CD8+ T cells promote HIV latency in CD4+ T cells through the downmodulation of NF-kB

Simona Mutascio
Emory National Primate Research Center

December 15th, 2022

Pro-latency activity of CD8$^+$ T cells

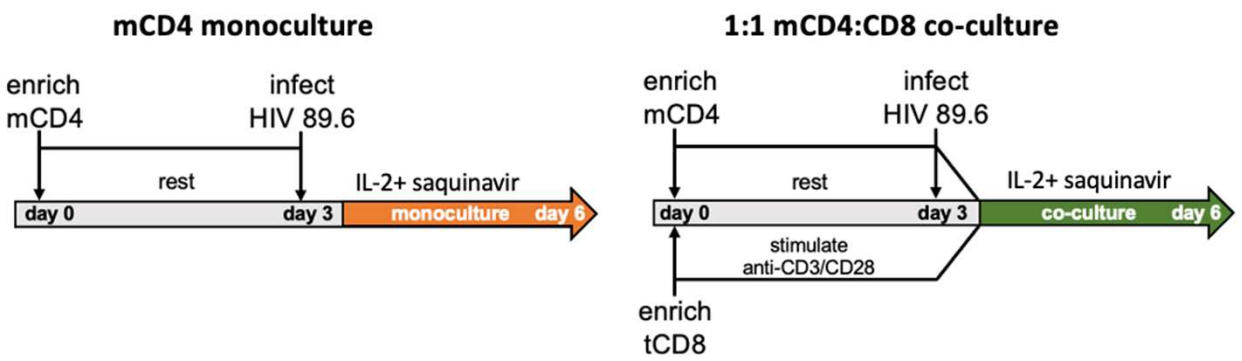
A small pool of non-productively infected, resting CD4$^+$ T cells which harbor replication-competent virus survive and transition to a long-lived, memory resting state (Chomont at al., Nat Med. 2009). This reservoir of latently-infected CD4$^+$ T cells persists for years despite prolonged suppression of viral replication during ART (Finzi et al., Science 1997; Siliciano et al., Nat Med. 2003)

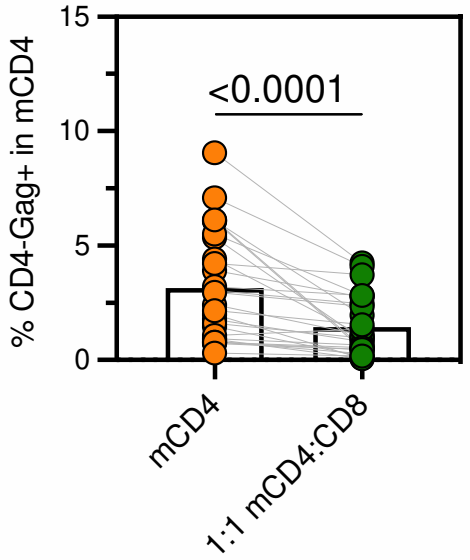
CD8$^+$ T cells from people leaving with HIV may suppress HIV expression via non-cytolytic mechanisms related to the secretion of soluble factors (Mackewicz et al., PNAS 1995, Li-Yun Chang et al., J Virol 2002, Wallace et al., J Immunol 2020)

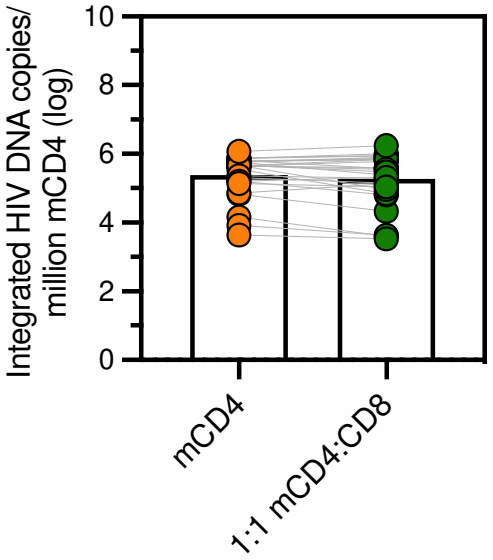
CD8$^+$ T cells can suppress viral gene expression independent of blocking viral entry, integration, or reverse transcription (Cocchi et al., Science 1995; Schmitz et al., Science 1999; Wong et al., PLoS Pathog 2010)

In vitro studies show that innate, non-cytolytic CD8$^+$ T cell-mediated suppression of HIV replication by MHC-independent inhibition of virus transcription is a powerful mechanism of immune-mediated HIV silencing (Zanoni et al., PLoS Pathog 2020)

Pro-latency activity of CD8+ T cells

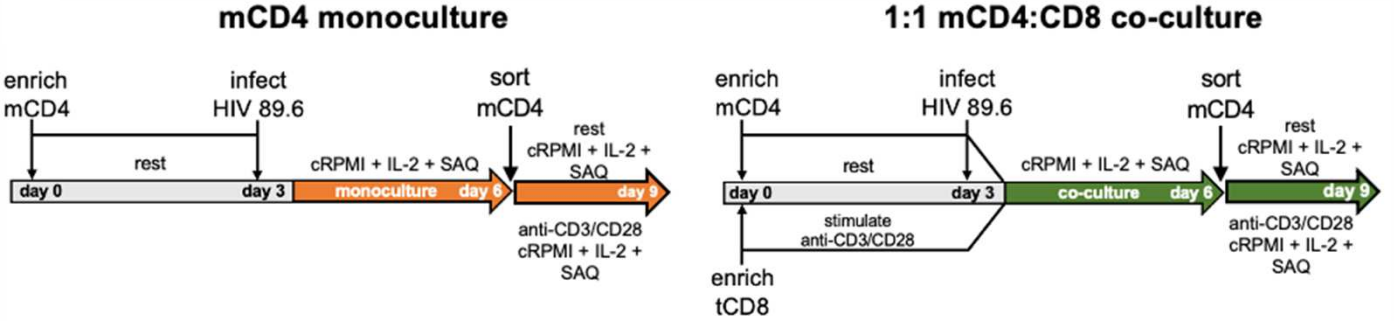


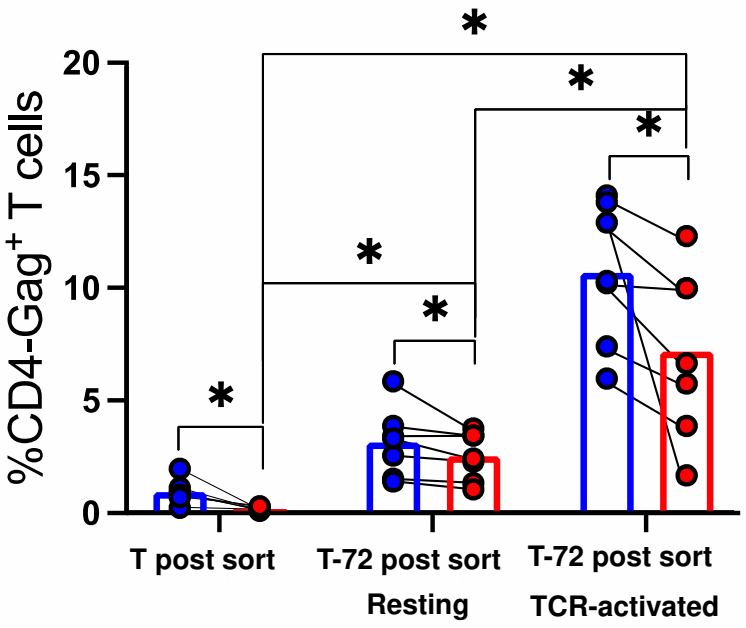


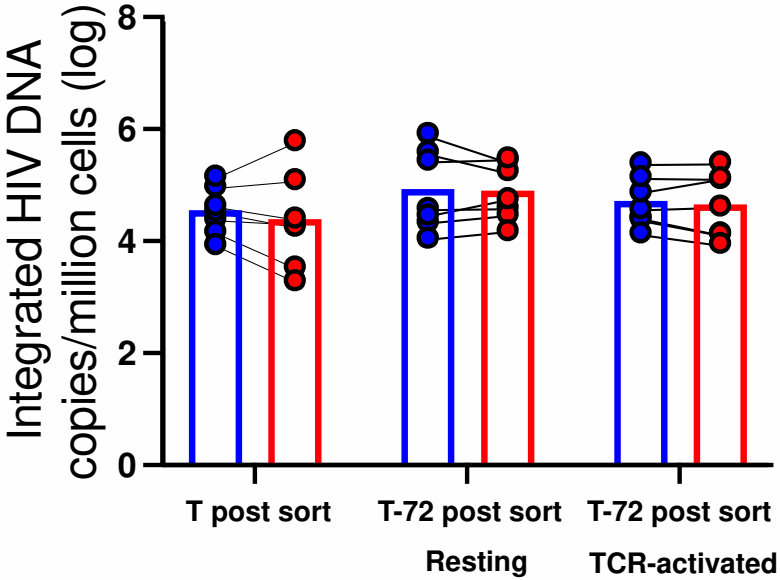


Mutascio et al., in review

Pro-latency activity of CD8+ T cells







ERASE HIV

mono mCD4 mCD4:CD8

Pro-latency activity of CD8$^+$ T cells

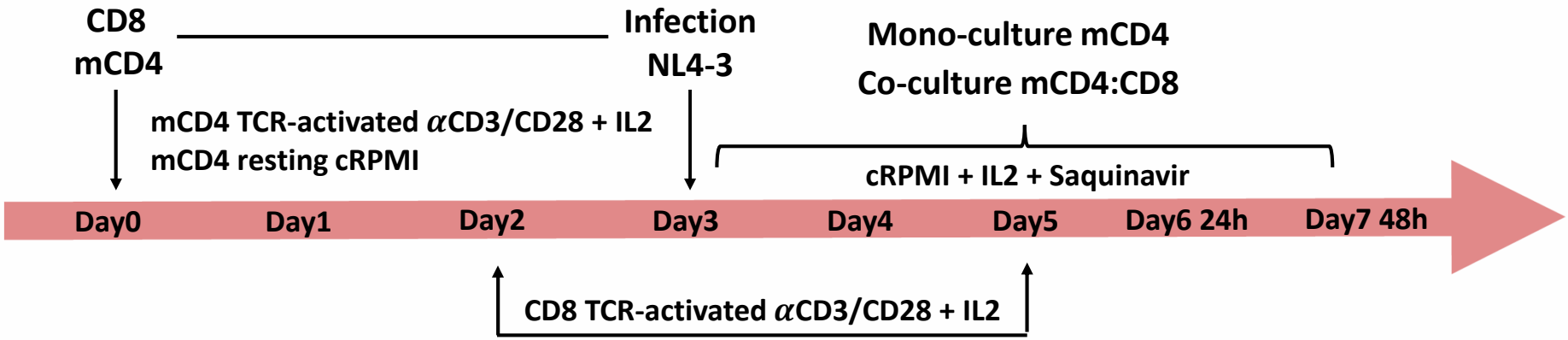
The active suppression of HIV transcription in CD4$^+$ T cells by non-cytolytic mechanisms may paradoxically favor and promote the establishment and the persistence of the reservoir by actively promoting latency

Pro-latency activity of CD8$^+$ T cells

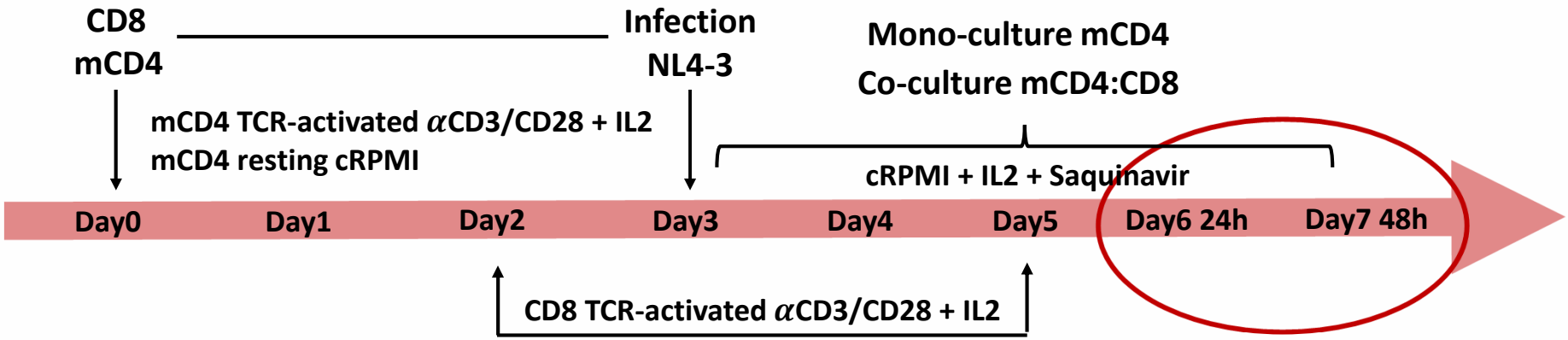
The active suppression of HIV transcription in CD4$^+$ T cells by non-cytolytic mechanisms may paradoxically favor and promote the establishment and the persistence of the reservoir by actively promoting latency

The aim of this study is to understand the molecular mechanisms involved in the silencing of HIV expression and in the establishment of HIV latency in memory CD4$^+$ T cells mediated by CD8$^+$ T cells

In vitro model of HIV latency establishment

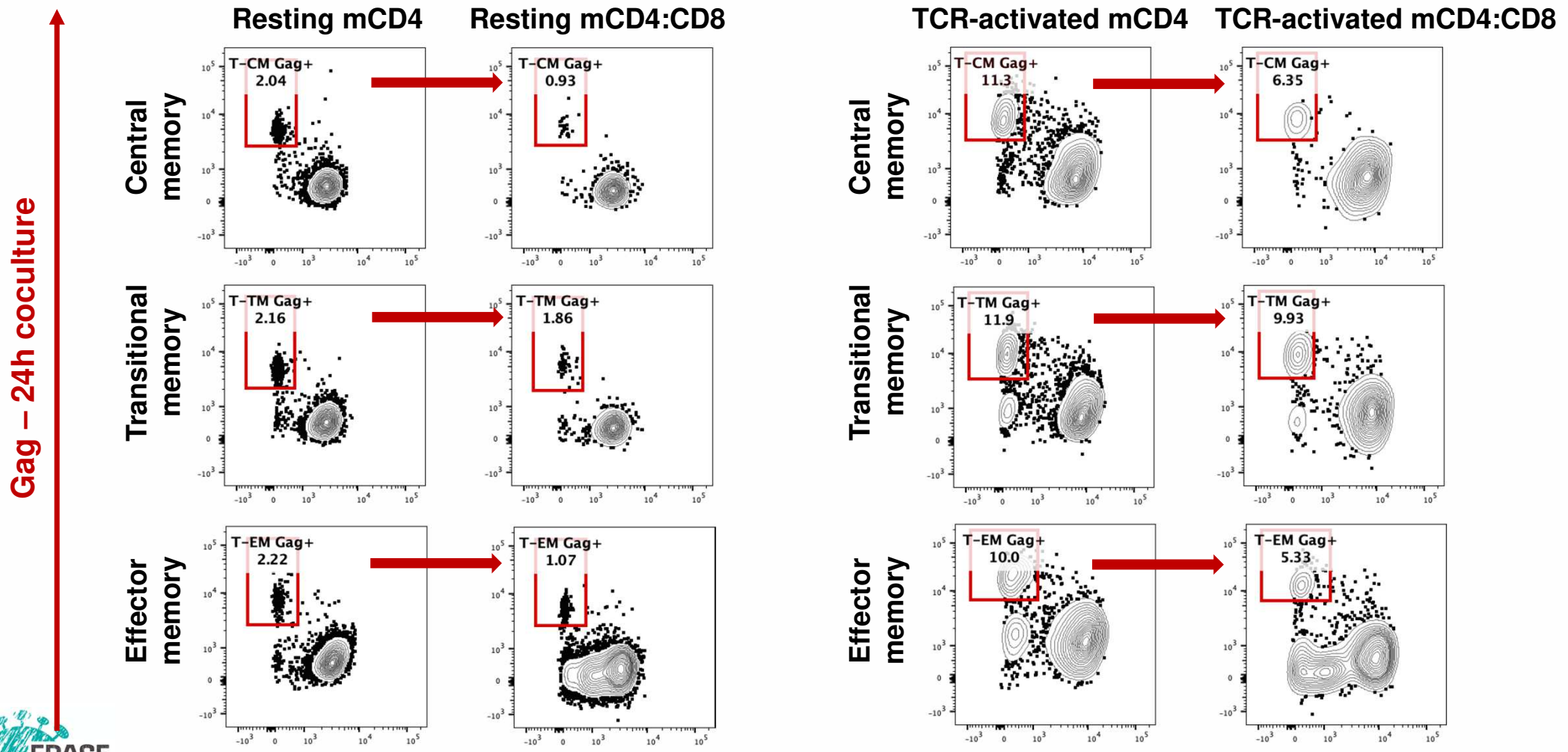


In vitro model of HIV latency establishment

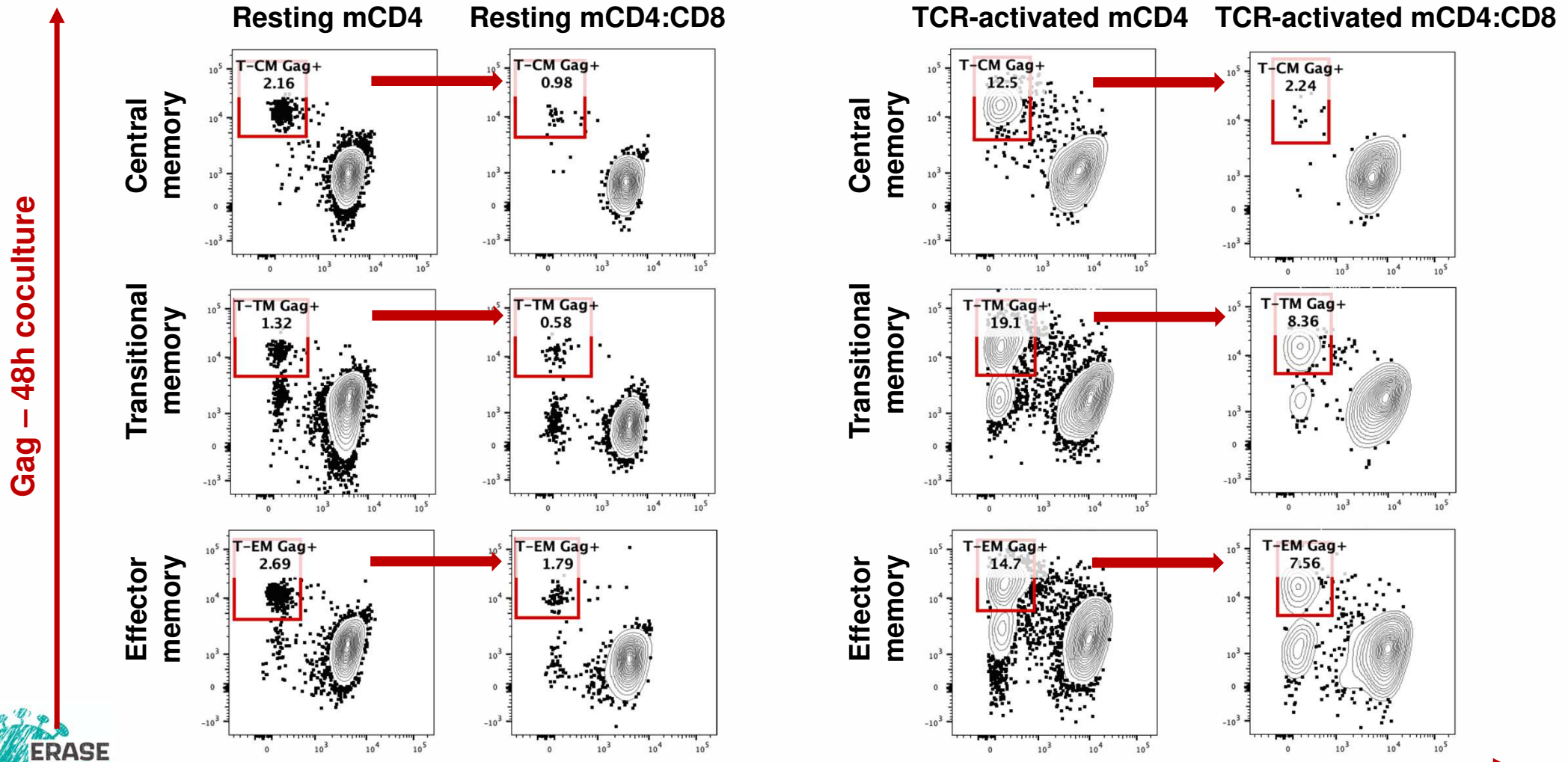


1. Analysis of the CD8⁺ T cells suppression activity of HIV expression in the central, transitional, and effector memory CD4⁺ subsets
2. Analysis of the CD8⁺ T cells involvement in the memory CD4⁺ subset distribution
3. Analysis of the impact of CD8⁺ T cells in the NF-kB activity in mCD4⁺ T cells

1. CD8⁺ T cells suppress HIV Gag expression in the CD4⁺ memory subsets



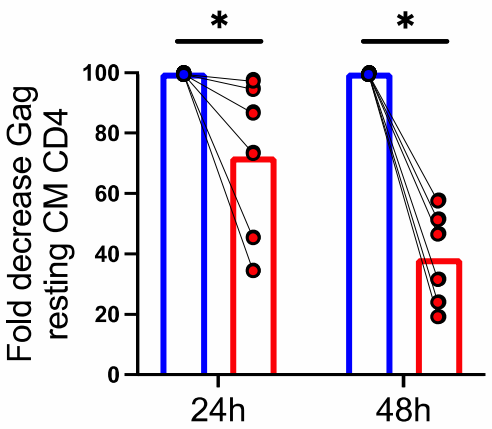
1. CD8⁺ T cells suppress HIV Gag expression in the CD4⁺ memory subsets



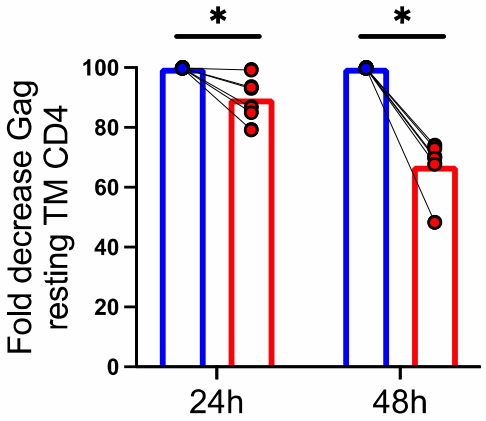
1. CD8+ T cells suppress HIV Gag expression in the CD4+ memory subsets

Resting

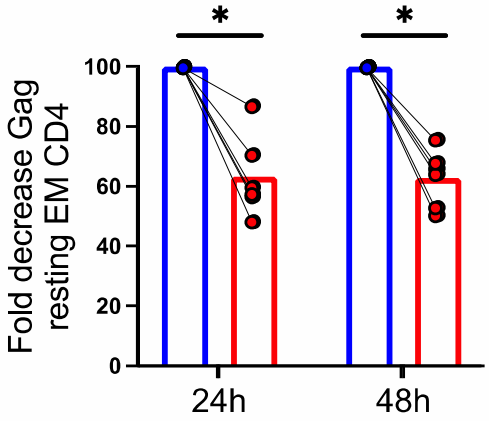
Central Memory CD4+



Transitional Memory CD4+

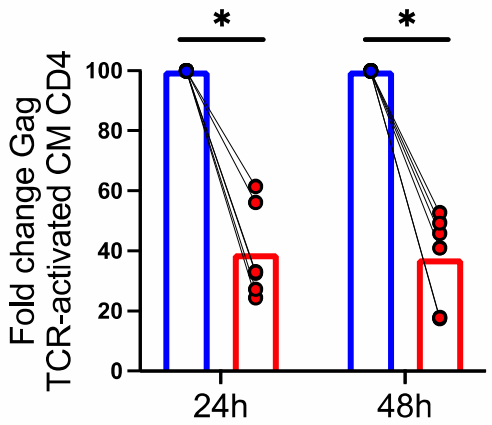


Effector Memory CD4+

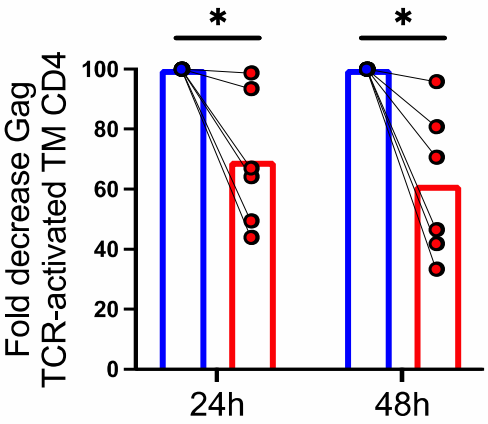


TCR-activated

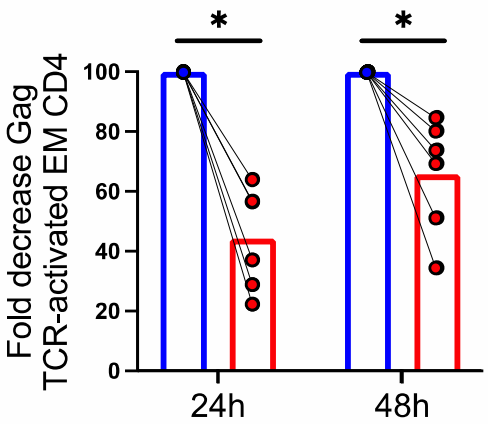
Central Memory CD4+



Transitional Memory CD4+



Effector Memory CD4+

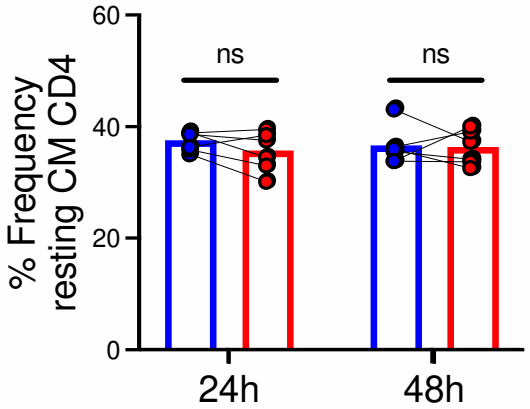


mono mCD4 mCD4:CD8

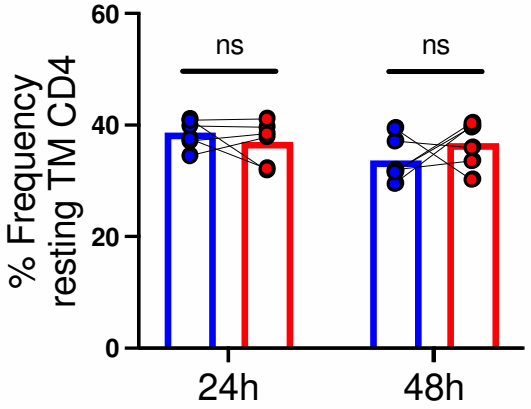
2. CD8⁺ T cells do not affect the memory CD4⁺ subset distribution

Resting

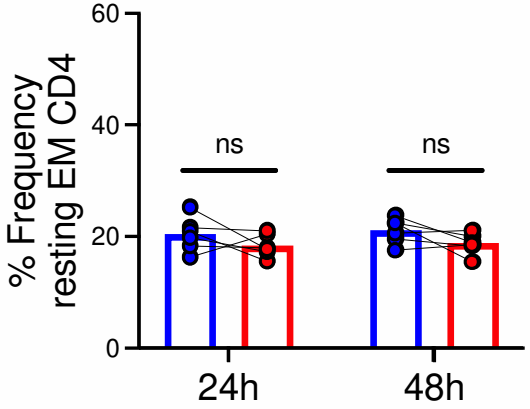
Central Memory CD4⁺



Transitional Memory CD4⁺

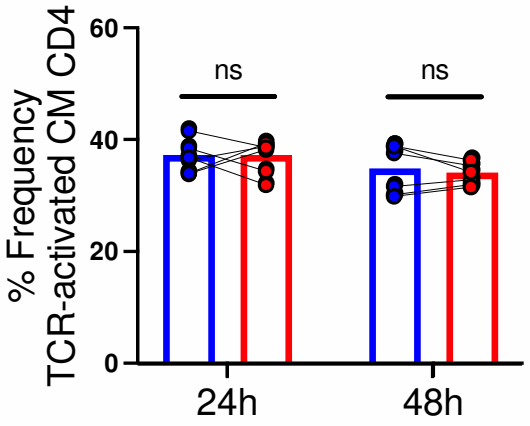


Effector Memory CD4⁺

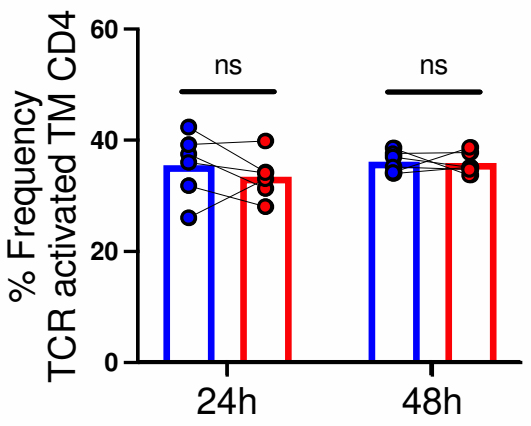


TCR-activated

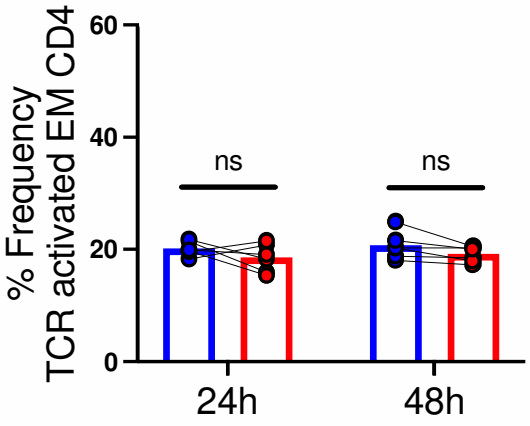
Central Memory CD4⁺



Transitional Memory CD4⁺



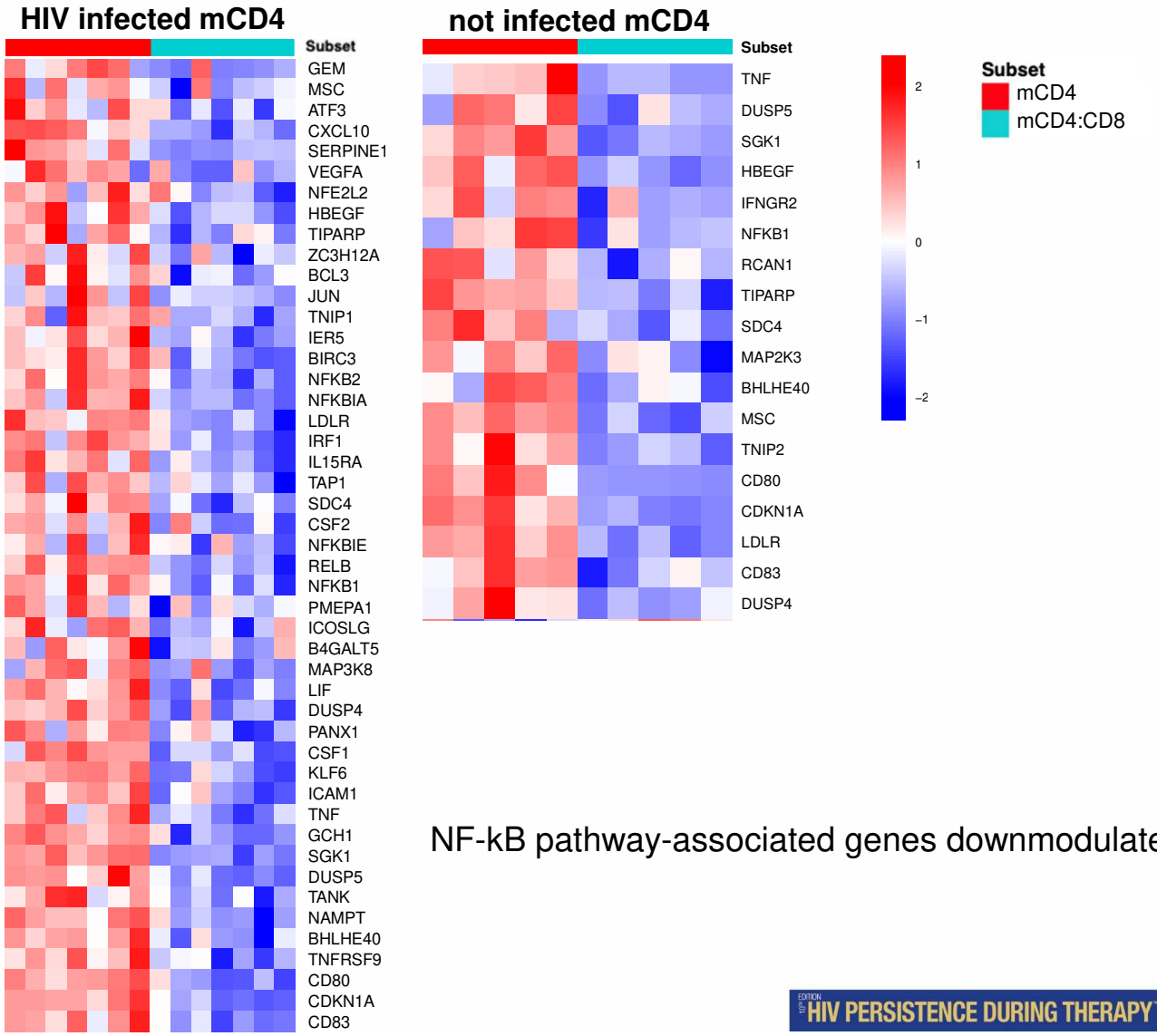
Effector Memory CD4⁺



mono mCD4 mCD4:CD8

ERASE HIV

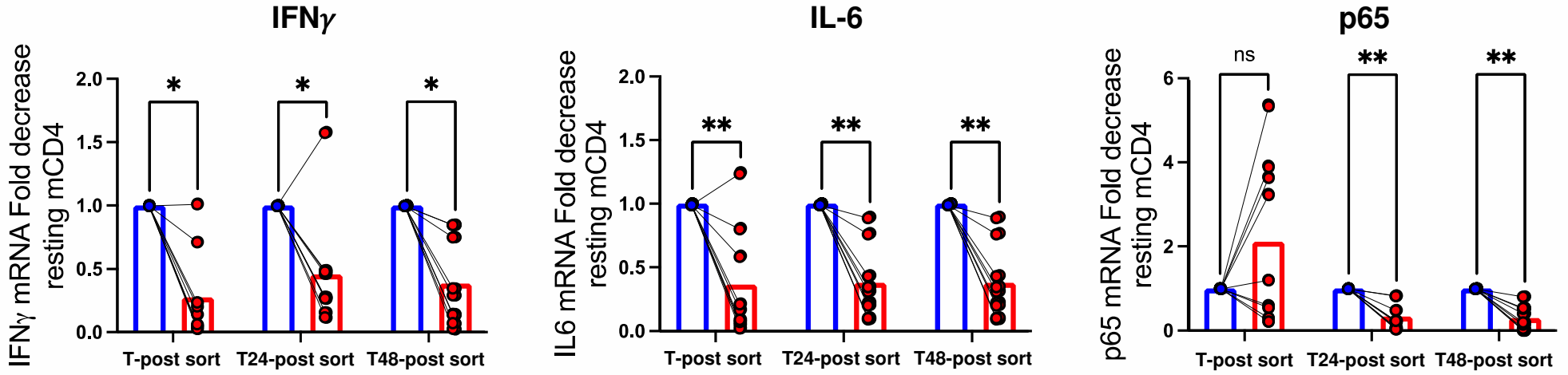
3. CD8+ T cells negatively affect the NF-kB activity in mCD4+ T cells



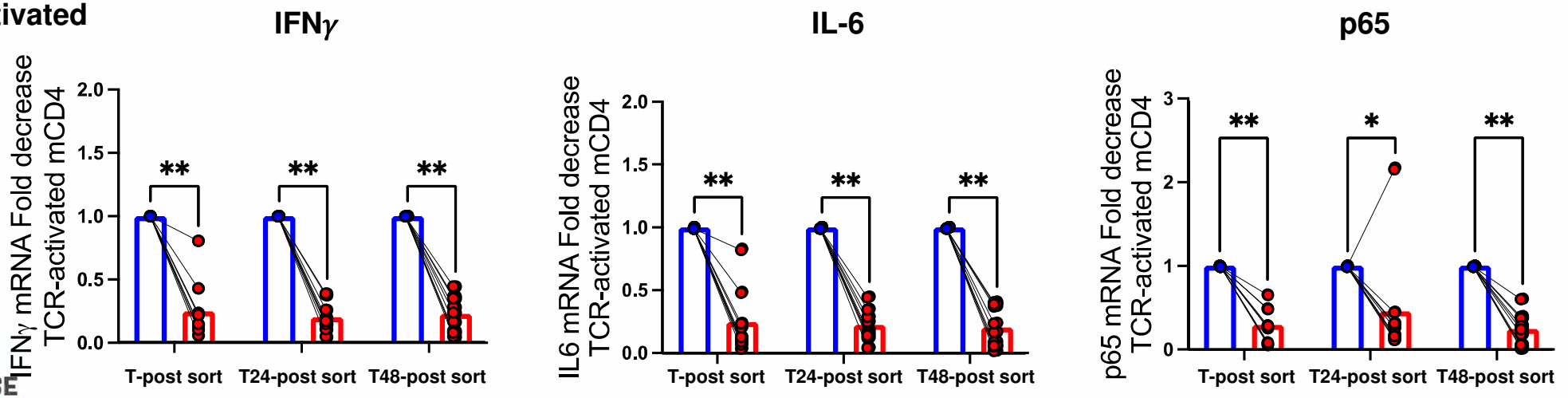
NF-kB pathway-associated genes downmodulated in mCD4:CD8

3. CD8+ T cells negatively affect the NF-kB activity in mCD4+ T cells

Resting



TCR-activated



mono mCD4 mCD4:CD8

Conclusions

- ✓ $CD8^+$ T cells promote the establishment of HIV latency by downmodulating HIV expression in the central, transitional, and effector memory $CD4^+$ subsets
- ✓ $mCD4^+$ T cells following exposure to $CD8^+$ T cells have a significant downmodulation of the NF-kB activity that persists over time
- ✓ After $CD8^+$ T cells removal from coculture, HIV latency is reversed but it does not reach levels comparable to monoculture, suggesting the existence of a sustained pro-latency effect exerted by $CD8^+$ T cells
- ✓ Our data suggest that $CD8^+$ T cells suppress HIV expression through the downmodulation of NF-kB
- ✓ Ongoing experiments are focused on the analysis of the role of $CD8^+$ T cells in the epigenetic remodeling and in the modulation of the differentiation of memory $CD4^+$ T cells

ERASE HIV

- **Key question(s)** To reveal the mechanism involved in the HIV infection of long lived $CD4^+$ T cells, which represent the main source of the reservoir in people living with HIV, mediated by $CD8^+$ T cells
- **Key finding(s) and take-home message** $CD8^+$ T cells change specific pathways in long lived $CD4^+$ T cells, thus favoring the establishment of the HIV reservoir
- What are the **next steps**? The characterization of the mechanism of the infection of long lived $CD4^+$ T cells will allow us to design a new intervention strategy to specifically target the HIV reservoir

Acknowledgments

Kulpa Lab

Deanna Kulpa

Lavinia Franchitti

Maura Statzu

Sydney Bergstresser

Yury Kuzmichev

Christina Mallarino-Haeger

Cristina Ceriani

Negar Neshat

Hong Wang

Johnny Abraham

Emory University

Guido Silvestri

Mirko Paiardini

Emory - ENPRC

EPC Genomics Core

Steven Bosinger

Gregory Tharp

EVC Flow cytometry core

Barbara Cervasi

Kiran Jill

Emory – Sekaly Lab

Rafick Sekaly

Ashish Sharma

Cornell University

Brad Jones

Talia Mota

Martin Delaney Collaboratories for HIV Cure Research
NIAID/NHLBI/NIDDK/NINDS/NIDA **UM1AI164562**

EMORY | NATIONAL PRIMATE RESEARCH CENTER