Targeting Anti-apoptotic Molecules to Eliminate the SIV Reservoir

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CONFLICTS OF INTEREST

No conflicts

Plain Language Summary

Goals of our study

- Blocking molecules helping infected CD4 T cells to survive.
- We are using a drug (venetoclax) that promotes cell death and should be more effective in eliminating infected cells as compared to those without the virus.

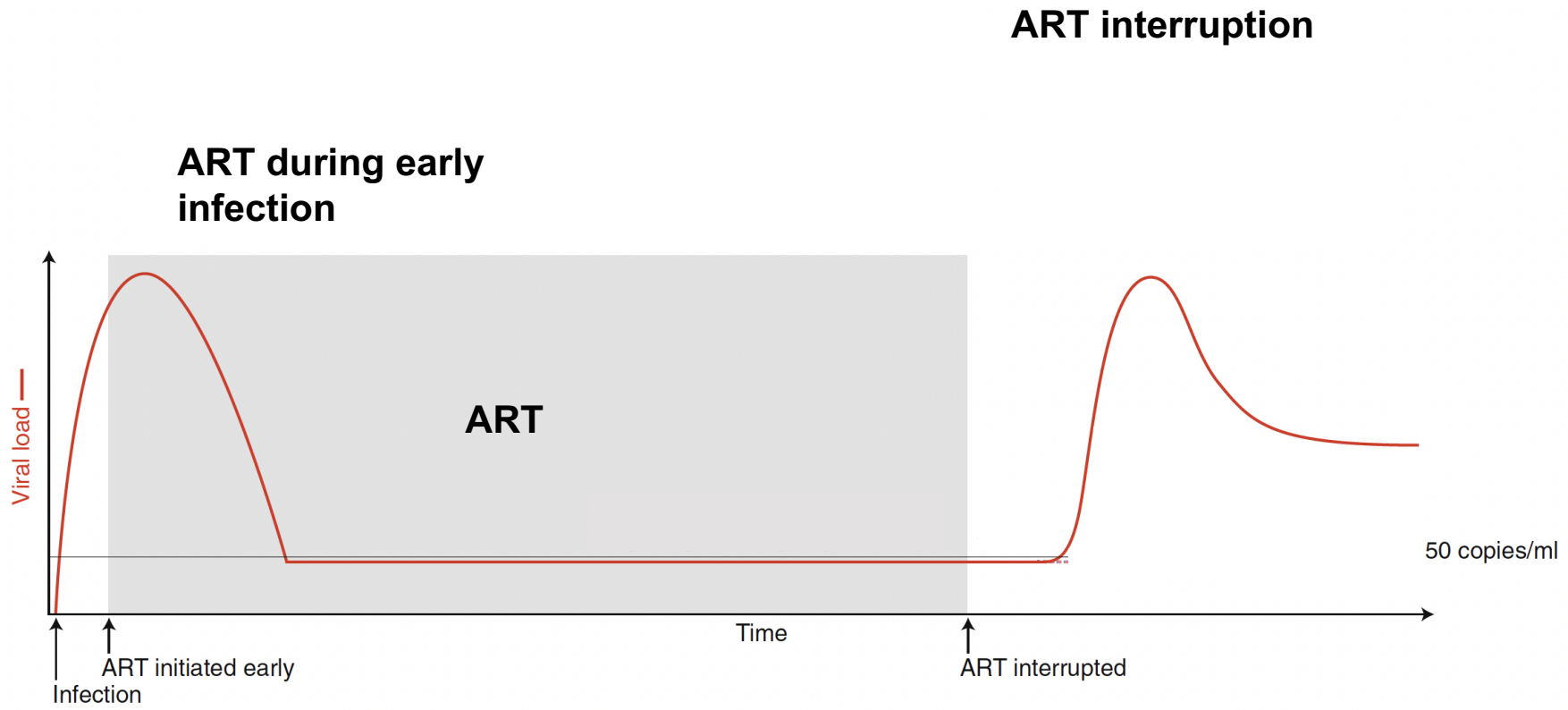
What we did and learn from this study?

- We have tested this approach in the NHP animal model using SIV.
- The levels of SIV-containing cells decreased when animals received venetoclax at ART initiation

Why is this important in the search for an HIV cure?

Because the elimination of the long-lived cells that harbor HIV is a key step toward HIV cure

Antiretroviral therapy (ART) does not eradicate HIV



HIV hides in reservoirs that are not sensitive to current therapies

Deeks & Lewin et al., *Nat Med* 2021

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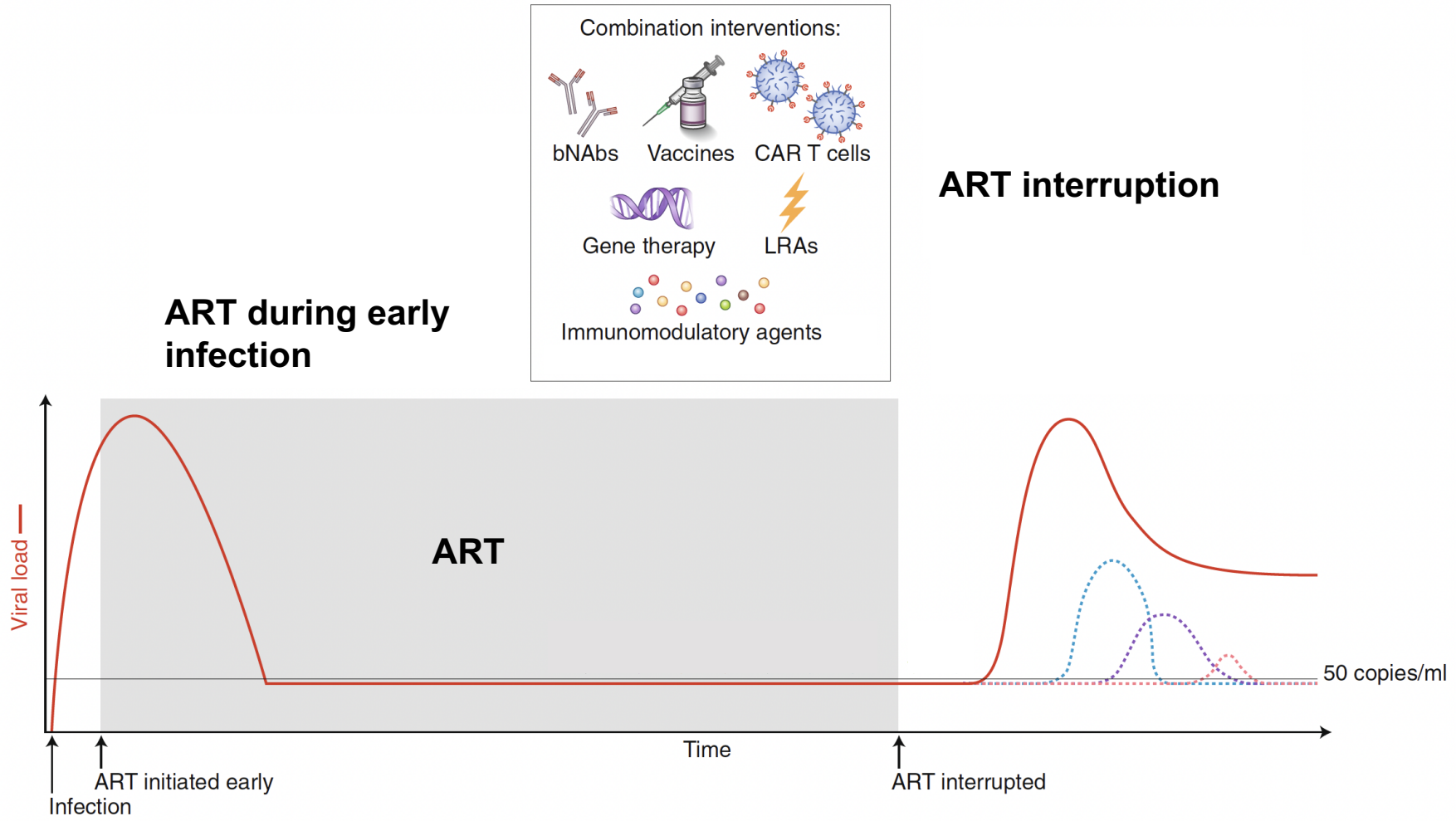

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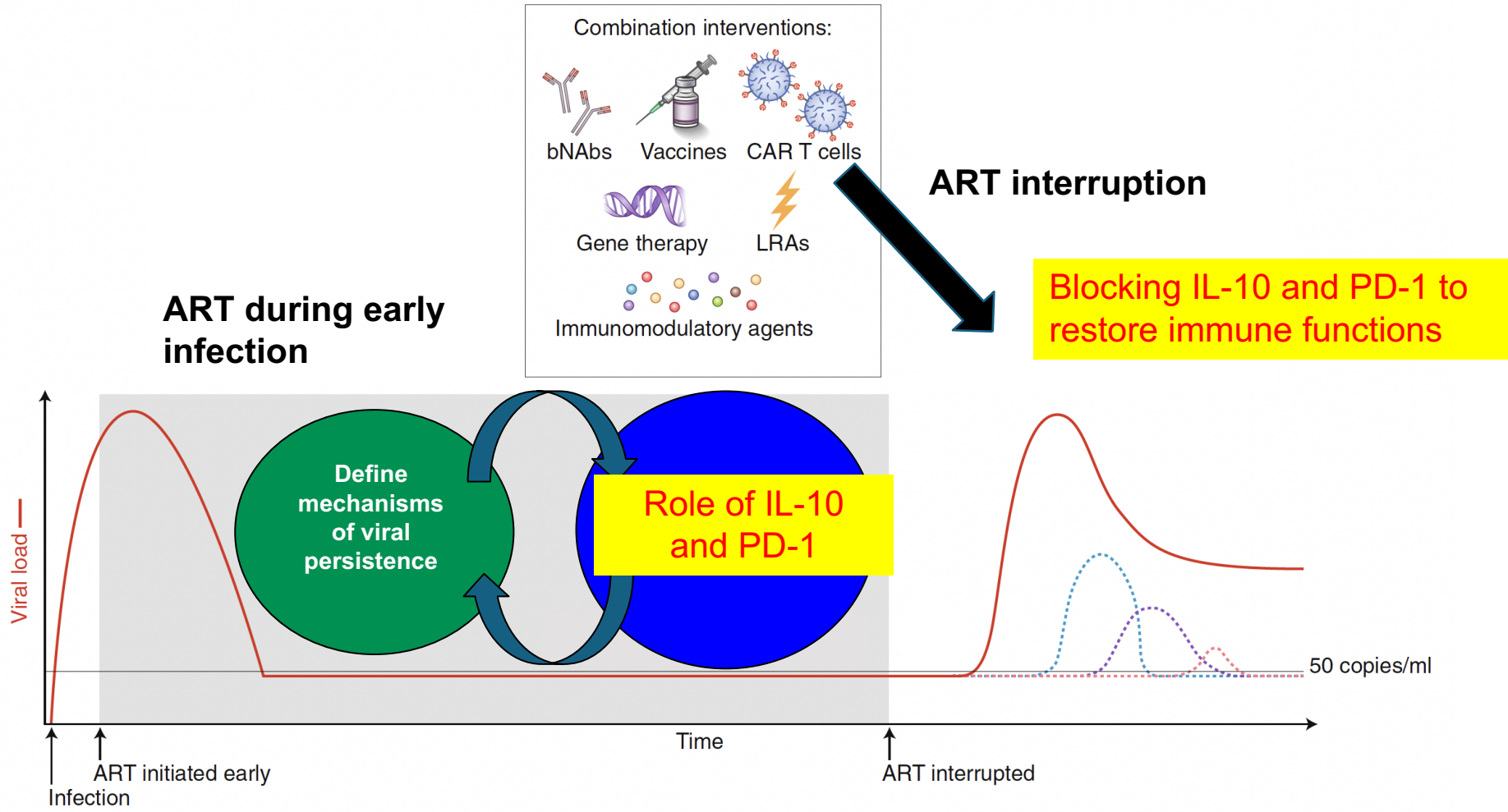
Deeks & Lewin et al., *Nat Med* 2021

Immunotherapy-based cure interventions: the “ERASE HIV” approach

1. Immune-mediated clearance/control of HIV will require combined approaches that take fully into account the remarkable complexity of the HIV reservoir
2. A better understanding of the mechanisms regulating HIV persistence is absolutely needed to design the most effective and safe combined strategy

- **What is the nature of the HIV reservoir?**
- **What are the mechanisms favoring its persistence?**
- **How to target/harness them with immune-based interventions to safely achieve sustained control of HIV?**

Antiretroviral therapy (ART) does not eradicate HIV



HIV hides in reservoirs that are not sensitive to current therapies

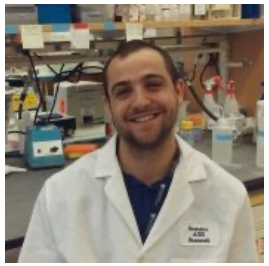
Dual IL-10 and PD-1 blockade improves SIV control after ATI in RMs

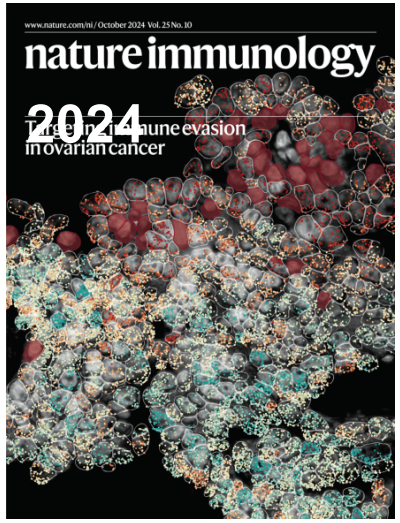
Interleukin-10 contributes to reservoir establishment and persistence in SIV-infected macaques treated with antiretroviral therapy

Justin Harper,[1] Susan P. Ribeiro,[2] Chi Ngai Chan,[3] Malika Aid,[4] Claire Deleage,[5] Luca Micci,[1,6] Maria Pino,[1] Barbara Cervasi,[7] Gopalan Raghunathan,[8] Eric Rimmer,[9] Gulesi Ayanoglu,[9] Guoxin Wu,[10] Neeta Shenvi,[11] Richard J.O. Barnard,[10] Gregory Q. Del Prete,[5] Kathleen Busman-Sahay,[3,12] Guido Silvestri,[1,13] Deanna A. Kulpa,[1,13] Steven E. Bosinger,[1,13] Kirk A. Easley,[11] Bonnie J. Howell,[10] Dan Gorman,[8] Daria J. Hazuda,[10] Jacob D. Estes,[3,12] Rafick-Pierre Sekaly,[2] and Mirko Paiardini[1,13]


Rafick Sekaly


Susan Ribeiro


Zach Strongin



Dual blockade of IL-10 and PD-1 leads to control of SIV viral rebound following analytical treatment interruption

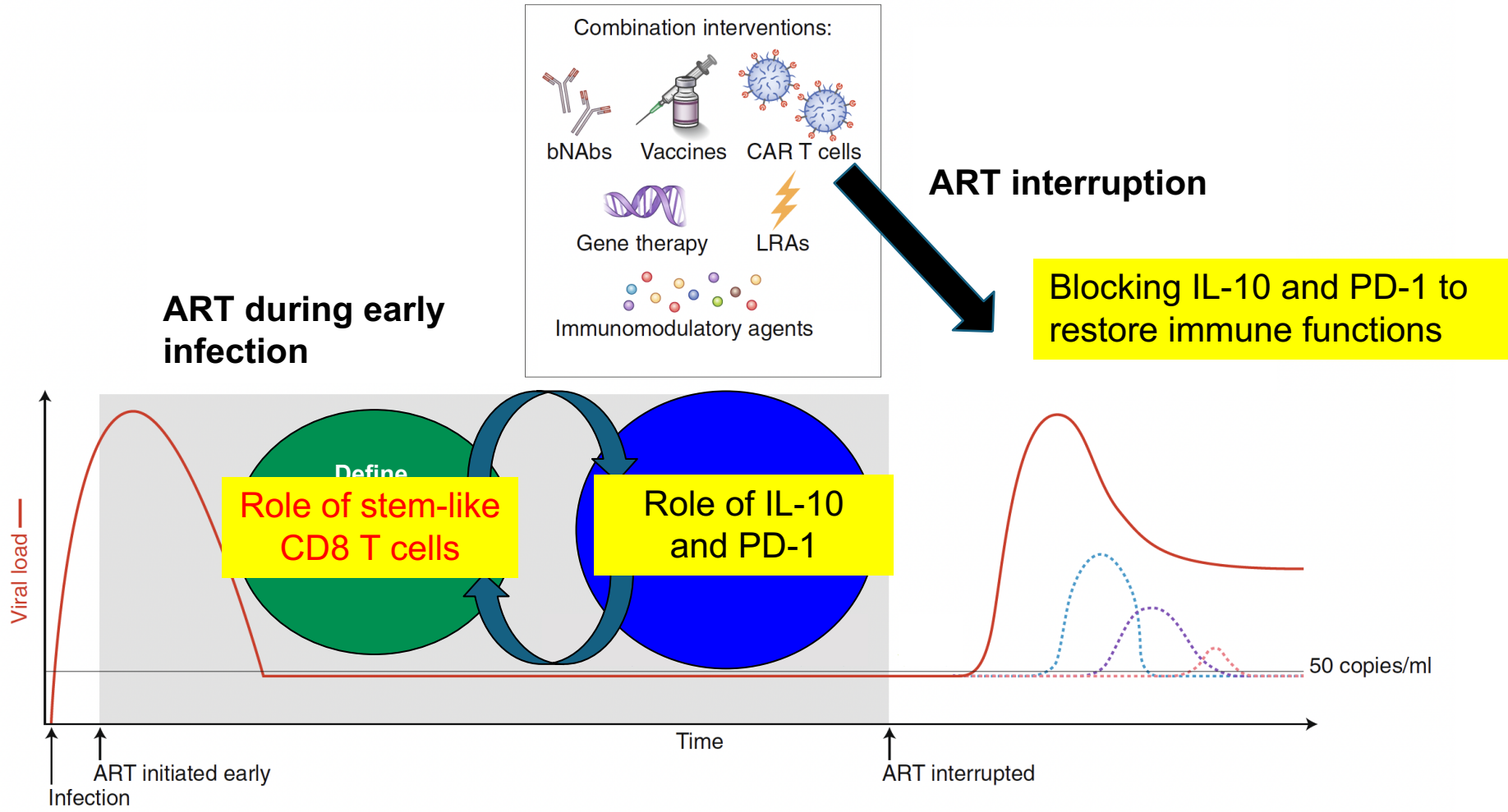
Susan Pereira Ribeiro[1,2,3,18], Zachary Strongin[4,18], Hugo Soudeyns[1,5,6], Felipe ten-Caten[1], Khader Ghneim[1], Gabriela Pacheco Sanchez[1], Giuliana Xavier de Medeiros[1], Perla Mariana Del Rio Estrada[1,7], Adam-Nicolas Pelletier[8], Timothy Hoang[4,19], Kevin Nguyen[4], Justin Harper[4], Sherrie Jean[4], Chelsea Wallace[4], Robert Balderas[9], Jeffrey D. Lifson[10], Gopalan Raghunathan[11], Eric Rimmer[12], Cinthia Pastuskova[12], Guoxin Wu[13], Luca Micci[14], Ruy M. Ribeiro[15], Chi Ngai Chan[16,17], Jacob D. Estes[16,17], Guido Silvestri[1,4], Daniel M. Gorman[11], Bonnie J. Howell[13], Daria J. Hazuda[13], Mirko Paiardini[1,4,20] & Rafick P. Sekaly[1,2,3,20]


Bonnie Howell


Jeff Lifson


Justin Harper

Antiretroviral therapy (ART) does not eradicate HIV



HIV hides in reservoirs that are not sensitive to current therapies

Long-term memory CD8 T cells with effector profile while maintaining stem-like features favor SIV control

nature immunology

Article

https://doi.org/10.1038/s41590-024-01875-0

Distinct SIV-specific CD8$^+$ T cells in the lymph node exhibit simultaneous effector and stem-like profiles and are associated with limited SIV persistence

Zachary Strongin[1,16], Laurence Raymond Marchand[1,16], Claire Deleage[2], M. Betina Pampena[3,4], Maria Andrea Cardenas[5], Christian Michel Beusch[6,7], Timothy N. Hoang[1,15], Elizabeth A. Urban[2], Mael Gourves[8,9], Kevin Nguyen[1], Gregory K. Tharp[1], Stacey Lapp[1], Andrew R. Rahmberg[10], Justin Harper[1], Perla M. del Rio Estrada[6,11], Mauricio Gonzalez-Navarro[11], Fernanda Torres-Ruiz[11], Yara Andrea Luna-Villalobos[11], Santiago Avila-Rios[11], Gustavo Reyes-Teran[12], Rafick Sekaly[6,13,14], Guido Silvestri[1,6,13], Deanna A. Kulpa[1,6], Asier Saez-Cirion[8,9], Jason M. Brenchley[10], Steven E. Bosinger[1,6,13], David Ezra Gordon[6], Michael R. Betts[3,4], Haydn T. Kissick[5,13,14] & Mirko Paiardini[1,6,13]

Research briefing

Check for updates

Lymphoid TCF1$^+$CD39$^+$ CD8$^+$ T cells maintain stem-like features and contribute to viral control

The question

Much of our understanding of CD8$^+$ T cell functionality, stemness and exhaustion in chronic antigen settings comes from work in lymphocytic choriomeningitis virus (LCMV) and cancer. This work has identified TCF1$^+$CD8$^+$ T cells as the stem-like population that fuels the differentiated effector and exhausted CD8$^+$ T cell populations, typically identified by lack of TCF1 expression and high expression of inhibitory receptors and markers of terminal differentiation, including CD39[1,2]. To design better T cell therapeutic approaches for HIV, we aimed to understand the kinetics and relevance of these same CD8$^+$ T cell subsets after HIV infection. In addition, we wanted to explore this question with a particular focus on lymph node CD8$^+$ T cells, given the role of lymph nodes as primary sites of viral replication and previous demonstrations of unique CD8$^+$ T cell biology within lymph nodes[3,4].

were preferentially located within B cell follicles, a site of high viral replication with the potential to serve as an immune sanctuary, and were found to be in closer proximity to SIV$^+$ CD4$^+$ T cells than SIV$^-$ CD4$^+$ T cells.

In addition to SIV-infected macaques, we investigated these same CD8$^+$ T cell dynamics in lymph nodes from antiretroviral therapy (ART)-naive and ART-suppressed PLWH and found that TOX^{hi}TCF1$^+$CD39$^+$CD8$^+$ T cells with a highly similar phenotype are also expanded in PLWH and associated with lower intact reservoir size in ART-suppressed PLWH.

The implications

This study provides insight into the dynamics of canonical stem-like and terminally differentiated CD8$^+$ T cells in lymphoid tissue, and identifies a previously undescribed population of TCF1$^+$CD39$^+$CD8$^+$ T cells that are associated with viral control

- **Early and significant expansion of TCF1$^+$CD39$^+$ CD8 T cells (GzmB$^-$GzmK$^+$) in the LN of SIV-infected RMs and PLWH.**
- **These cells exhibit both effector and stem-like profiles and are associated with better SIV control (including intact SIV-DNA)**
- **TCF1$^+$CD39$^+$ CD8 T cells express more CXCR5 than traditional effector CD8 T cells**
- **They are preferentially localized in BCF and in proximity of vRNA+ cells**

Mike Betts

Betina Pampena

Santiago Avilar

Gustavo Reyes-Teran

Haydn Kissick

Long-term memory CD8 T cells with effector profile while maintaining stem-like features favor SIV control

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nature communications

Article

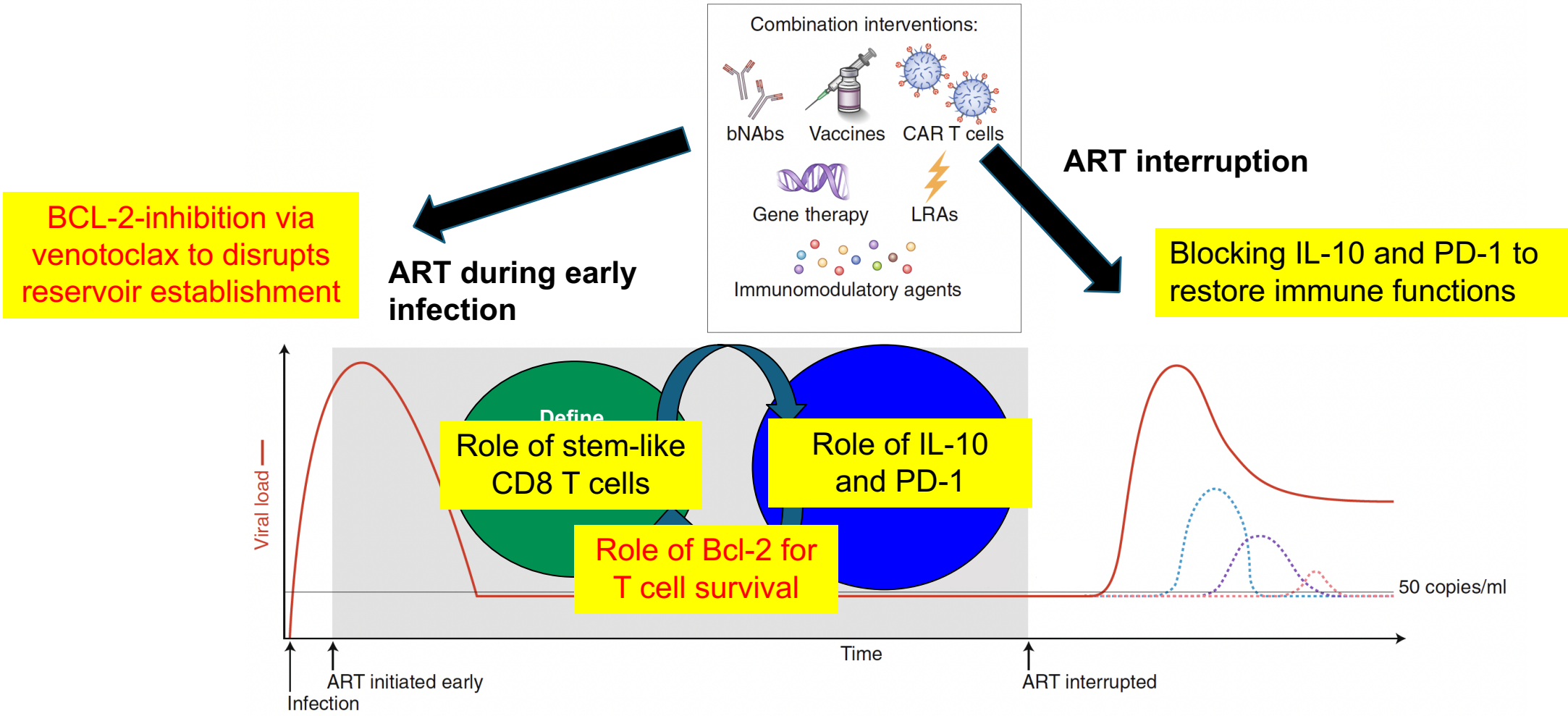
https://doi.org/10.1038/s41467-023-44389-3

Early antiretroviral therapy favors post-treatment SIV control associated with the expansion of enhanced memory CD8$^+$ T-cells

Caroline Passaes[1,2], Delphine Desjardins[3], Anaïs Chapel[1,2], Valérie Monceaux[1,2], Julien Lemaitre[3], Adeline Mélard[4], Federico Perdomo-Celis[2], Cyril Planchais[5], Maël Gourvès[1], Nastasia Dimant[3], Annie David[2], Nathalie Dereuddre-Bosquet[3], Aurélie Barrail-Tran[3,6], Hélène Gouget[3], Céline Guillaume[3], Francis Relouzat[3], Olivier Lambotte[3,7], Jérémie Guedj[8], Michaela Müller-Trutwin[2], Hugo Mouquet[5], Christine Rouzioux[9], Véronique Avettand-Fenoël[4,10], Roger Le Grand[3,11] & Asier Sáez-Cirión[1,2,11]

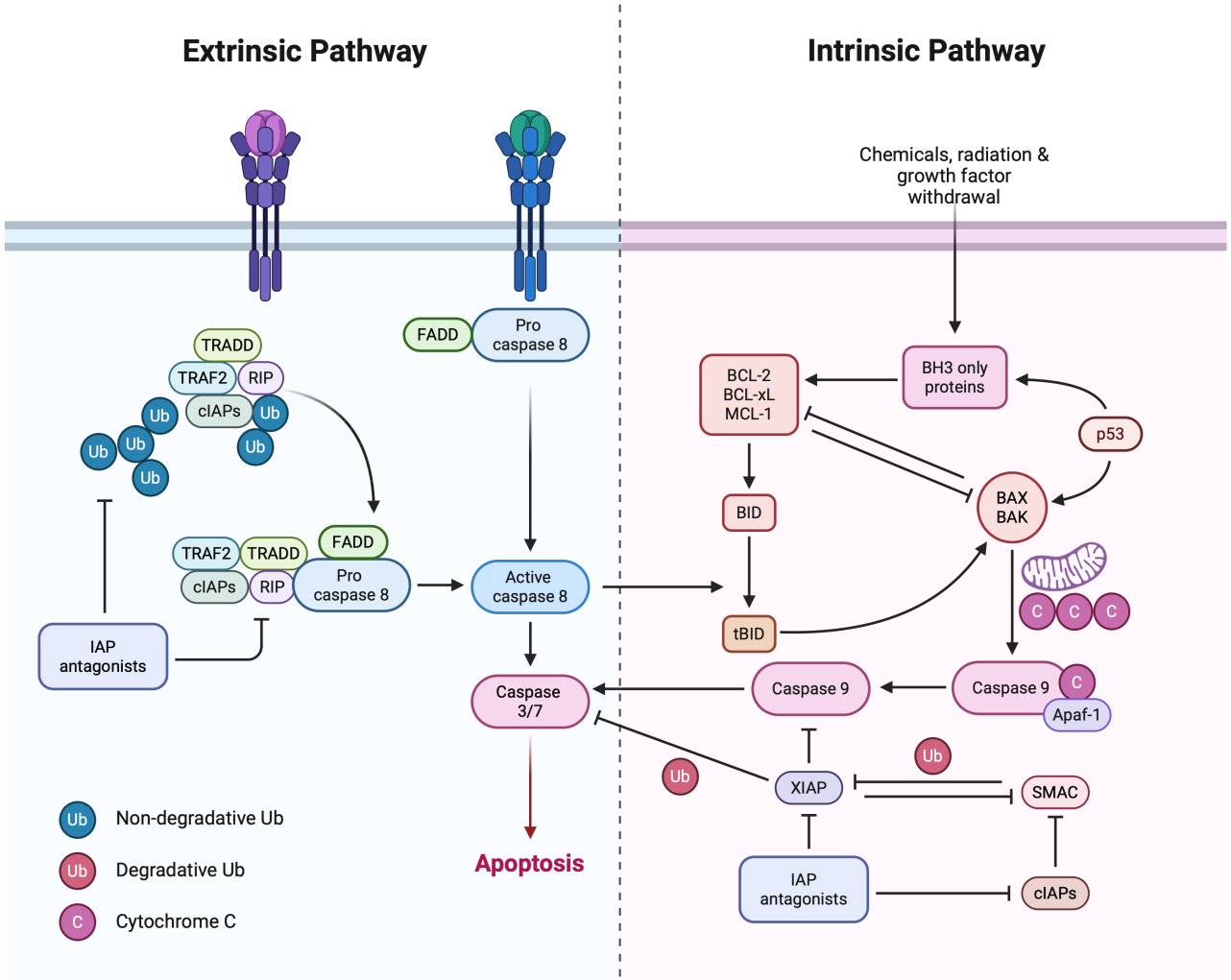
Early treatment favors the development of long-term memory, TCF1$^+$ CD8$^+$ T cells with enhanced proliferative and SIV suppressive capacity that are able to mediate a robust secondary-like response upon viral rebound.

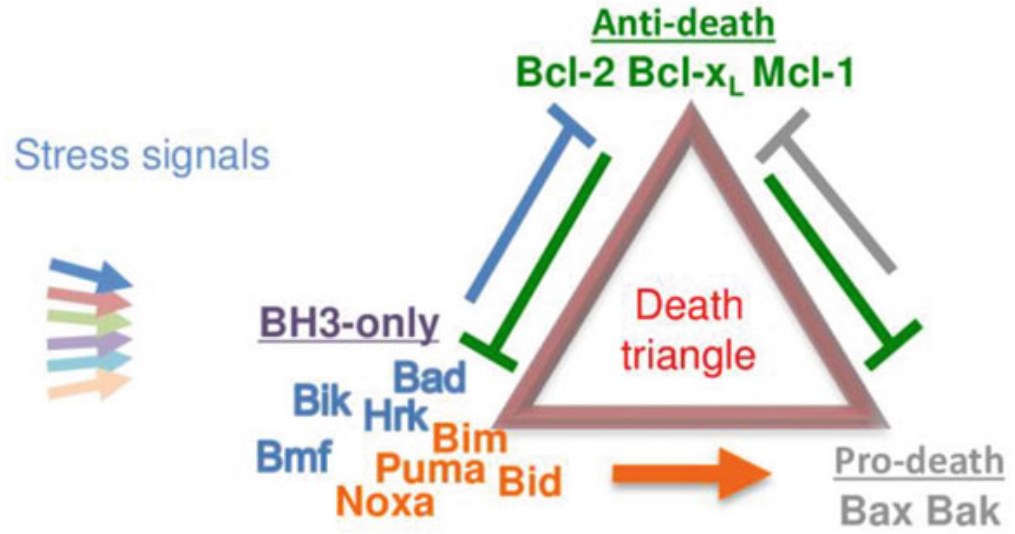
Antiretroviral therapy (ART) does not eradicate HIV



HIV hides in reservoirs that are not sensitive to current therapies

BCL-2 Family Proteins and Apoptosis

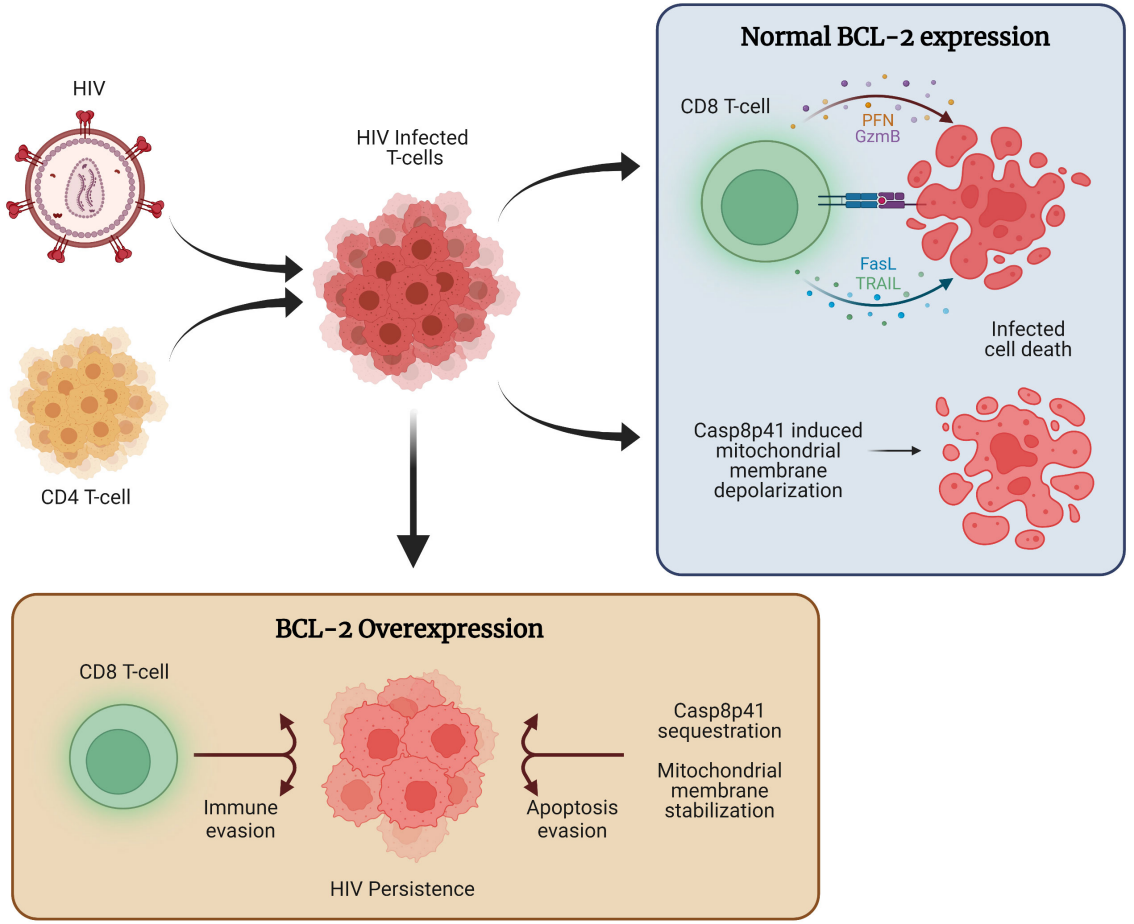




(Jason D. Huska et al., BCL-2 Family Proteins, Springer Protocols, 2019)

BCL-2 protects infected cells from HIV or CD8 T cell-induced cell death, thereby contributing to the establishment and persistence of the HIV reservoir

- In vitro experiments have shown that BCL-2 counteracts the proapoptotic effect of HIV and increases the survival of HIV-infected cells, contributing to the establishment of the reservoir.
- BCL-2 antagonism sensitizes cytotoxic T cells-resistant HIV reservoirs to elimination ex vivo.
- HIV is enriched in BCL-2hi CD4+ T cells.



(Natesampillai et al., J Virol, 2018; Ren et al., J Clin Invest, 2020; Chandrasekar et al., Front Immunol., 2022; Kim et al., Nat Protoc, 2014)

Targeting BCL-2 at ART initiation

Hypotheses

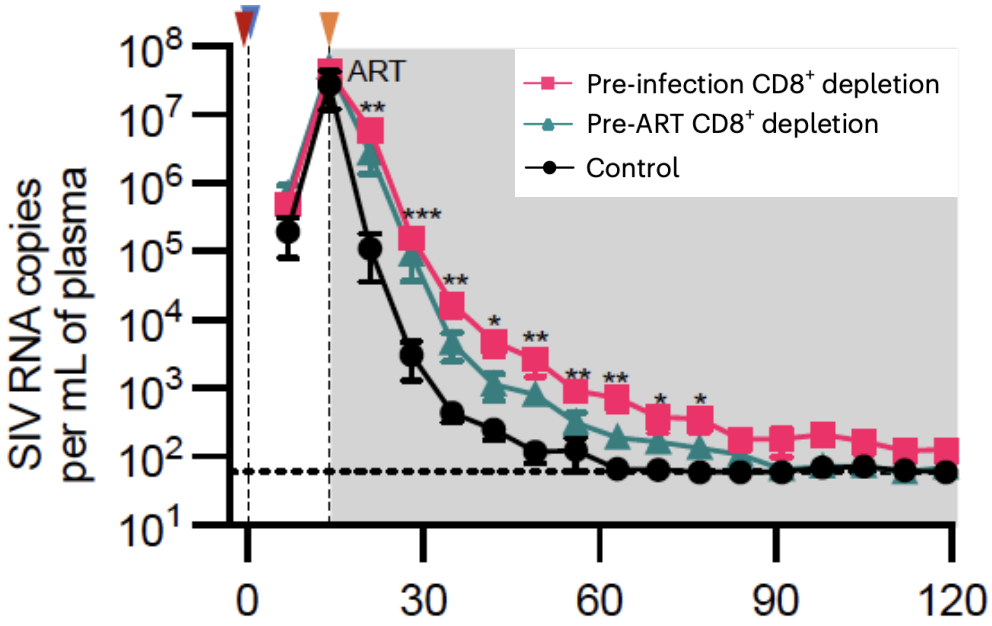
- **BCL-2 inhibition initiated with early ART will limit the establishment and maintenance of the latent reservoir.**

Targeting BCL-2 at ART initiation

Hypotheses

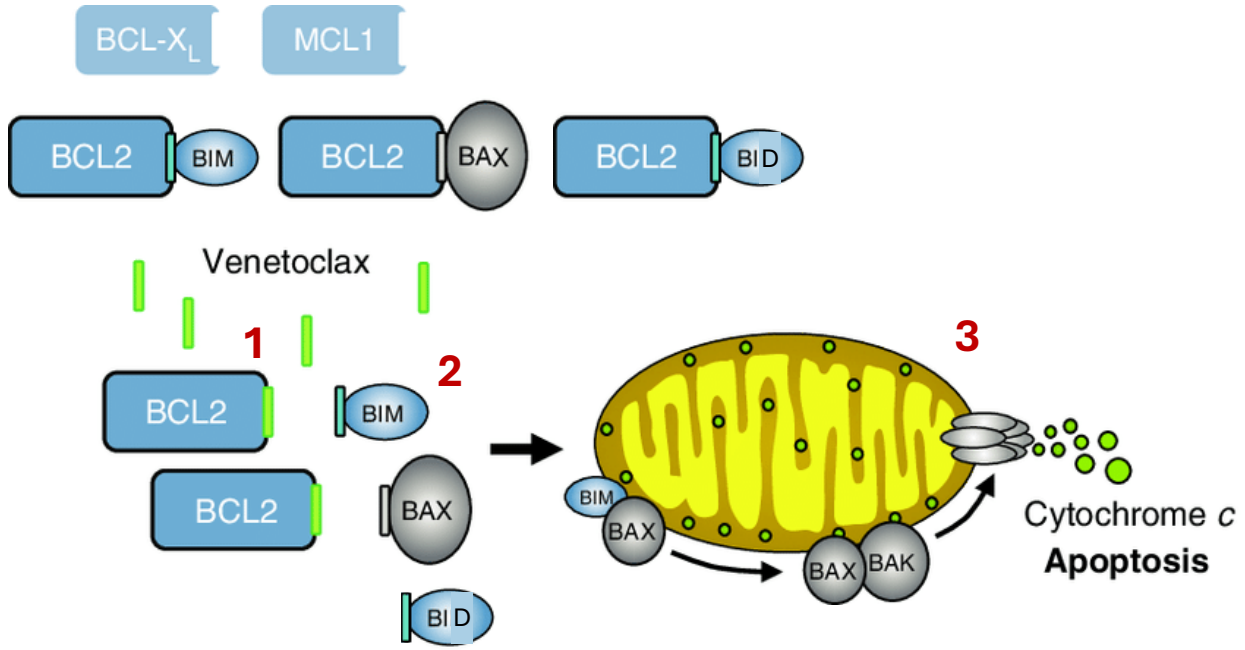
- BCL-2 inhibition initiated with early ART will limit the establishment and maintenance of the latent reservoir.
- BCL-2 inhibition combined with a latency-disrupting strategy (CD8α depletion) will expose more infected CD4+ T-cells to apoptosis, thus synergizing in limiting the SIV reservoir.

CD8 depletion immediately prior early ART initiation (day 14 post infection) resulted in slower decline of viremia without changes in the frequency of CD4+ T-cells harboring intact provirus. (*Statzu et al., Nat Micro,2023*)



BCL-2 inhibition: Venetoclax

- Selective inhibitor of BCL-2
- Induces apoptosis by binding directly to BCL-2(1), displacing proapoptotic proteins like BIM and BAX(2), triggering mitochondrial outer membrane permeabilization(3), and activating caspases.



FDA-approved for:

- Chronic Lymphocytic Leukemia
- Small Lymphocytic Lymphoma
- Acute Myeloid Leukemia

Recruiting

Administration of Venetoclax to Promote Apoptosis of HIV-infected Cells and Reduce the Size of the HIV Reservoir Among People Living With HIV on ART (AMBER)

ClinicalTrials.gov ID NCT05668026

Sponsor University of Aarhus

Information provided by University of Aarhus (Responsible Party)

Targeting BCL-2 with venetoclax: hu-mice studies

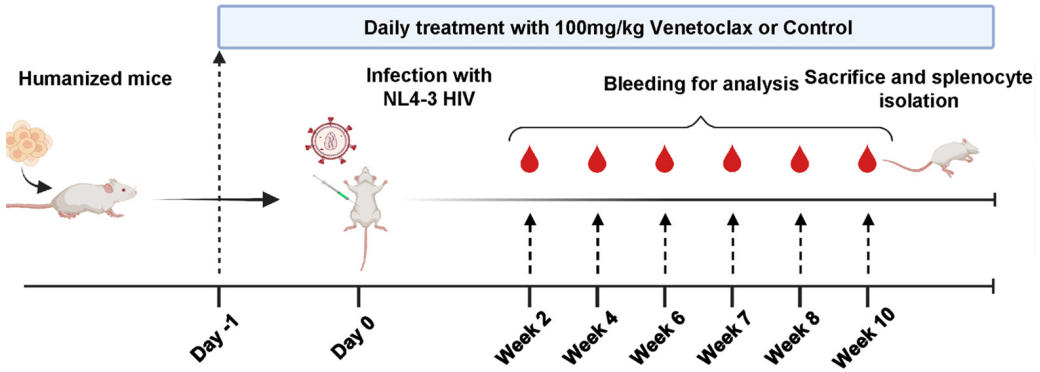
AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology®

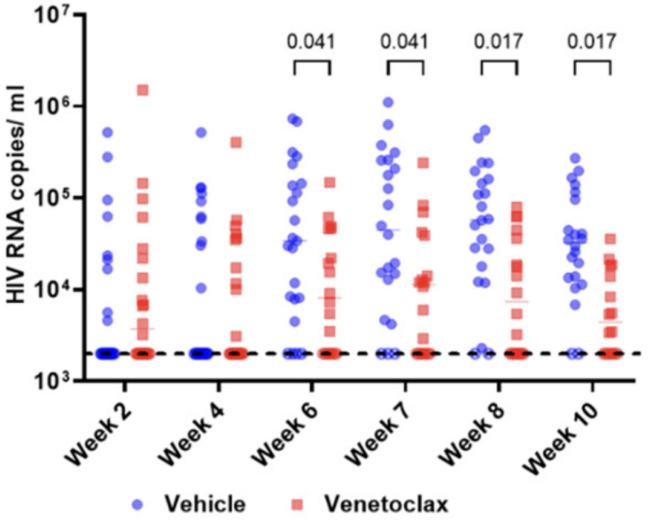
VACCINES AND ANTIVIRAL AGENTS

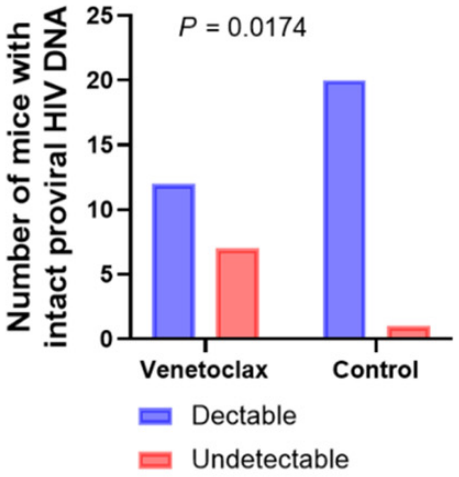
The BCL-2 Inhibitor Venetoclax Augments Immune Effector Function Mediated by Fas Ligand, TRAIL, and Perforin/ Granzyme B, Resulting in Reduced Plasma Viremia and Decreased HIV Reservoir Size during Acute HIV Infection in a Humanized Mouse Model

Aswath P. Chandrasekar,[a] Nathan W. Cummins,[a] Sekar Natesampillai,[a] Anisha Misra,[a] Alecia Alto,[a] Greg Laird,[c] Andrew D. Badley[a,b]

[a]Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota, USA
[b]Department of Molecular Medicine, Mayo Clinic, Rochester, Minnesota, USA
[c]Accelevir Diagnostics, Baltimore, Maryland, USA







(*Chandrasekar et al., J Virol., 2020*)

- **Venetoclax treatment reduced plasma viremia and resulted in more mice with undetectable intact HIV**

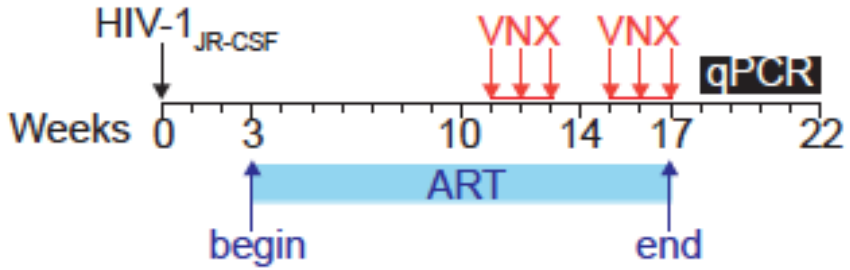
Targeting BCL-2 with venetoclax: hu-mice studies

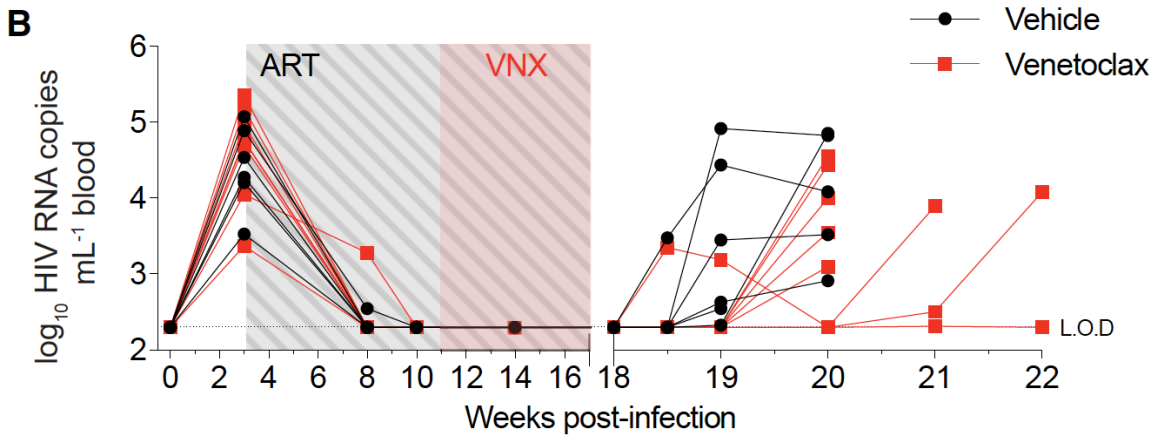
Cell Reports
Medicine

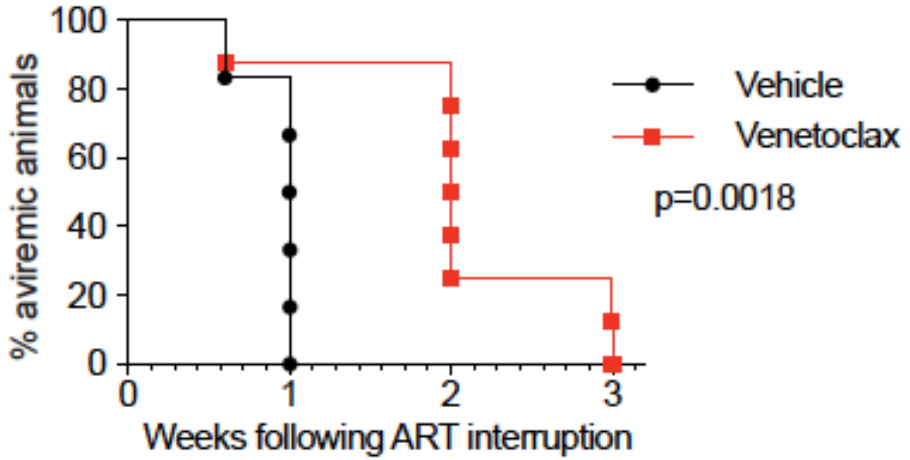
Article

Venetoclax, alone and in combination with the BH3 mimetic S63845, depletes HIV-1 latently infected cells and delays rebound in humanized mice

Philip Arandjelovic,[1,2,9] Youry Kim,[3,9] James P. Cooney,[1,2] Simon P. Preston,[1,2] Marcel Doerflinger,[1,2] James H. McMahon,[4] Sarah E. Garner,[1,2] Jennifer M. Zerbato,[3] Michael Roche,[3,8] Carolin Tumpach,[3] Jesslyn Ong,[3] Dylan Sheerin,[1,2] Gordon K. Smyth,[5,6] Jenny L. Anderson,[3,10] Cody C. Allison,[1,2,10] Sharon R. Lewin,[3,4,7,10] and Marc Pellegrini[1,2,10,11,*]



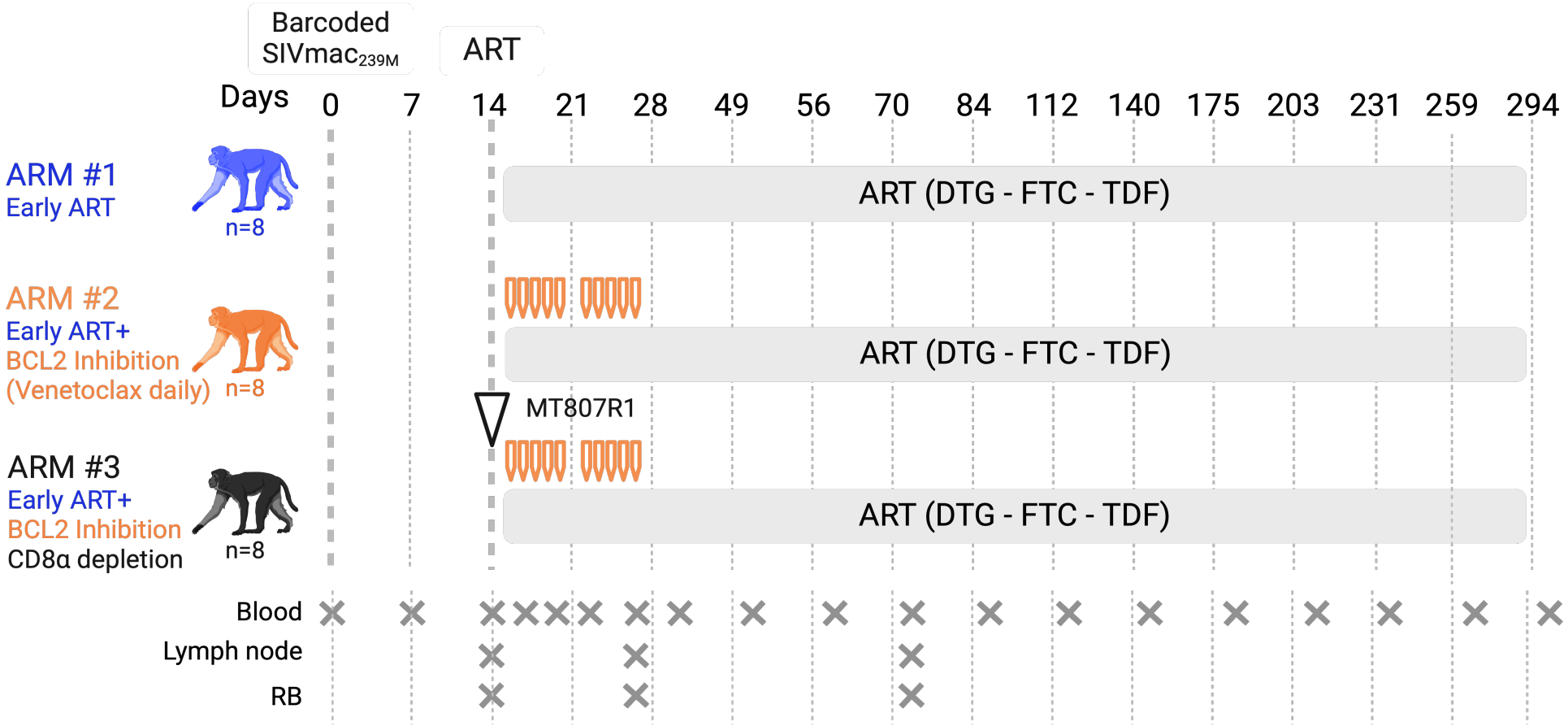




- Venetoclax delays viral rebound in a humanized mouse model of HIV infection

Targeting BCL-2 to limit the establishment and maintenance of the SIV reservoir: Study Design

Tomas Wiche Salinas



Immunologic Impact/Efficacy:

Cellular Dynamics
PBMCs
LNs
RBs

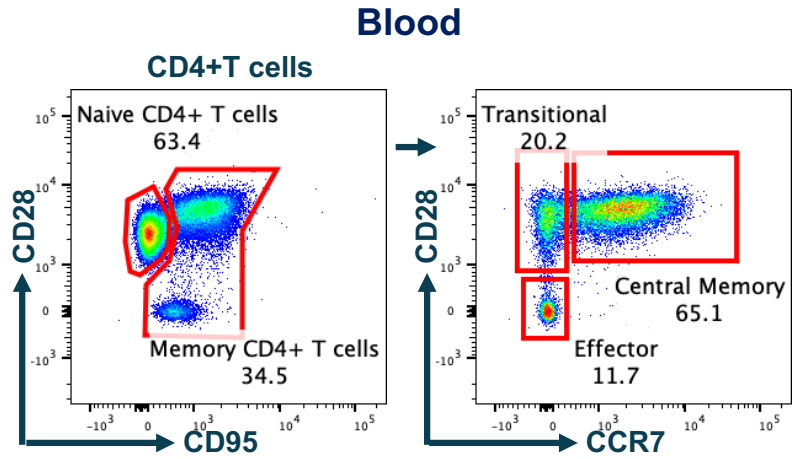
Virologic Impact:

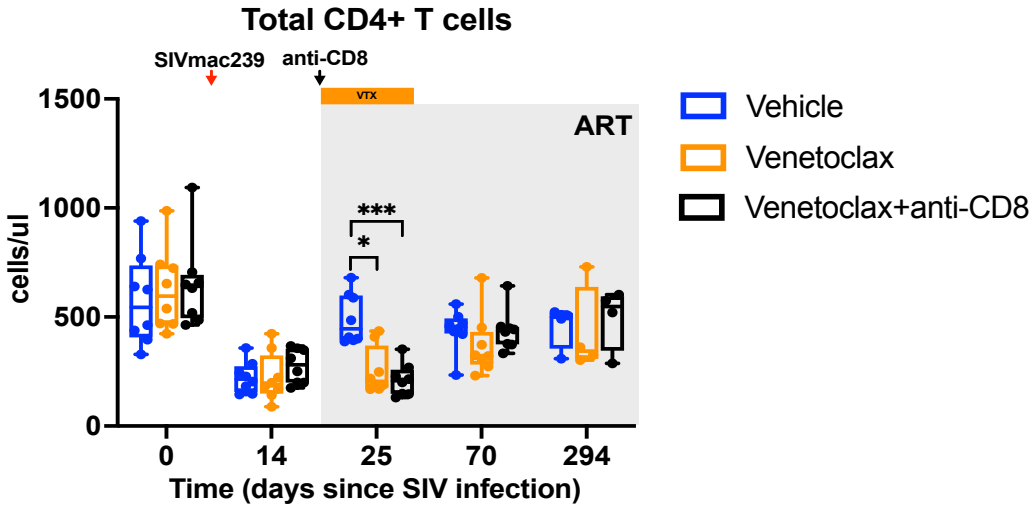
Plasma Viral Load
SIV Reservoir (IPDA)
PBMCs
LNs

Venetoclax: Subcutaneous (20mg/kg) or oral (venclexta 300mg +CYP3A inhibitor) during early ART

Anti-CD8α: Subcutaneous at ART initiation

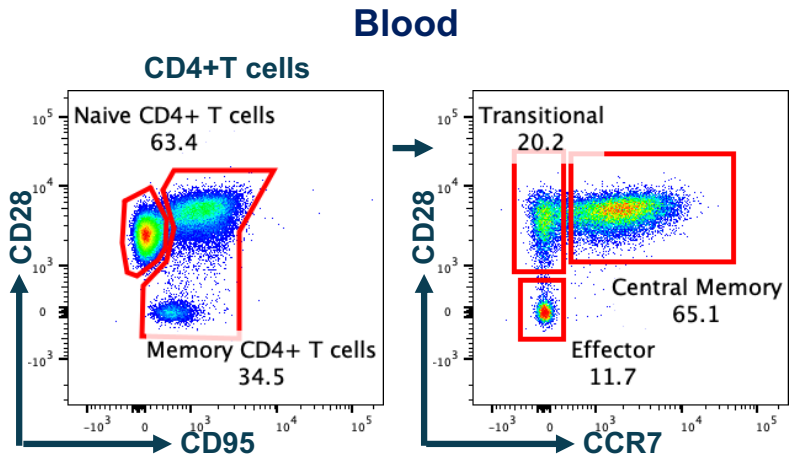
Immunological Impact of BCL-2 Inhibition

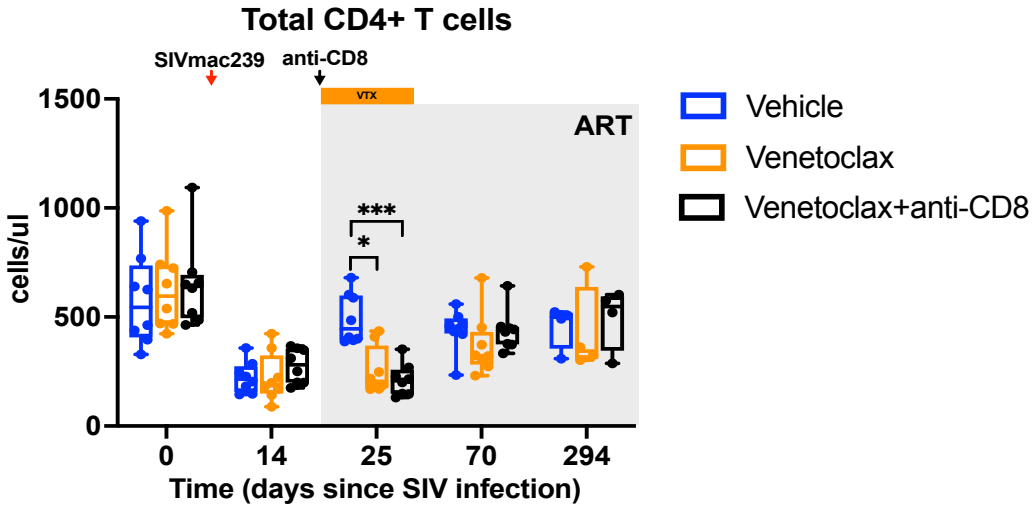


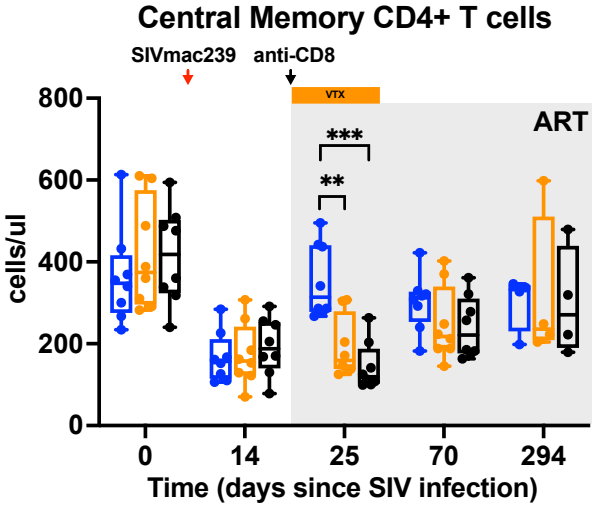


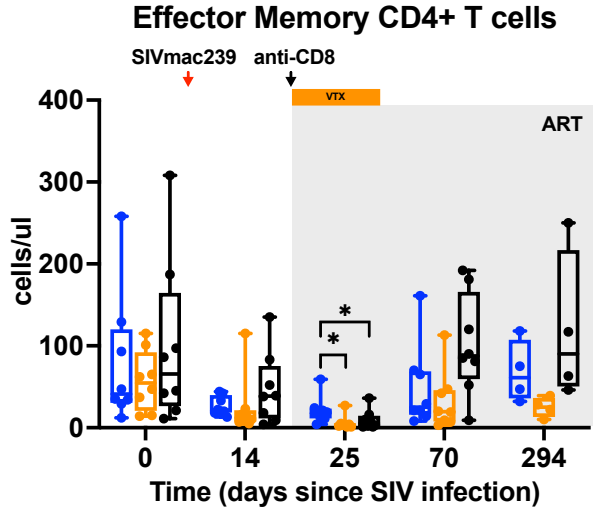
- Venetoclax-treated RMs showed an initial decrease in blood CD4+ T cell counts, with a long-term reconstitution comparable to controls.

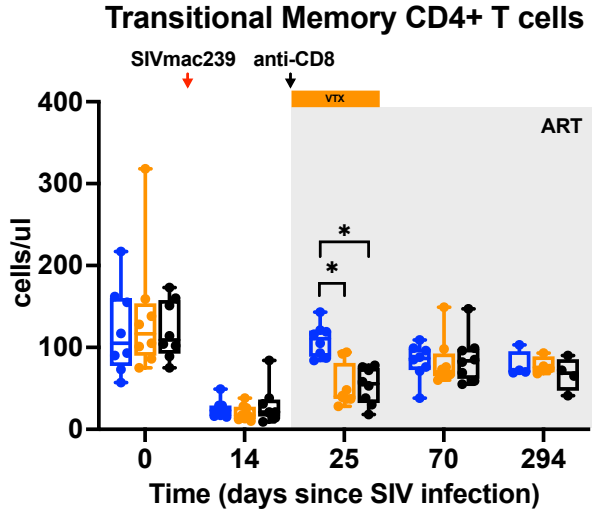
Immunological Impact of BCL-2 Inhibition

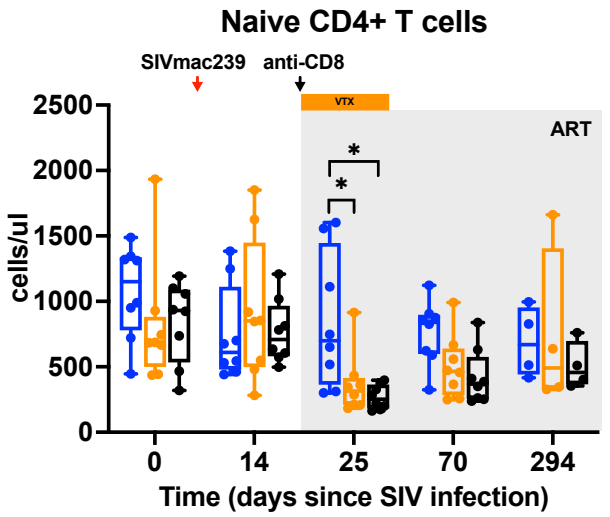






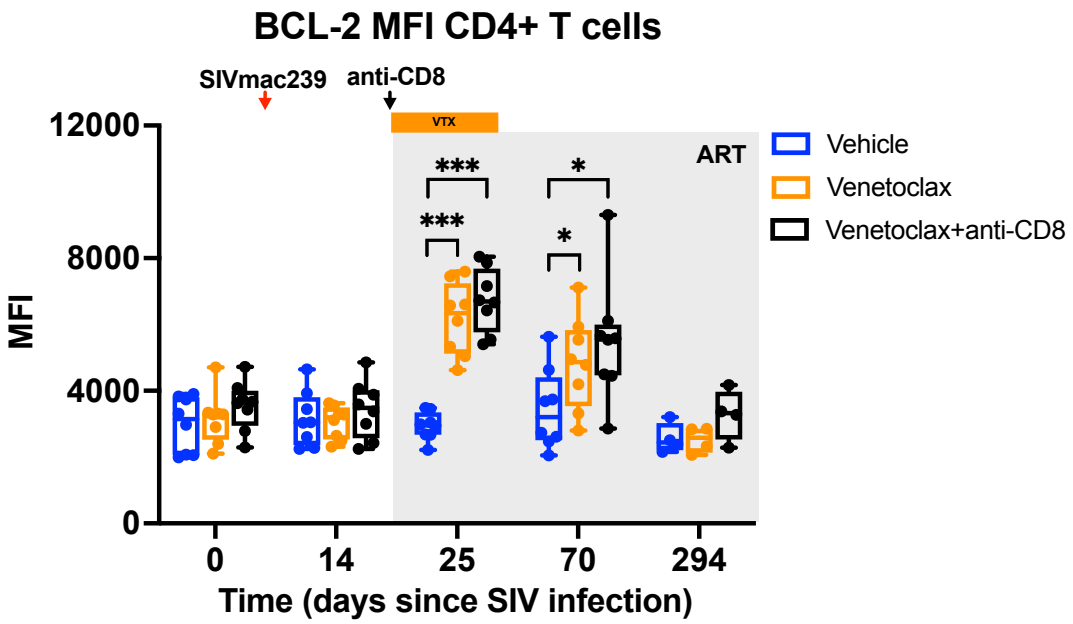


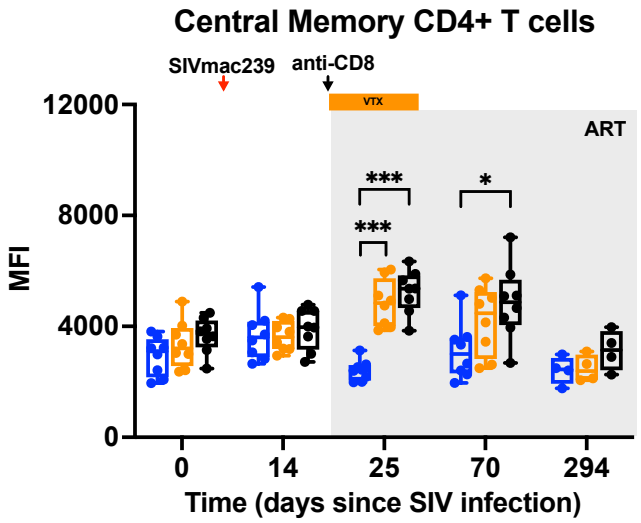


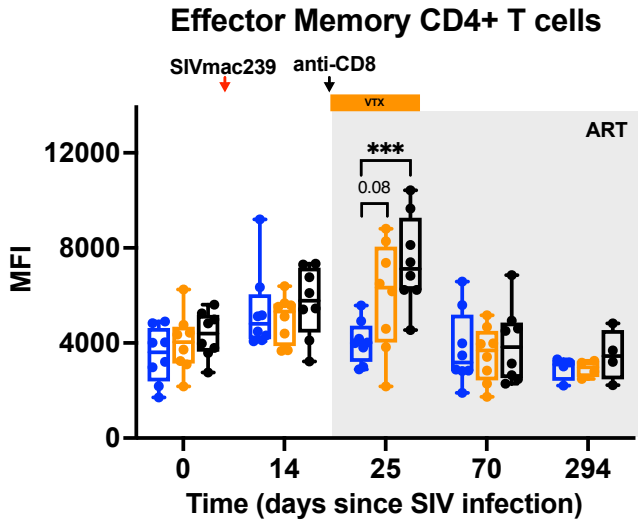


- Venetoclax-treated RMs showed an initial decrease in blood CD4+ T cell counts, with a long-term reconstitution comparable to controls.

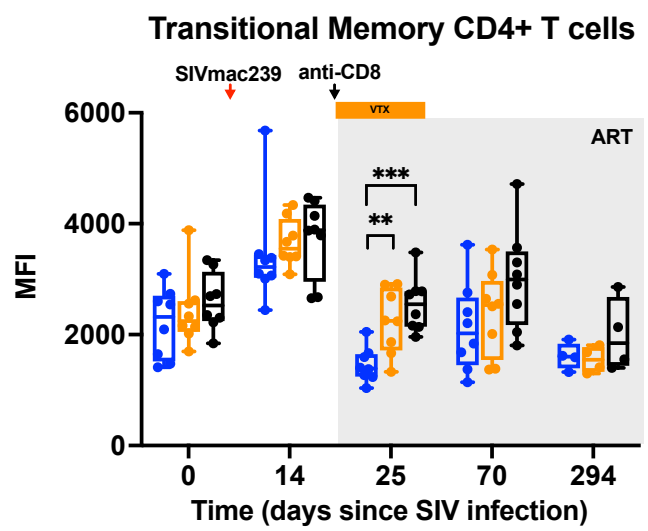
Immunological Impact of BCL-2 Inhibition

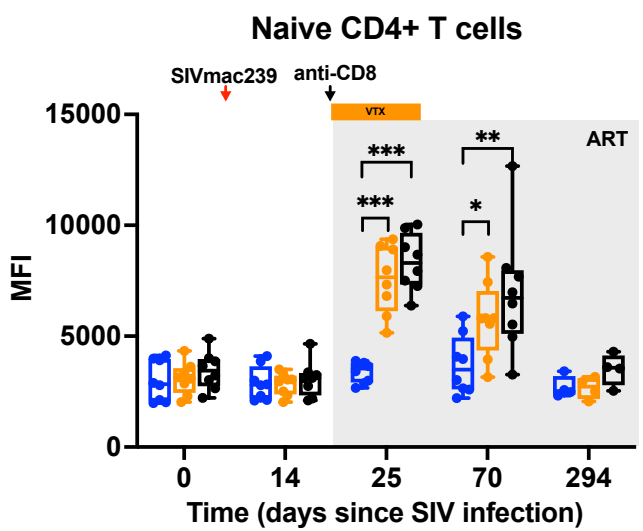






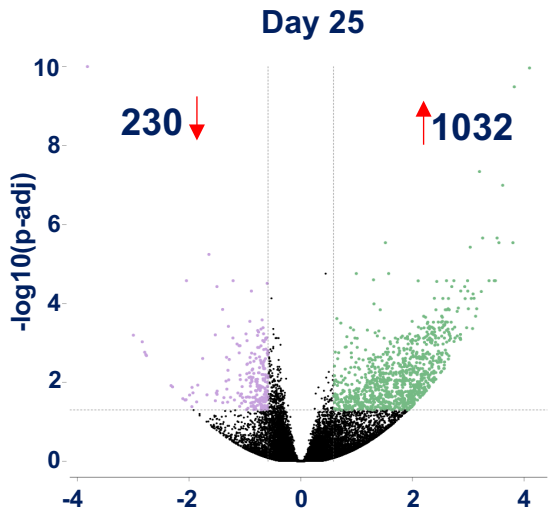
- Increased BCL-2 expression (MFI, via flow) in CD4+ T cells after VTX treatment

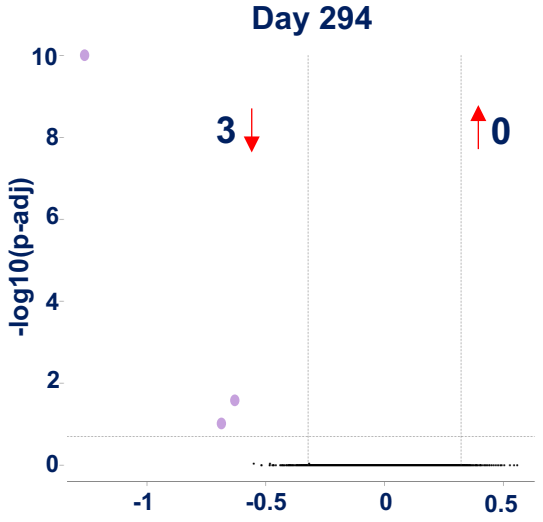


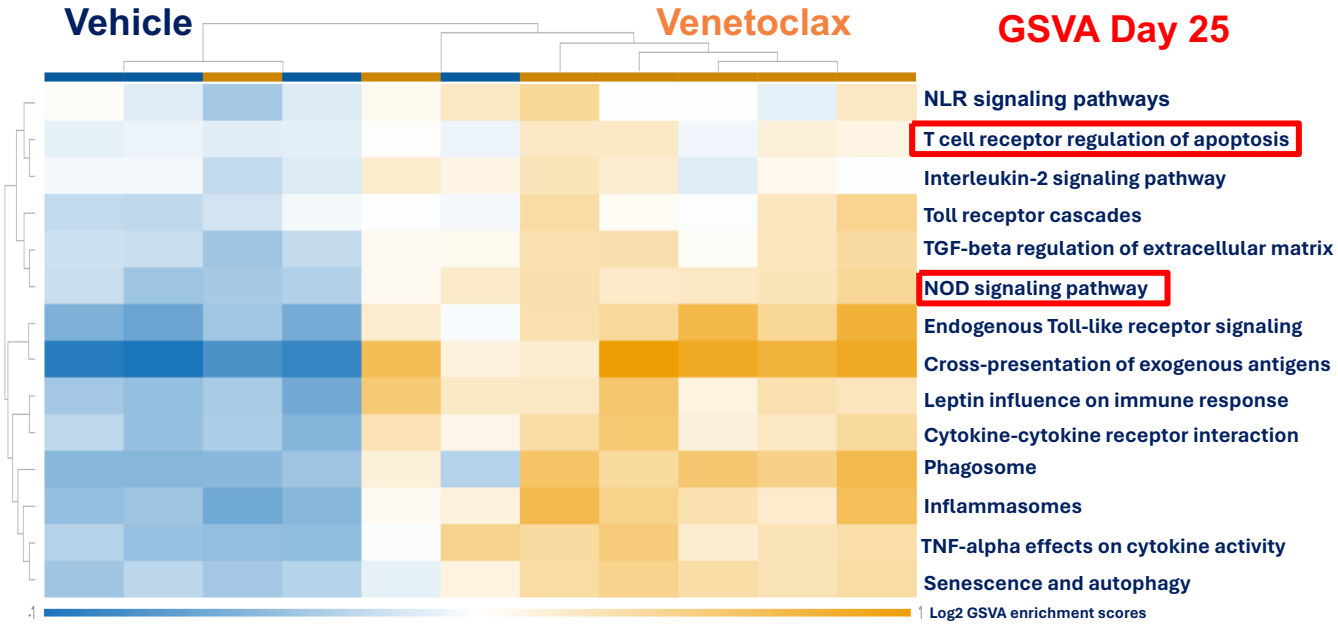


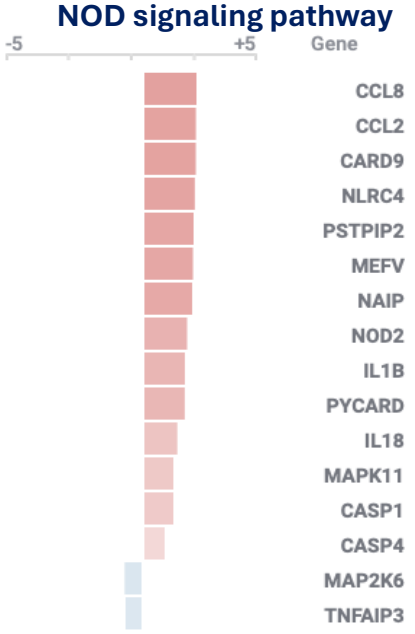
Immunological Impact of BCL-2 Inhibition

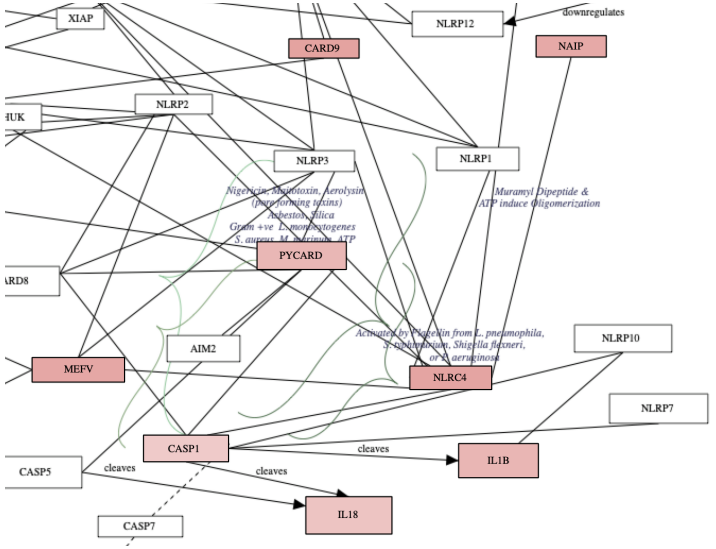
Bulk RNA-seq: Sorted CD4+T cells







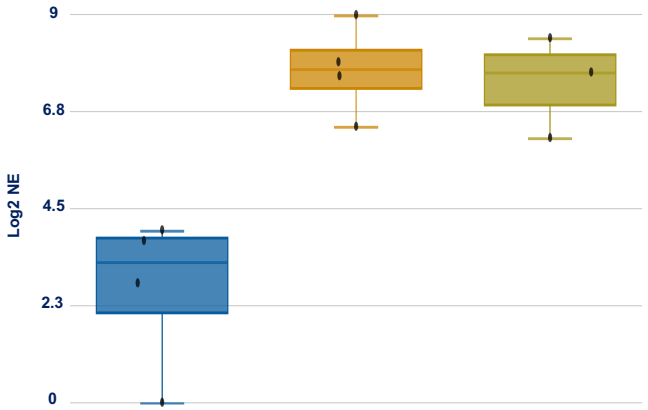




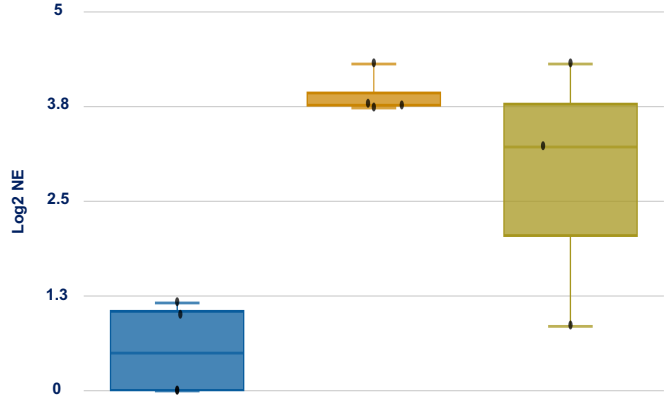
Immunological Impact of BCL-2 Inhibition (Day 25)

Vehi Vtx Vtx+CD8d

CLU



NOL-3



Clusterin inhibits apoptosis by interacting with activated Bax

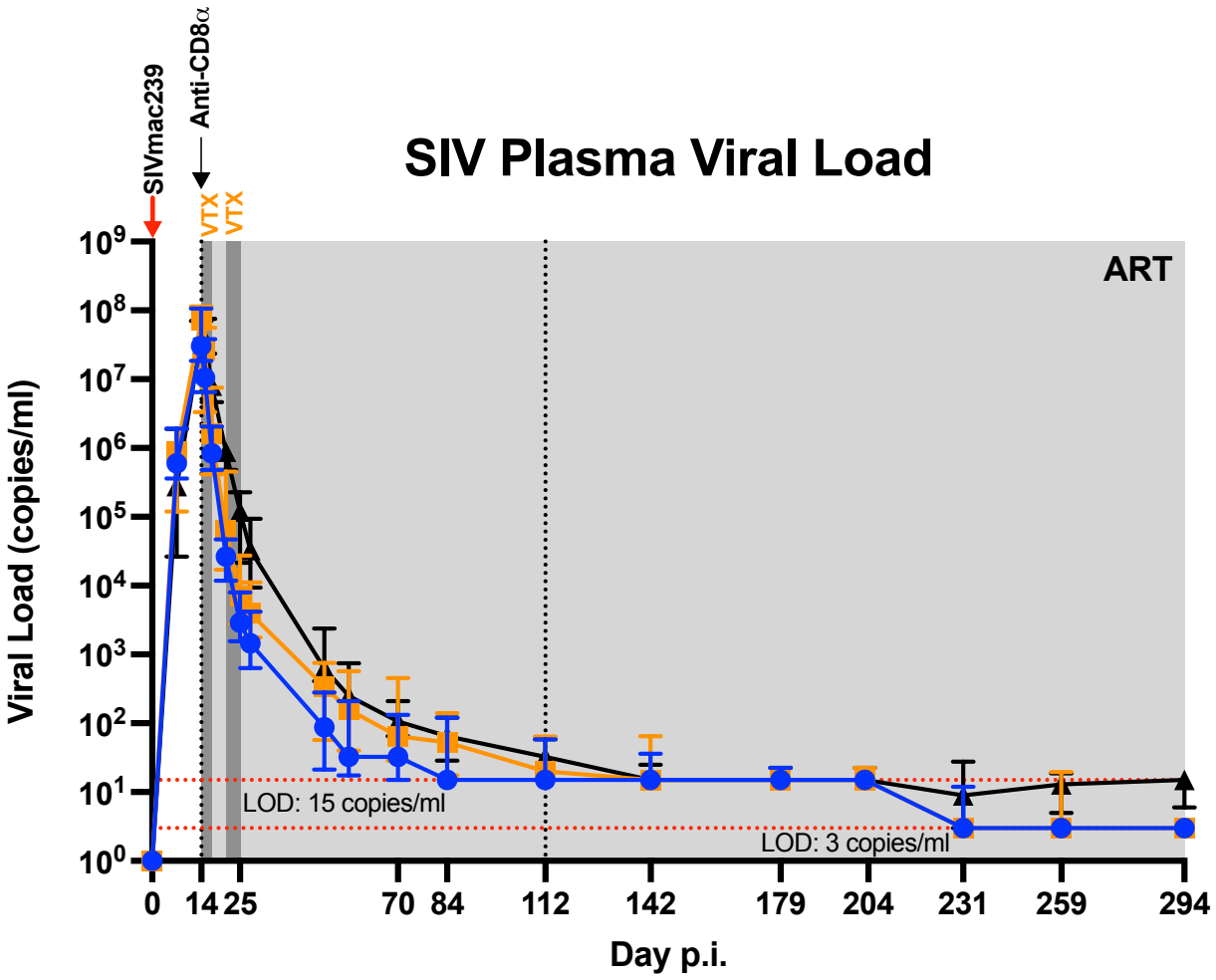
Honglai Zhang[1], Jin Koo Kim[1], Chris A. Edwards[2], Zhaohui Xu[3], Russell Taichman[4] and Cun-Yu Wang[1,5]

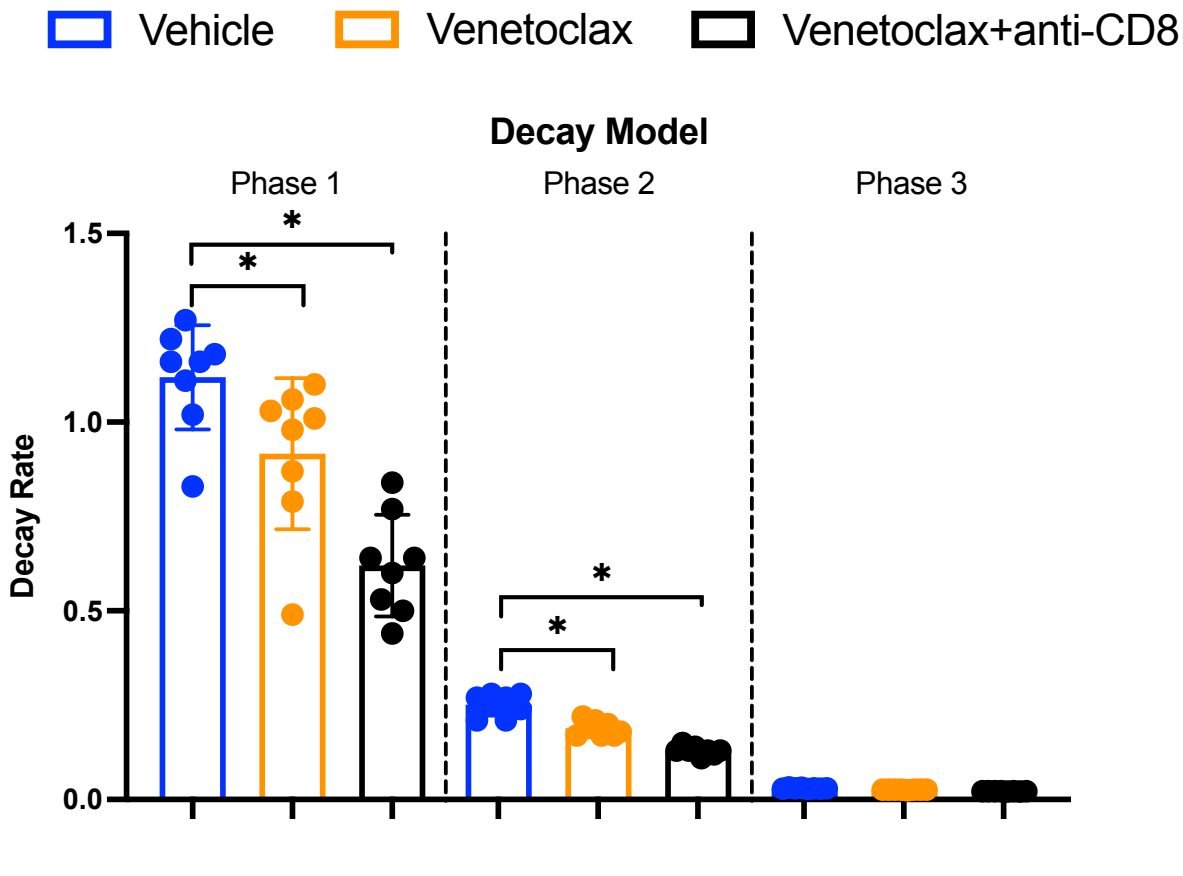
Inhibition of Both the Extrinsic and Intrinsic Death Pathways through Nonhomotypic Death-Fold Interactions

Young-Jae Nam,[1,2,3,6] Kartik Mani,[1,2,3,6]
Anthony W. Ashton,[1,2,3] Chang-Fu Peng,[1,2,3]
Barath Krishnamurthy,[1,3] Yukihiro Hayakawa
Peiyee Lee,[1,2,3] Stanley J. Korsmeyer,[5]
and Richard N. Kitsis[1,2,3,4,*]

- Some anti-apoptotic genes are also upregulated in CD4+ T cells after VTX treatment

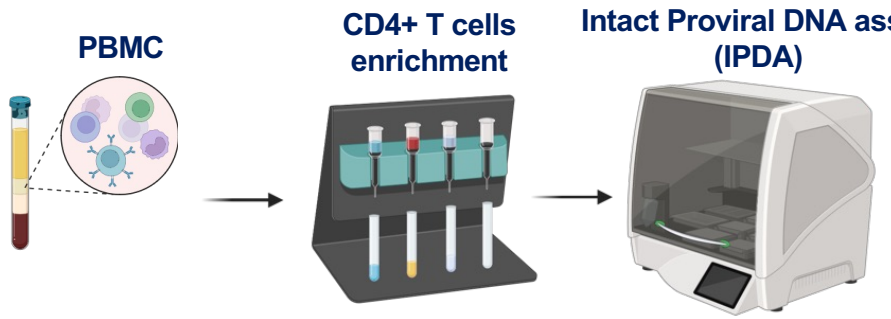
BCL-2 Inhibition, particularly with CD8 depletion, slowed plasma viral load decay, suggesting disruption of latency



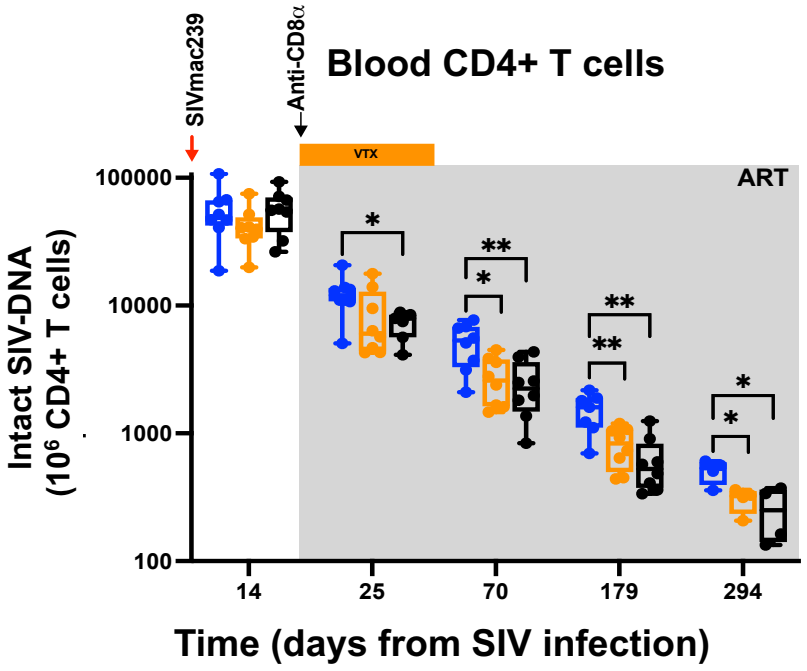


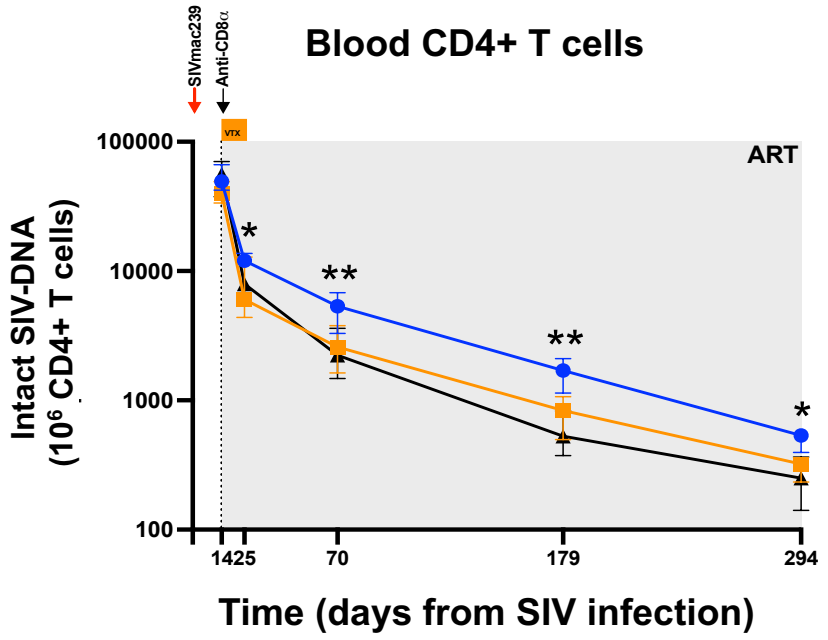
- This slower decline can be interpreted as prolonged lifespan of productively SIV-infected cells and/or higher per-cell virus production from these cells

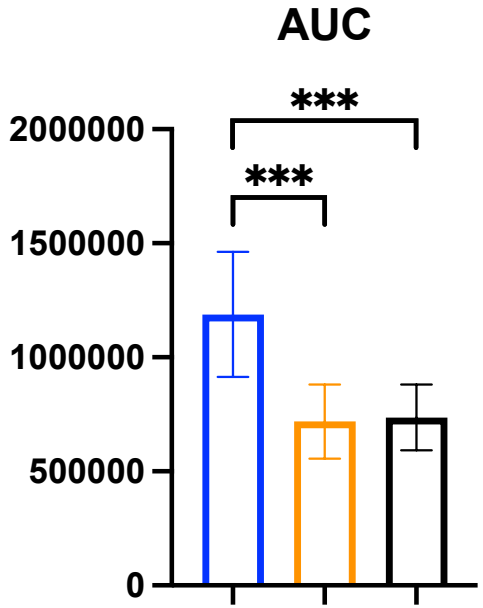
Inhibition of BCL-2 via venotoclax leads to a rapid and lasting reduction of the SIV- Reservoir



Vehicle Venetoclax Venetoclax+anti-CD8

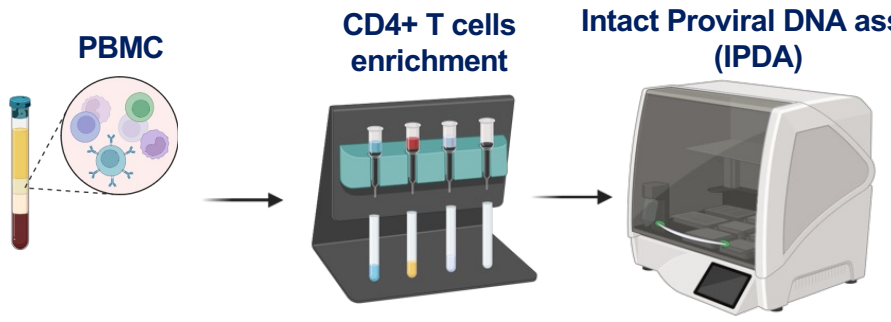




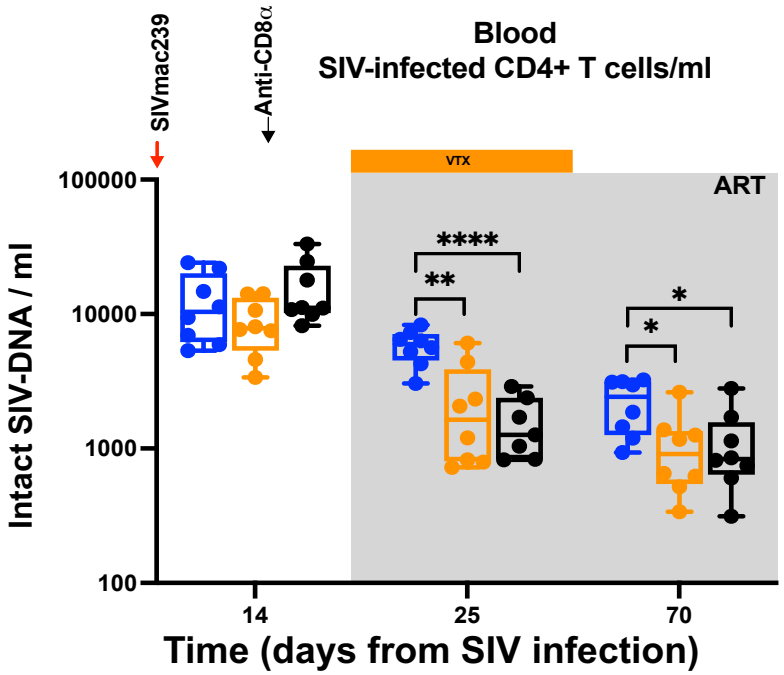


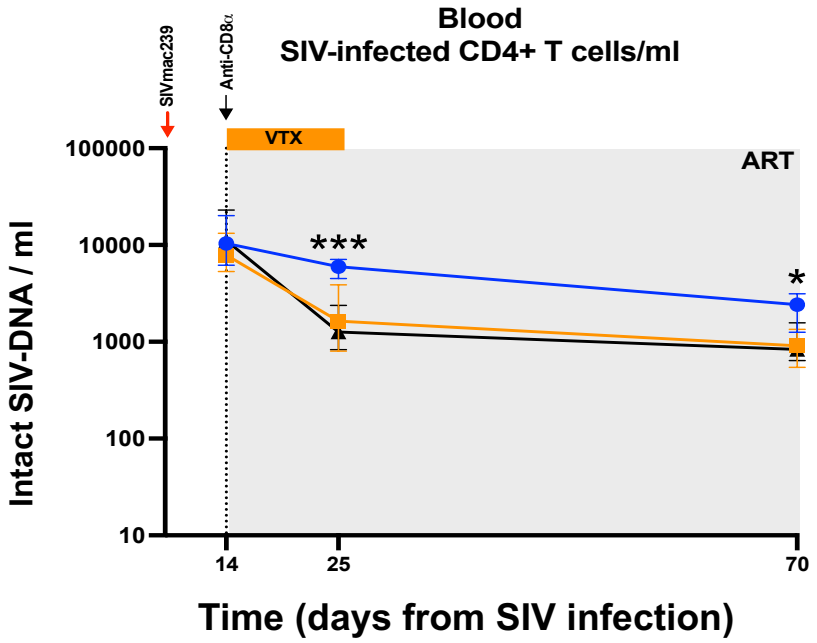
Rapid and sustained decrease in the frequency of blood CD4⁺ T cells with intact proviral genomes

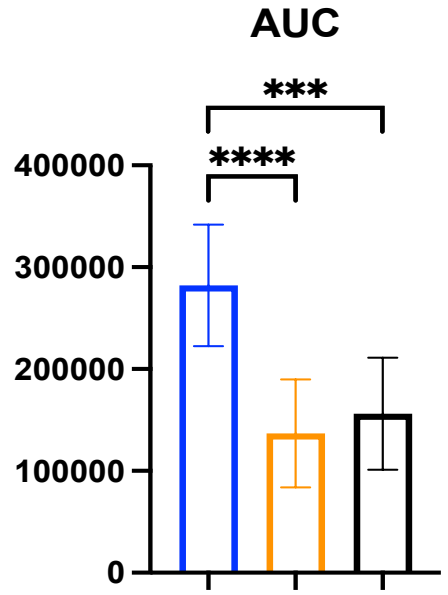
Inhibition of BCL-2 via venotoclax leads to a rapid and lasting reduction of the SIV- Reservoir



Vehicle Venetoclax Venetoclax+anti-CD8







The net reduction of the reservoir is higher when considering the absolute levels of CD4⁺ T cells

SIV-Reservoir Quantification in LNs PhenoCycler Fusion/DNA/RNAScope

Claire Deleage –NCI Frederick

Immune cells
CD14
CD4
CD3
CD8
CD68
CD163
CD20
MPO
DC-SIGN
CD21 (FDC)

Activation
PCNA / KI67

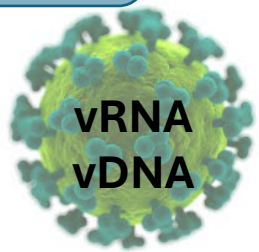
Cell death
BCL2
CD47

Inflammation
IDO
MxA
TGF-b

T cell activation
CD45-RO
CD45-RA
T-bet
Fox-P3
IL-10
CD25

Transcription factors
Tox-1
TCF-1

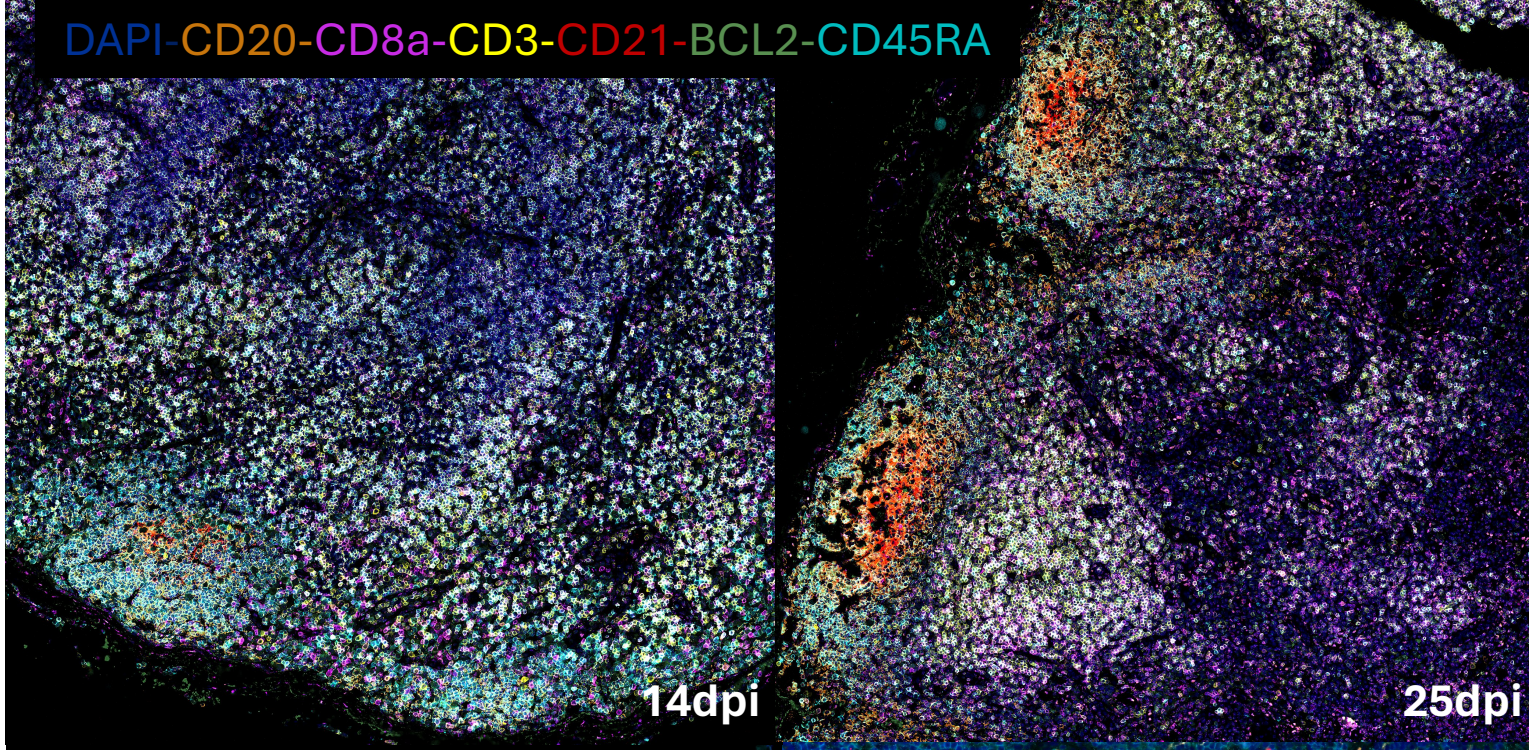
Immune checkpoints
PD1
CTLA-4

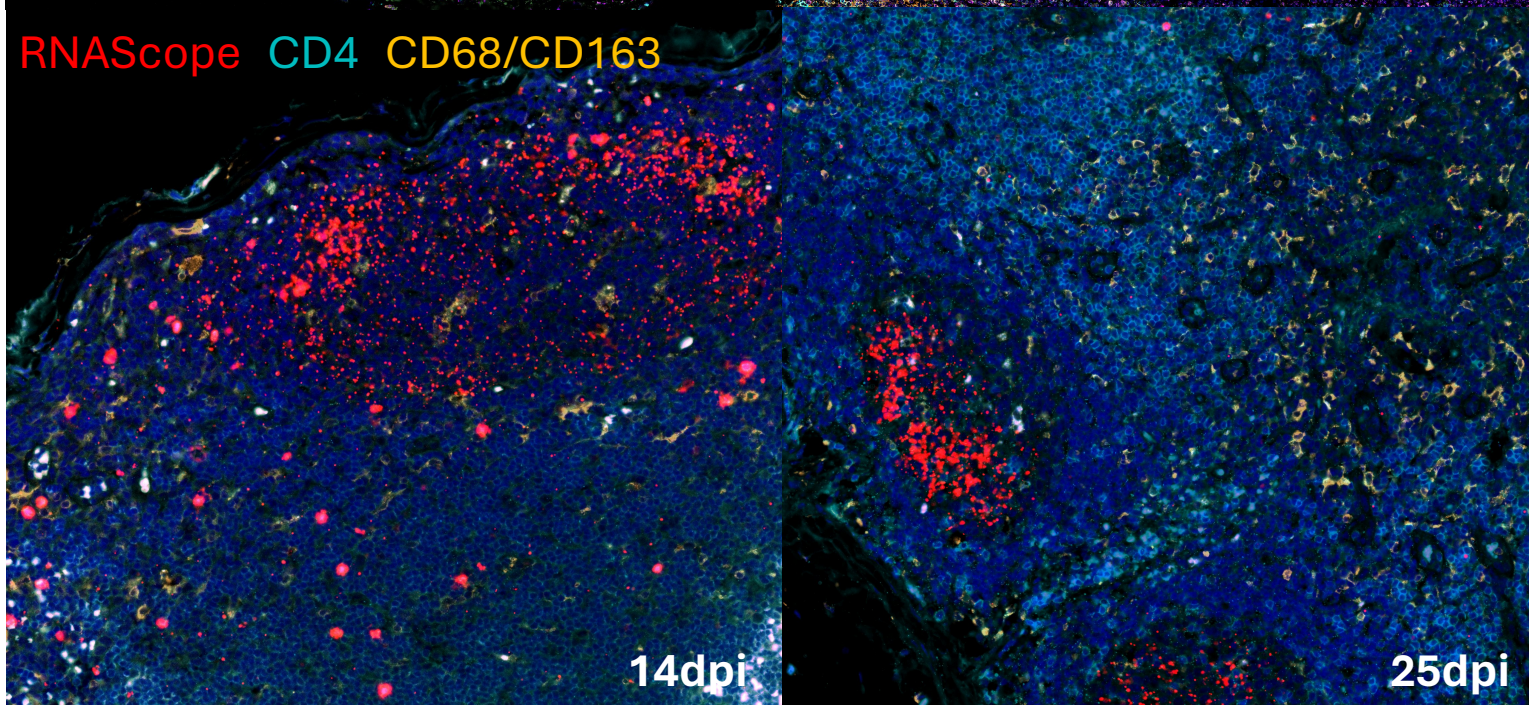


Cytotoxicity
GzB
Granulysin

B cell activity
CD27
BCL-6

Cell trafficking
CD34
CD49a (CD8+TRM)





Conclusions

BCL-2 inhibition at ART initiation:

- **Is associated with a slower decline of viremia (prolonged lifespan of productively infected cells and/or higher per-cell virus production)**
- **Significantly perturbs the establishment and maintenance of the intact SIV reservoir in blood**
- **Appears to preferentially impact circulating CD4+ T cells harboring intact SIV**

BCL-2 inhibition during long-term ART (2 years), combined with a latency-reversal strategy, reduces the size of the SIV reservoir (Sydney Bergstresser)

Bcl-2 inhibition, either at ART initiation or during long-term ART, warrants further studies as a novel approach to disrupt HIV and SIV persistence.

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EMORY NATIONAL PRIMATE RESEARCH CENTER

CFAR
Emory Center for AIDS Research

BCL-2 inhibition via Venetoclax in CD8a depleted, ART suppressed, SIV infected rhesus macaques

MT807R1 Ab
CD8α Depletion
50 mg/kg

Rh-heterodimeric IL-15
10-40 ug/kg

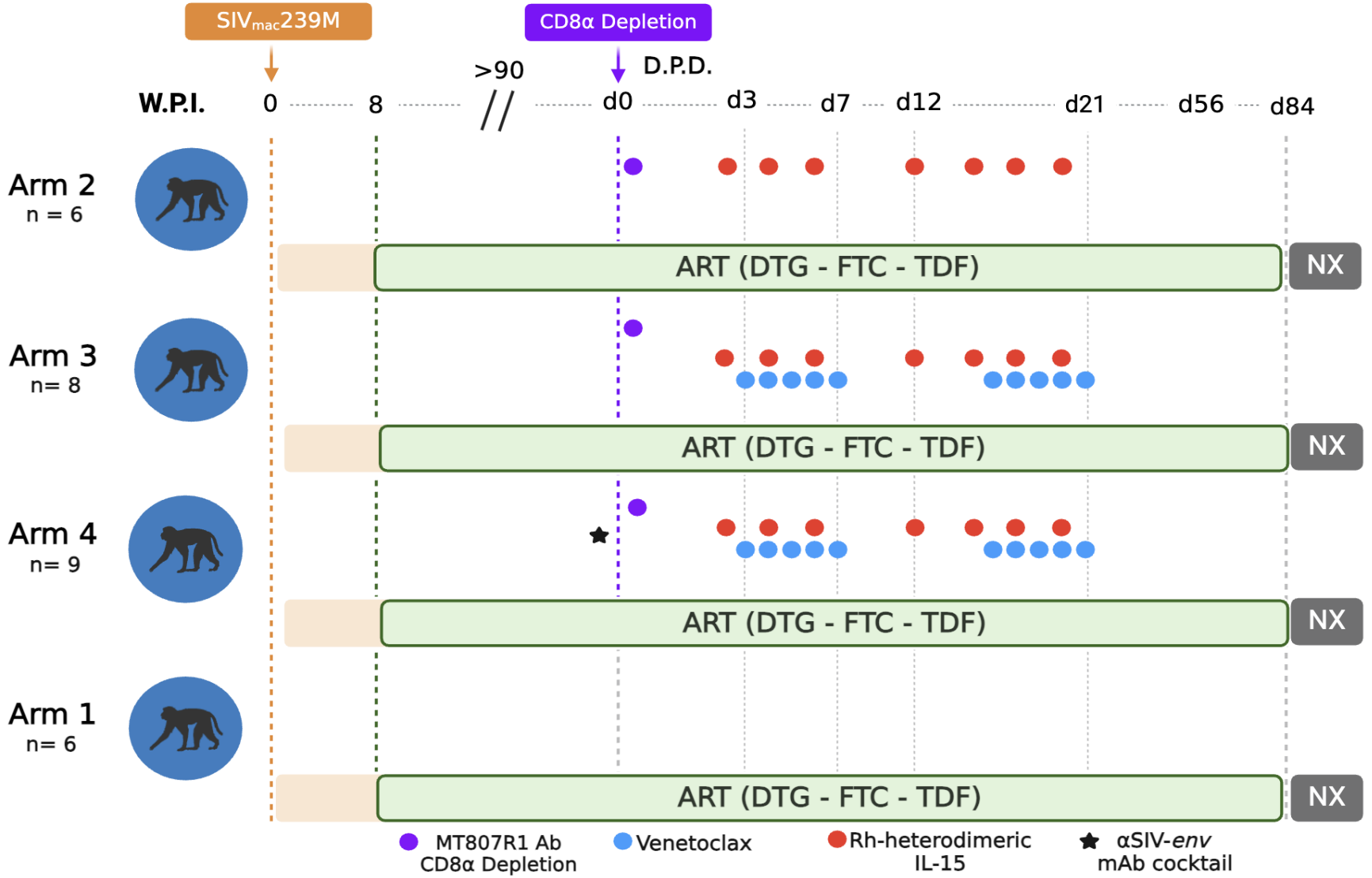
Venetoclax
300 mg/dose

αSIV-*env* mAb
ITS102.01-LS
ITS103.01-LS
ITS109-LS
ITS113.01-LS


Sydney Bergresser

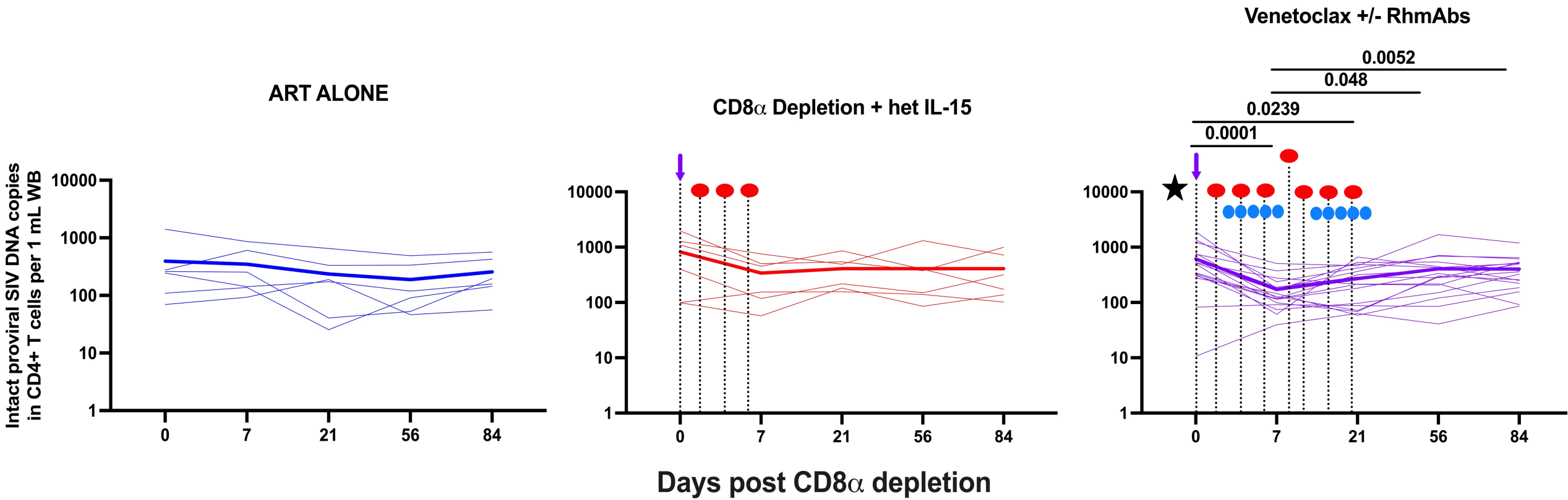
Guido Silvestri

Deanna Kulpa



- **2 years of ART before interventions**

BCL-2 inhibition perturbs the viral reservoir in CD8a depleted, ART suppressed, SIV infected rhesus macaques



MT807R1 Ab CD8α Depletion

Venetoclax

Rh-heterodimeric IL-15

αSIV-*env* mAb cocktail

Bergstresser et al in preparation