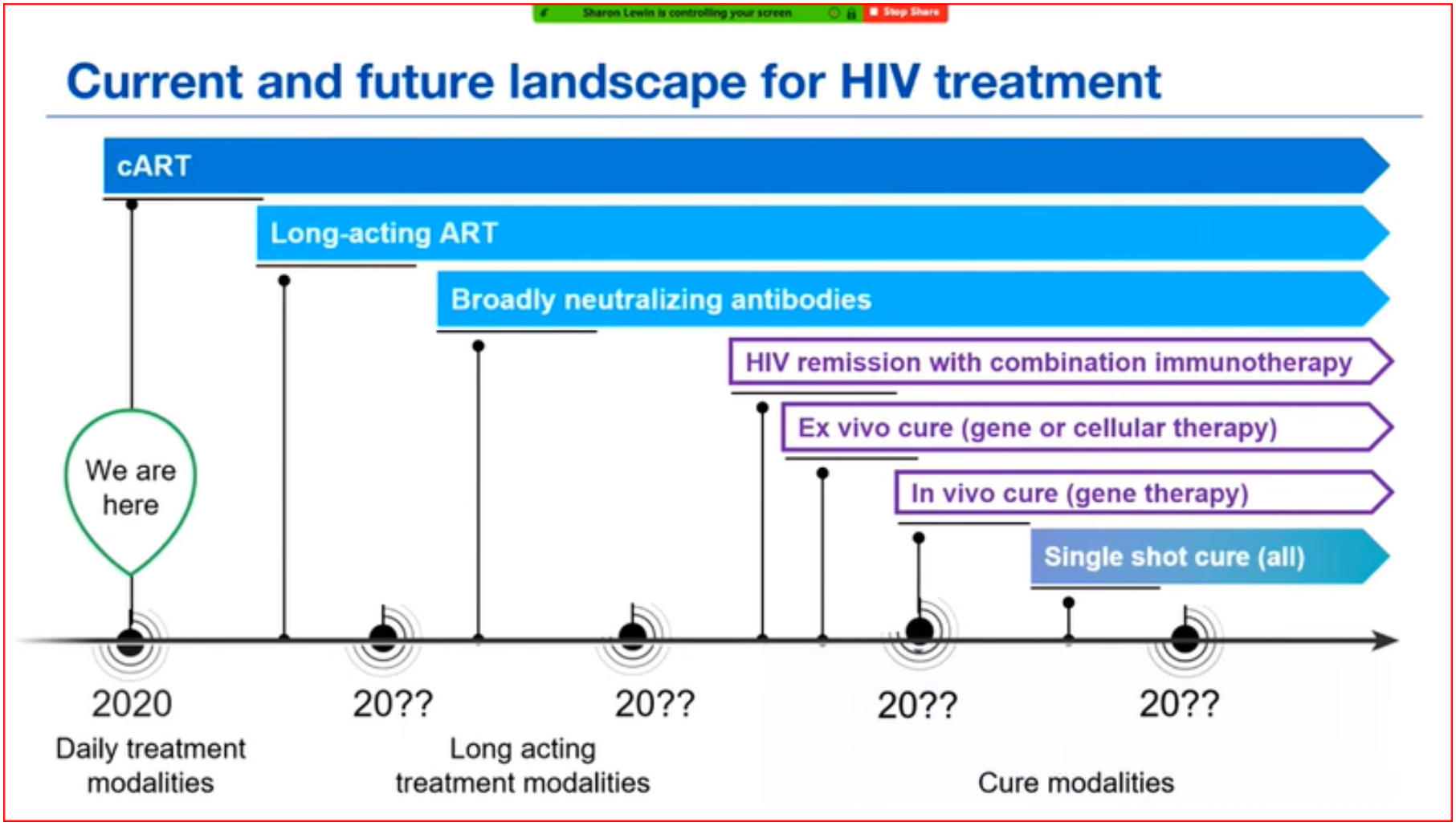

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AVANCES EN LA CURA DEL VIH

Oral Abstract O-03 THERAPEUTIC INTERVENTIONS FOR HIV TREATMENT AND ERADICATION
Auditorium 10:00 AM - 12:00 PM

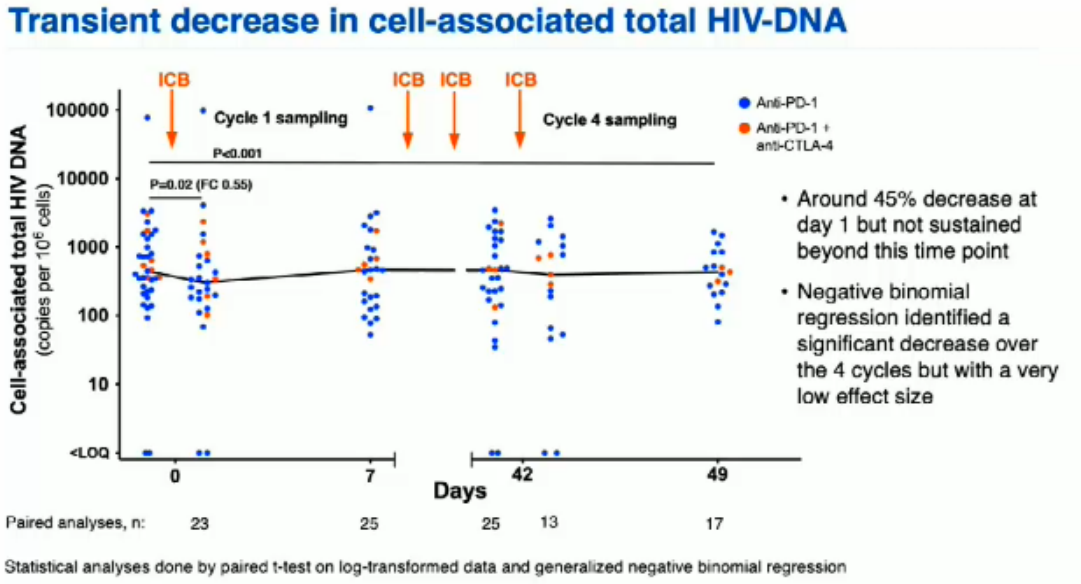
Oral Abstract Moderators
María J. Buzón, *Vall d'Hebrón Research Institute, Barcelona*
Aadia Rana, *University of Alabama, Birmingham, AL, USA*

37 *10:45* **IMPACT OF ANTI-PD-1 AND ANTI-CTLA-4 ON THE HIV RESERVOIR IN VIVO: THE AMC-095 STUDY**
Thomas A. Rasmussen, Laskhmi Rajdev, Ajantha Solomon, Ashanti Dantanarayana, Surekha Tennakoon, Socheata Chea, Rachel L. Rutishauser, Danielle Rigau, Shelly Lensing, Sonia Bakkour, Michael P. Busch, Dirk Dittmer, Steven G. Deeks, Christine Durand, Sharon R. Lewin

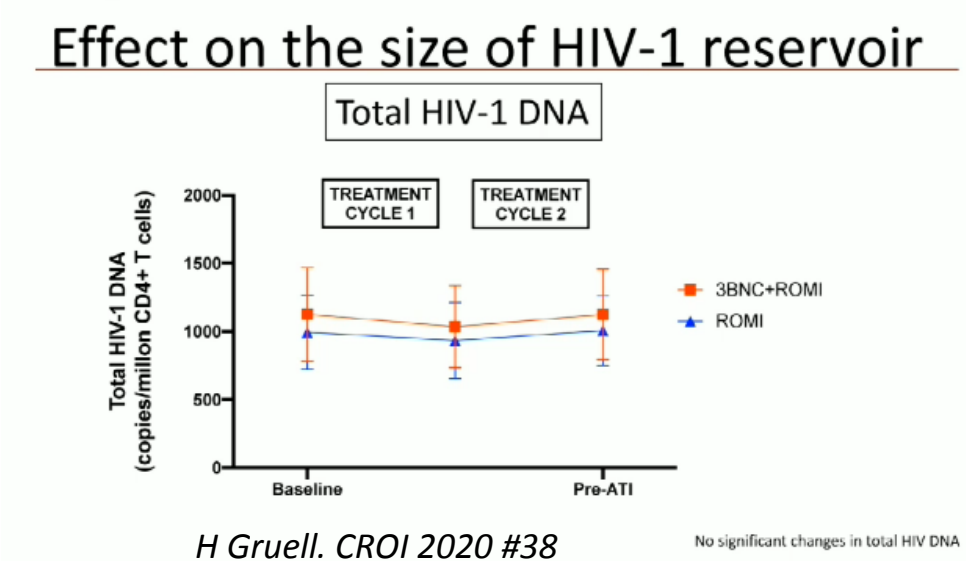
38 *11:00* **A RANDOMIZED TRIAL OF THE IMPACT OF 3BNC117 AND ROMIDEPSIN ON THE HIV-1 RESERVOIR**
Henning Gruell, Yehuda Z. Cohen, Jesper D. Gunst, Marie H. Pahus, Clara Lehmann, Katrina Millard, Martin Tolstrup, Julio C. Lorenzi, Michel Nussenzweig, Gerd Fätkenheuer, Florian Klein, Marina Caskey, **Ole S. Søgaard**

39 *11:15* **SAFETY & PHARMACOKINETICS OF GS-9722 IN HIV-NEGATIVE PARTICIPANTS AND PEOPLE WITH HIV**
Peter Ruane, Eric Daar, Kimberly Workowski, Rebecca Begley, Rita Humeniuk, Tariro Makadzange, Steve K. West, Hui Liu, Yizhao Li, John Ling, Luisa M. Stamm, Polina German, Joseph J. Eron, Princy N. Kumar, Edwin DeJesus

40 *11:30* **SAFETY AND ANALYTIC TREATMENT INTERRUPTION OUTCOMES OF VESATOLIMOD IN HIV CONTROLLERS**
Devi Sengupta, Moti Ramgopal, Cynthia Brinson, Edwin DeJesus, Anthony Mills, Peter Shalit, Scott McCallister, Hiba Graham, Heena Patel, Lijie Zhong, Joseph Hesselgesser, Brian Doehle, Susan Guo, Diana Brainard, Steven G. Deeks

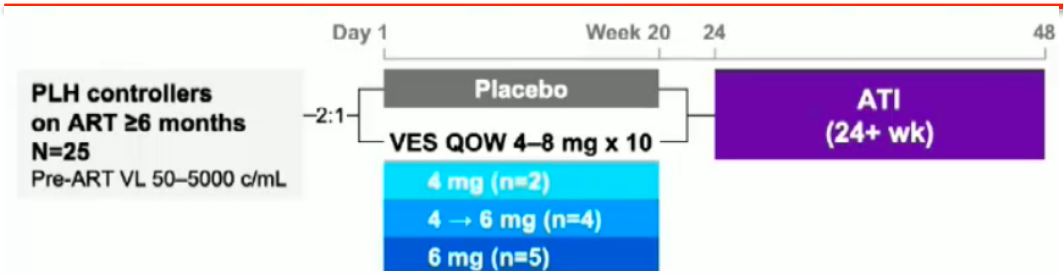


TA Rasmussen. CROI 2020 #37

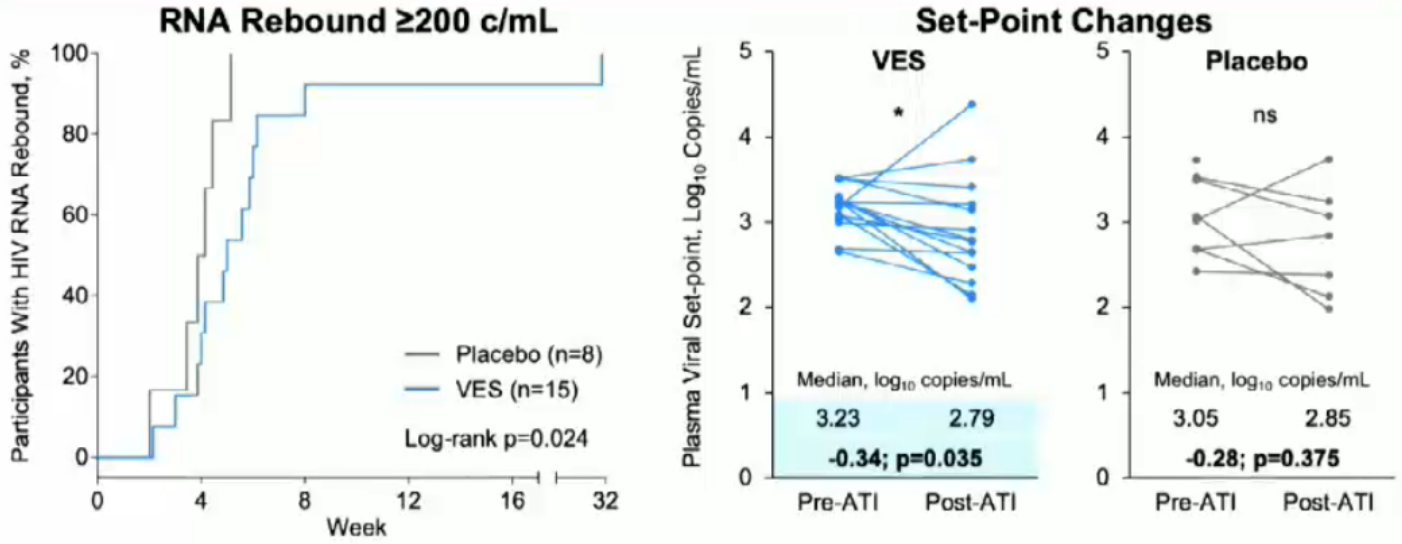


H Gruell. CROI 2020 #38

Safety & Analytic Treatment Interruption Outcomes of Vesatolimod in HIV Controllers



ATI Results by Group



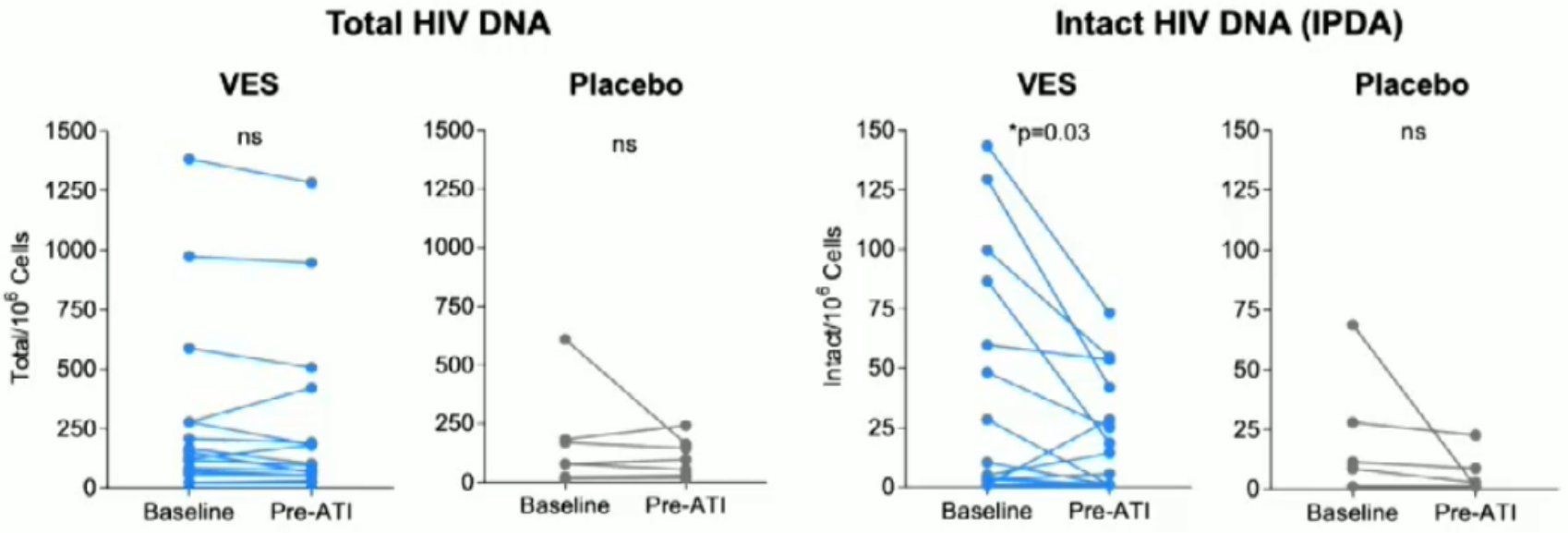
- Median time to ART restart: VES 47 wk, Placebo 28 wk
- Participant with longest time to rebound (31 wk) received 6 mg VES
  - Maintained low viral loads <200 c/mL x 48 wk; ~1 $\log_{10}$ decrease in set-point

Time to virologic rebound = wk from start of ATI to two consecutive HIV-1 RNA ≥200 c/mL; plasma viral set-point following ATI calculated as the geometric mean of all HIV-1 RNA measurements between start date and end date; start date and end date were determined by blinded clinical data review of each participant profile.

D Sengupta. CROI 2020 #40

Safety & Analytic Treatment Interruption Outcomes of Vesatolimod in HIV Controllers

Changes in HIV DNA



- No consistent impact on total DNA
- IPDA (designed to assess replication-competent reservoir) decreased in VES group

Accelevir Diagnostics; IPDA, intact proviral DNA assay.

D Sengupta. CROI 2020 #40

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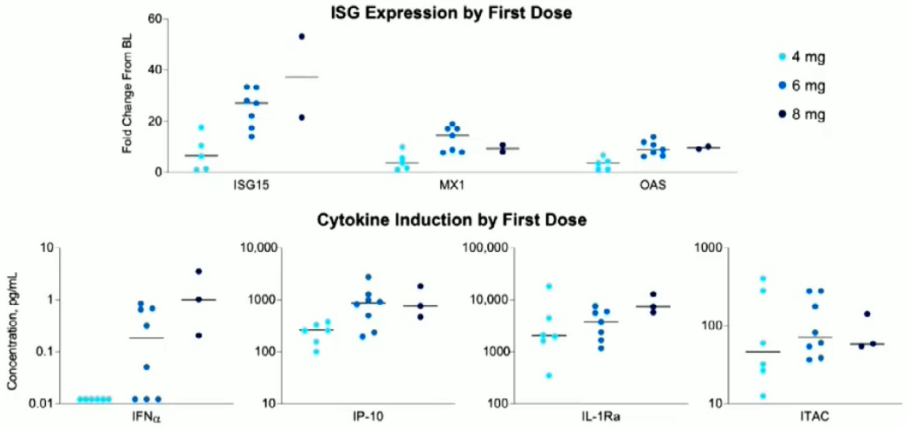
Conference on Retroviruses and Opportunistic Infections

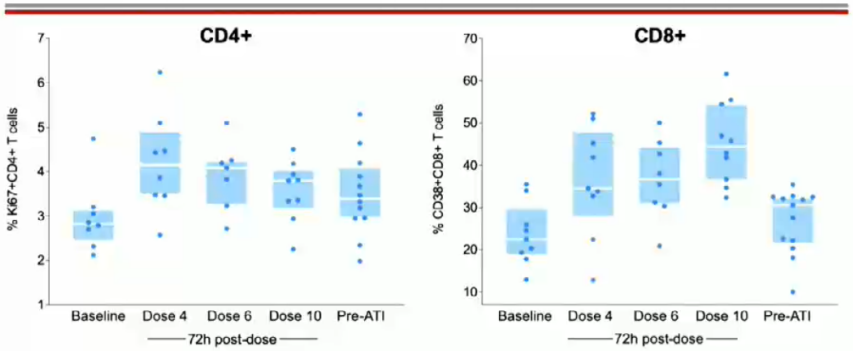
Safety & Analytic Treatment Interruption Outcomes of Vesatolimod in HIV Controllers

Vesatolimod Induces ISG & Cytokines in a Dose-dependent Manner



ISG, interferon-stimulated gene; IL-1Ra, interleukin-1 receptor antagonist; IP-10, IFNγ-induced protein 10; ITAC, IFN-induced T-cell alpha chemoattractant; MX1, IFN-induced guanosine triphosphate-binding protein Mx1; OAS, oligoadenylate synthetase.

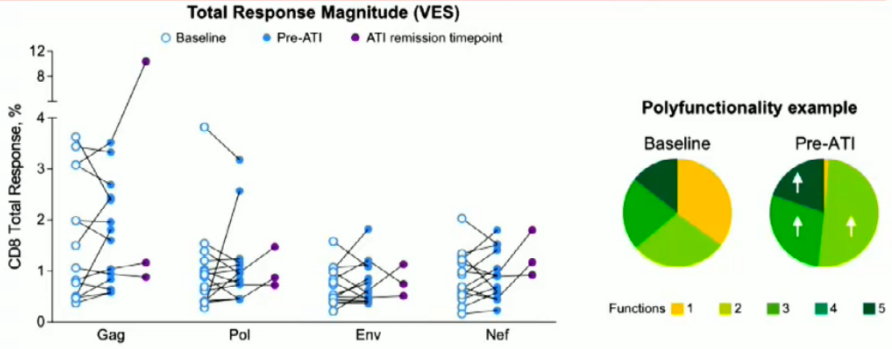
Vesatolimod Increases CD4+ and CD8+ T Cell Activation



- CD4 and CD8 transitional and effector memory subsets had the largest post-dose increase in activation
- Participants with delayed rebound had higher activation in CD8+ TM, EM, and TEMRA

UCSF Core Immunology Lab. Immune cell phenotyping by flow cytometry. EM, effector memory; TEMRA, CD45RA+ EM; TM, transitional memory.

HIV-specific CD8+ Responses by Intra-cellular Cytokine Staining



- Cytokines tested: IFNγ, TNFα, CD107a, MIP-1β, IL-2, IL-17

UC Davis Shacklett lab; MIP-1β, macrophage inflammatory protein-1β; TNFα, tumor necrosis factor α.

Conclusions

In HIV controllers, compared to placebo, multiple VES doses up to 8 mg:

- Were well-tolerated
- Did not impact total HIV DNA, but were associated with decreases in intact DNA, as estimated by the IPDA
- Modestly increased time to viral rebound after ATI and decreased viral set point compared to pre-ART
- These effects are potentially due to an augmented antiviral immune response
  - Induced ISG expression, cytokines
  - Activated immune cells
  - Increased polyfunctional HIV-specific CD8+ responses in a subset of participants

Trials evaluating the efficacy of VES in combination with other agents such as CD8-inducing vaccines and monoclonal antibodies are warranted

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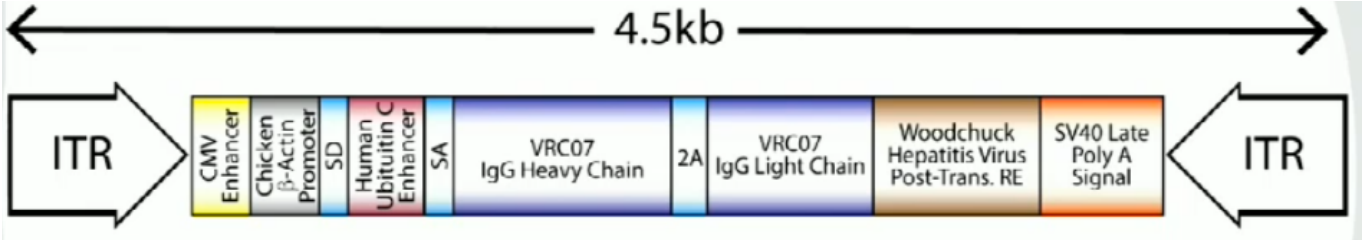
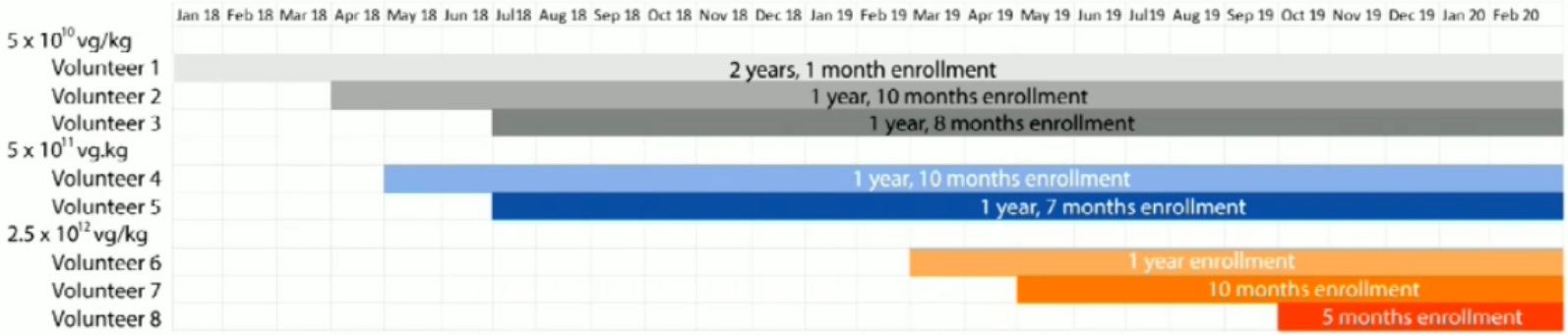
AVANCES EN LA CURA DEL VIH

DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV8-MEDIATED GENE TRANSFER



VRC 603 Enrollment



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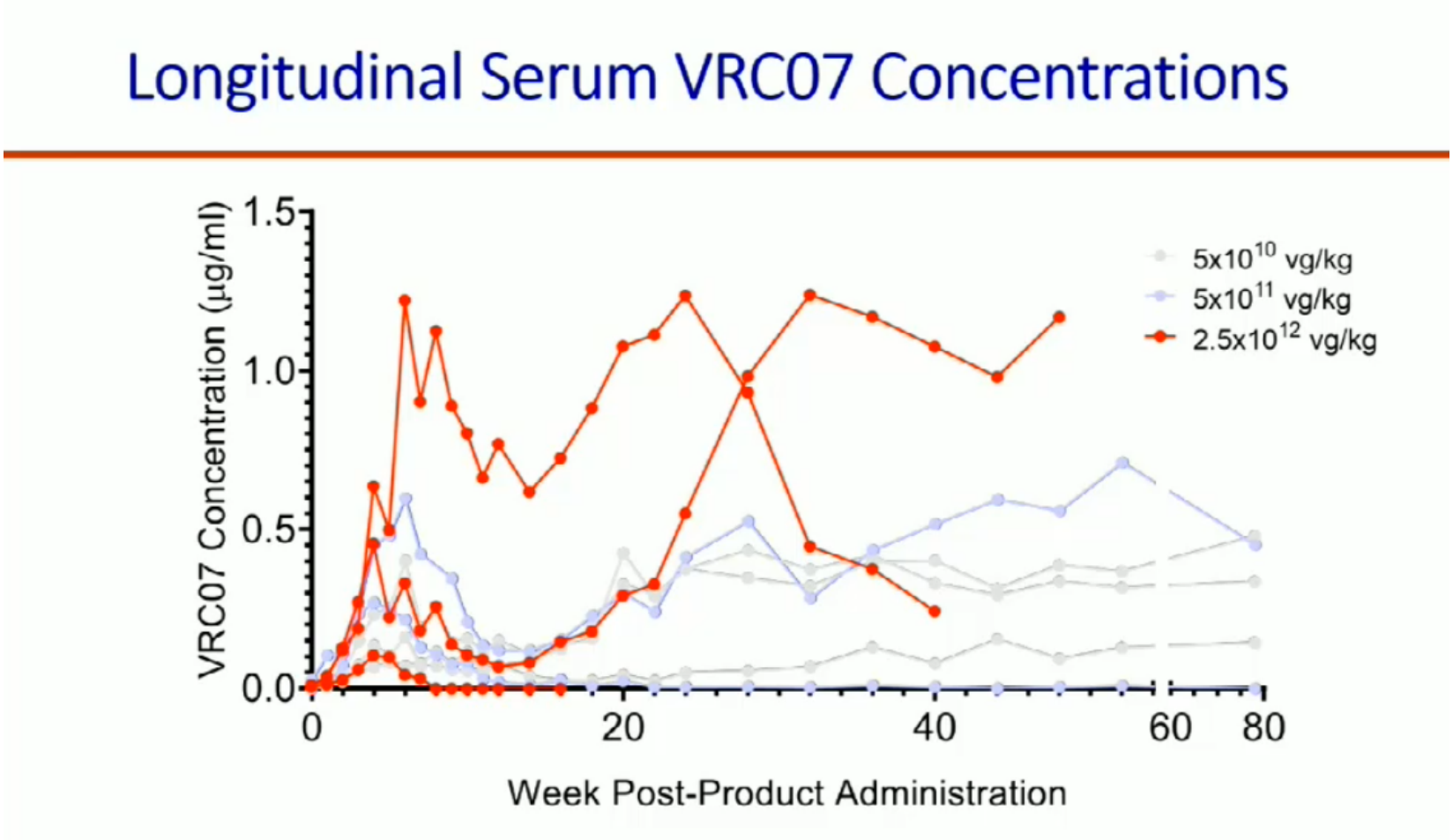
AVANCES EN LA CURA DEL VIH

DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV8-MEDIATED GENE TRANSFER



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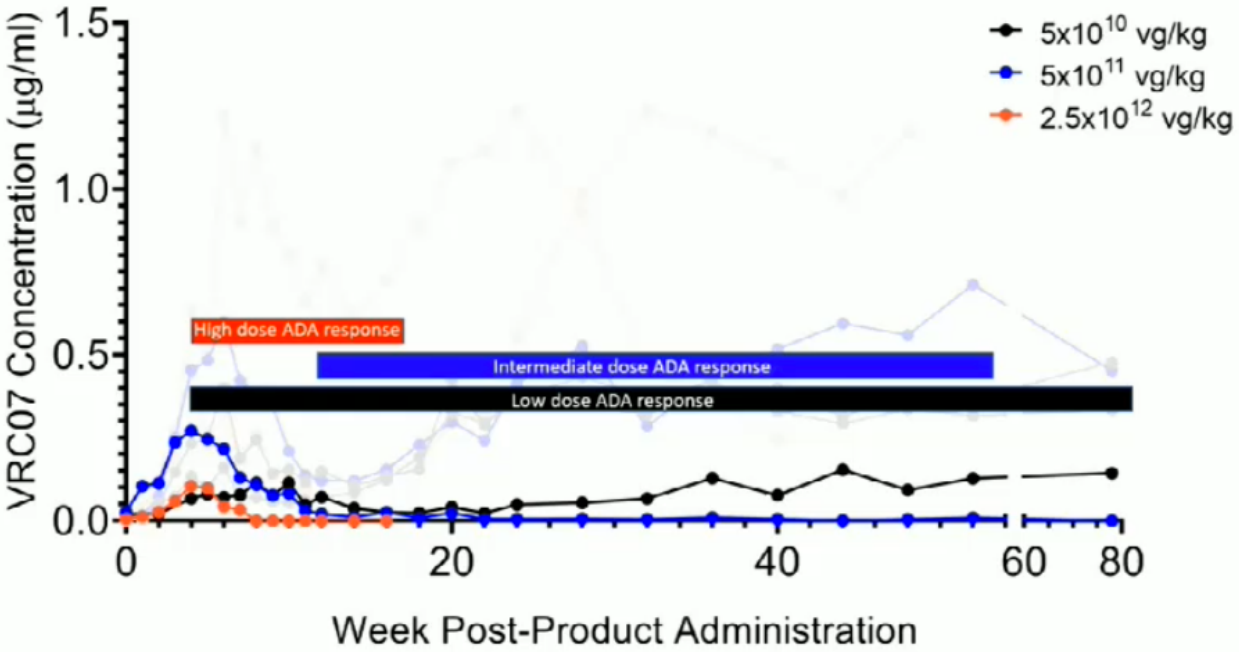
DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV8-MEDIATED GENE TRANSFER

Three Volunteers Developed ADA Responses to VRC07



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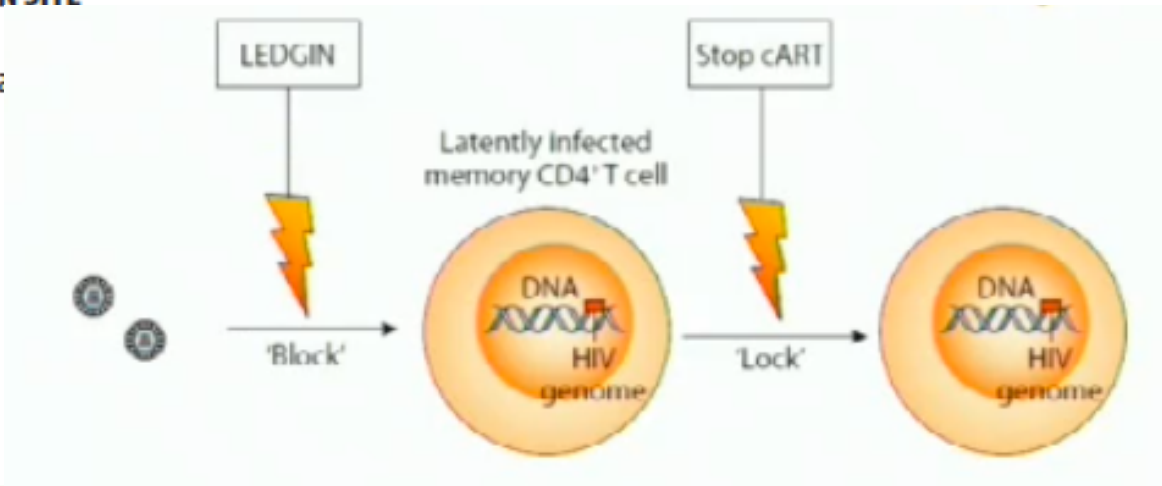
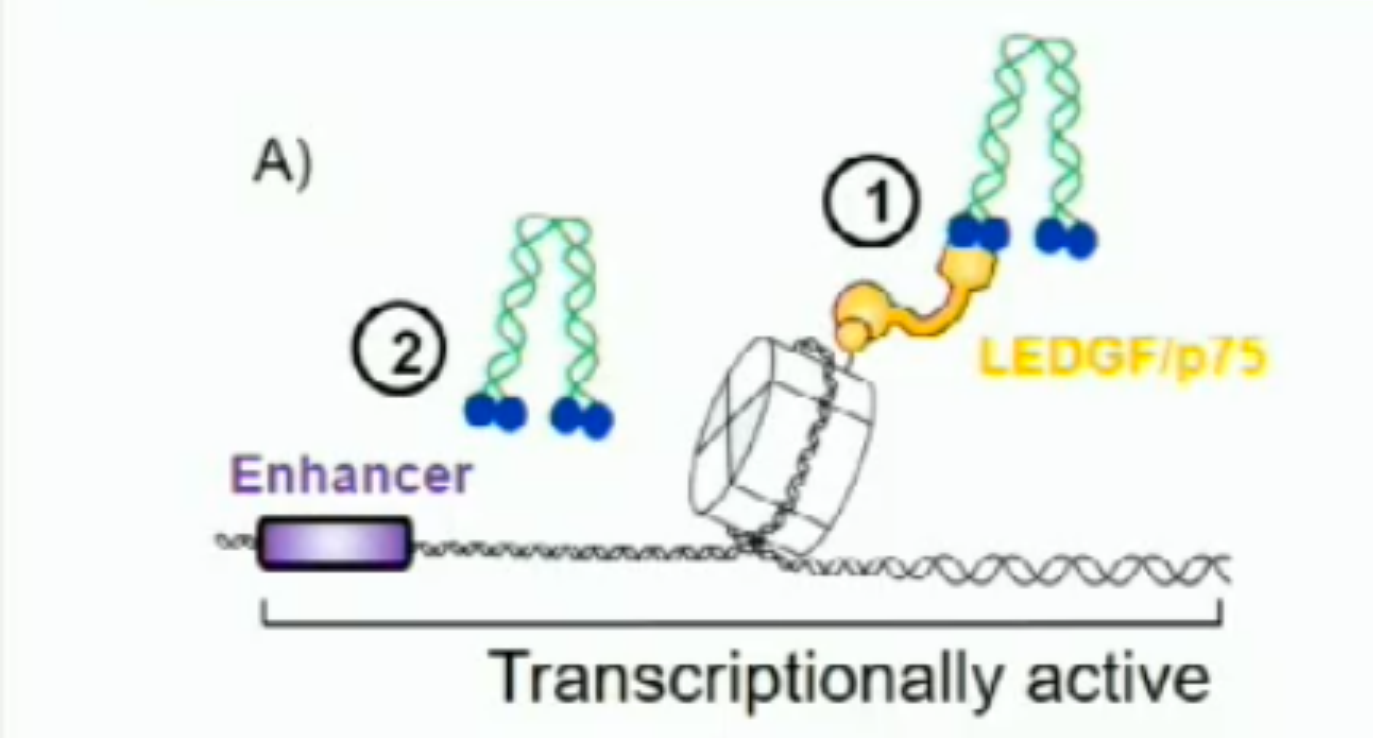
AVANCES EN LA CURA DEL VIH

THE CHROMATIN LANDSCAPE AT THE HIV-1 INTEGRATION SITE DETERMINES VIRAL EXPRESSION

Gerlinde Vansant, Julie Janssens, Heng-Chang Chen, Eduard Zbrita
Frauke Christ, Guillaume Filion, **Zeger Debyser**

Block and lock





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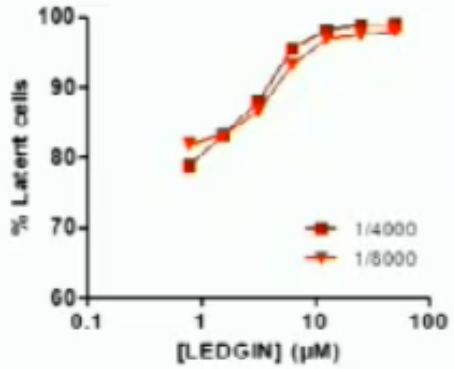
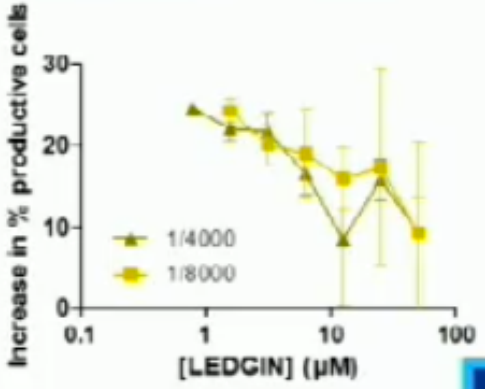
AVANCES EN LA CURA DEL VIH

The impact of LEDGINs on latency/ block-and-lock strategy

Increase the latent reservoir fraction



Decrease the reactivation potential



KU LEUVEN

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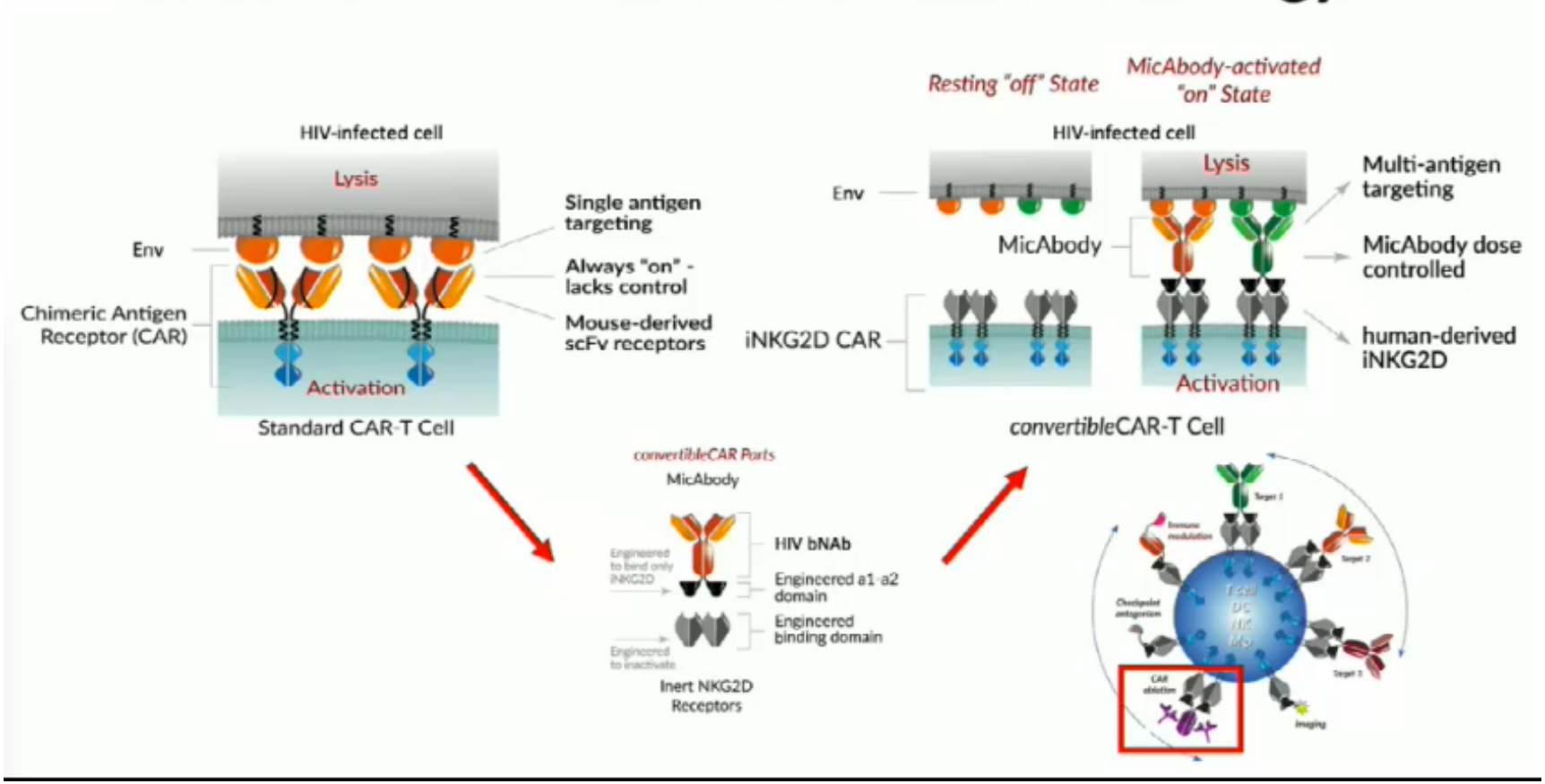
AVANCES EN LA CURA DEL VIH

ATTACKING LATENT HIV WITH *CONVERTIBLE* CAR-T CELLS, A MODULAR KILLING PLATFORM

Eytan Herzig, Kaman Chan Kim, Thomas A. Packard, Noam Vardi, Roland Schwarzer, Andrea Gramatica, Steven G. Deeks, Steven R. Williams, Kyle Landgraf, Nigel Killeen, David W. Martin, Leor Weinberger, Warner C. Greene

From CAR-T to "convertible" CAR-T technology



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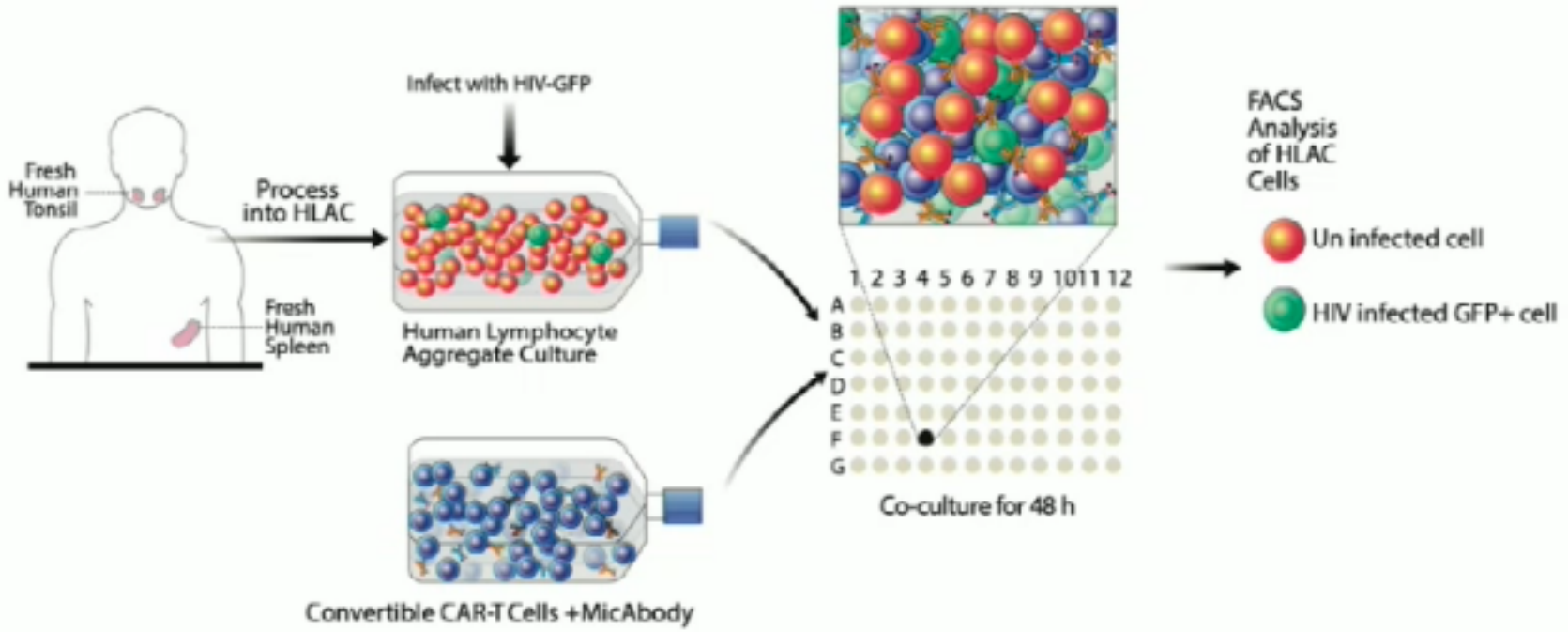
Lymphoid tissue used for HIV infection and study of convertibleCAR-T function



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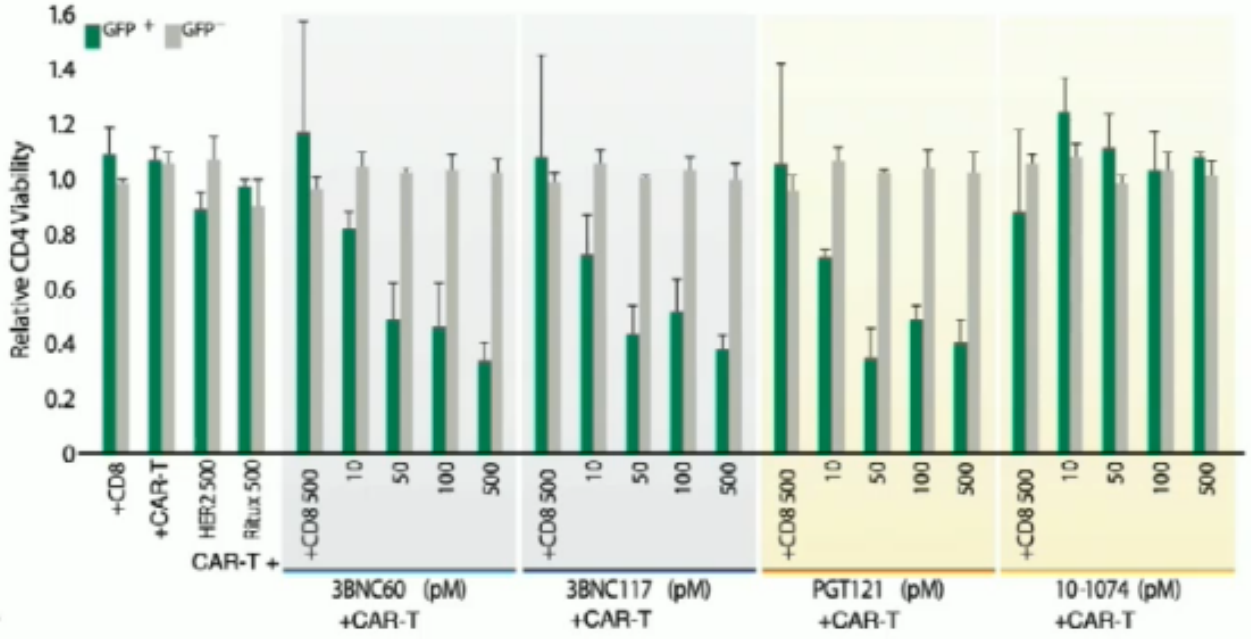
AVANCES EN LA CURA DEL VIH

Specific killing of Transmitted/Founder Virus-infected primary CD4 T cells by cCAR-T combined with specific HIV MicAbodies



n=3 donors. Average + SEM

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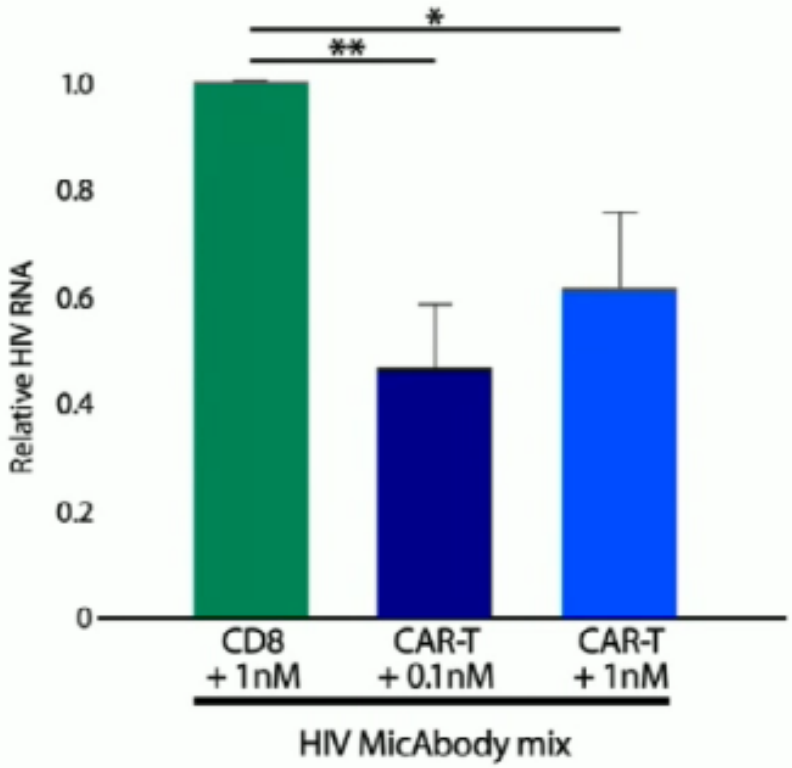
AVANCES EN LA CURA DEL VIH

Killing of reactivated CD4 T-cells from HIV+ individuals by cCAR-T and MicAbodies



n=6 HIV infected individuals' blood. Average +SEM

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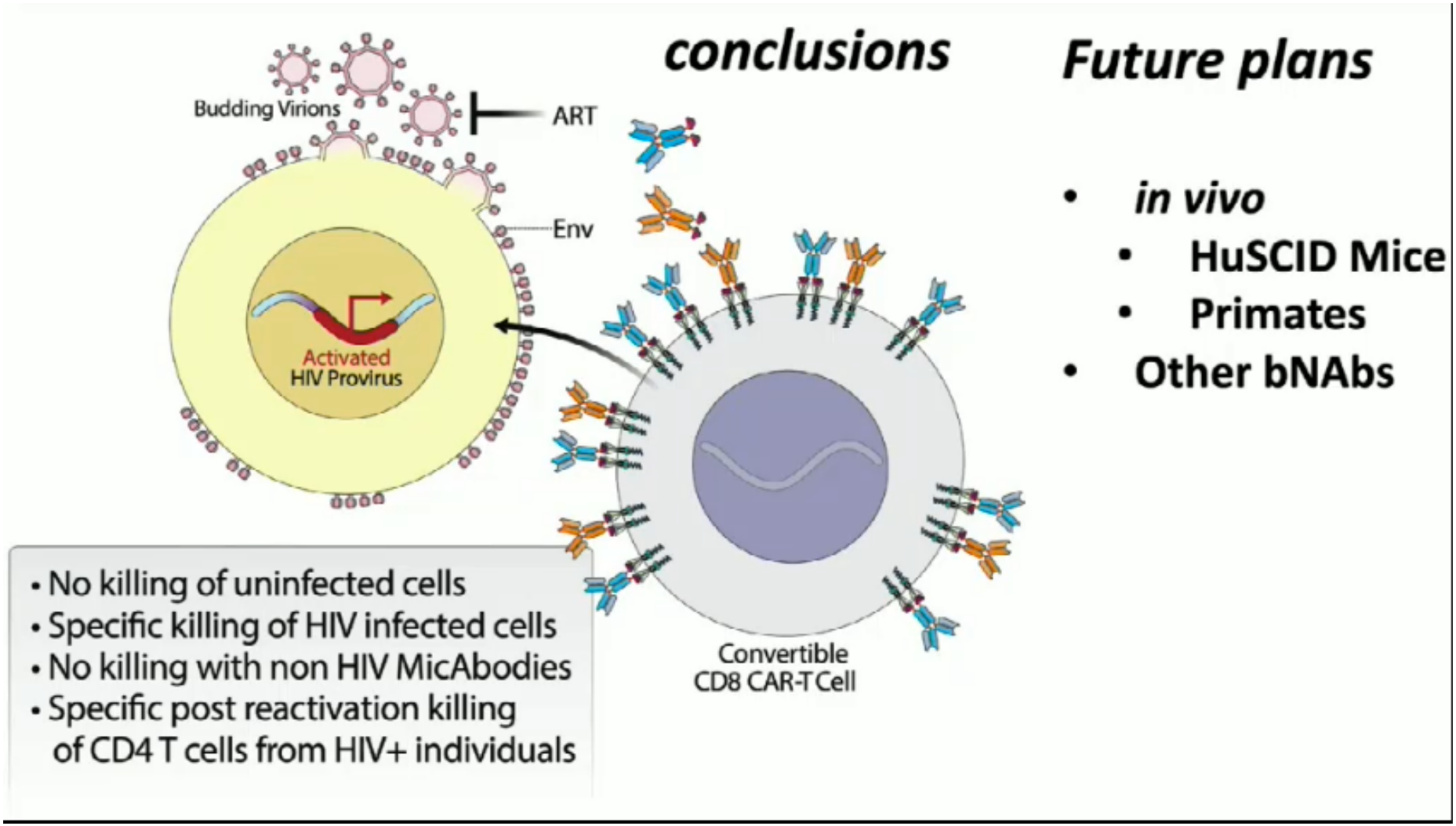

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AVANCES EN LA CURA DEL VIH

TAKE HOME MESSAGES

- ✓ Atentos a las nuevas técnicas de cuantificación del reservorio
- ✓ Expansión del reservorio
  - Sitios de integración próximos de oncogenes y factores de crecimiento
  - Células activadas por antígenos
- ✓ La integración como un factor implicado en la latencia
  - Importancia de determinar los sitios de integración
- ✓ Estrategias de Shock → agonistas de TLR7 agonist
- ✓ Estrategias de Lock → LEDGIN inhibitors
- ✓ Estrategias con CART-cells modificados

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