

11<sup>TH</sup> EDITION

DECEMBER 10-13, 2024

# HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



## **BACH2 controls seeding of HIV reservoirs in memory CD4<sup>+</sup> T cells**

Liang Shan

*Washington University in St. Louis*

[www.hiv-persistence.com](http://www.hiv-persistence.com)

# CONFLICTS OF INTEREST

None

## Community summary:

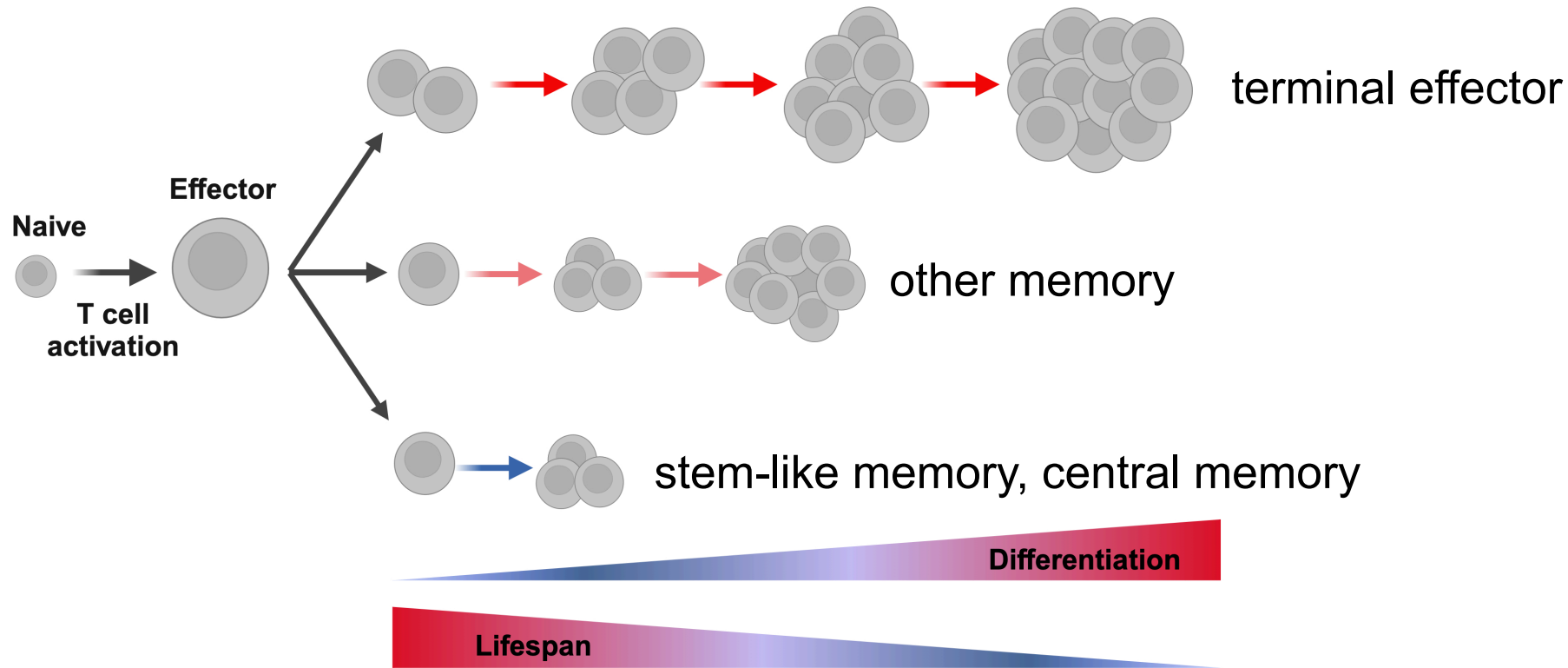
- During untreated infection, most T cells infected by HIV die within a few days due to cell death pathway (intrinsic) as well as immune clearance (extrinsic).
- A long-lived reservoir cell in PLWH on suppressive ART must have overcome both intrinsic and extrinsic selection pressure after being infected.
- We aimed to identify the cellular force(s) utilized by viral reservoir cells to avoid cell death.
- Targeting such intrinsic mechanism(s) will reduce or prevent seeding of long-lived viral reservoirs.

## Limitations:

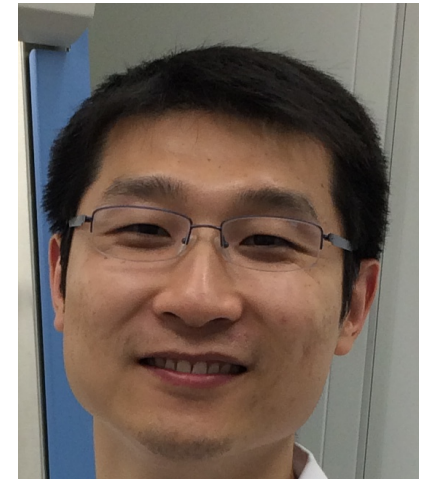
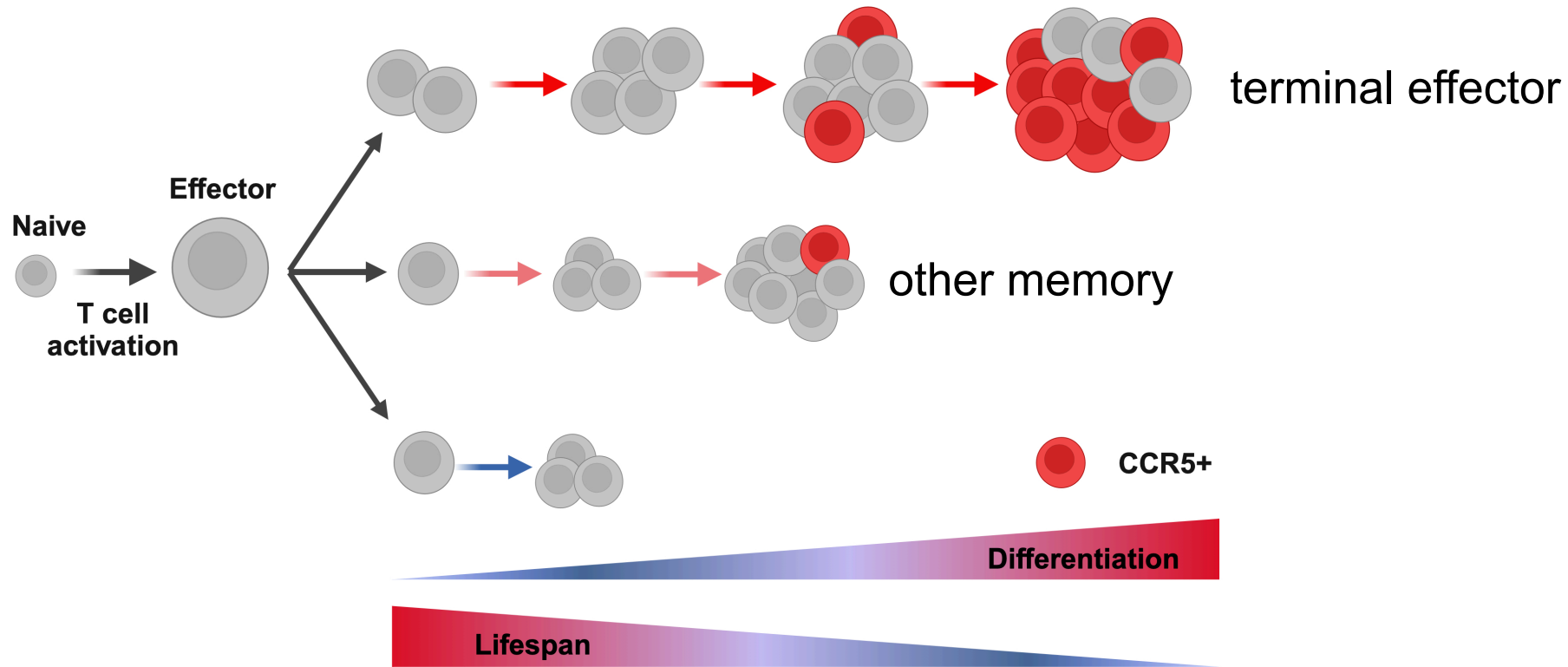
- This mechanism does not contribute to the seeding of naïve CD4<sup>+</sup> T cells harboring X4-tropic latent HIV
- BACH2 is unlikely involved in macrophage reservoirs.
- The contributions of HIV proteins to T cell reprogramming are not evaluated.



# The vast majority (>95%) of effector T cells are victims of clonal contraction

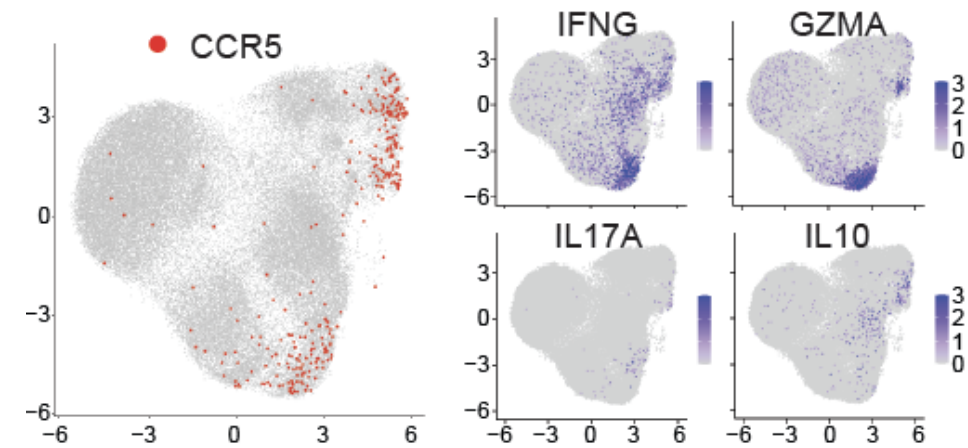
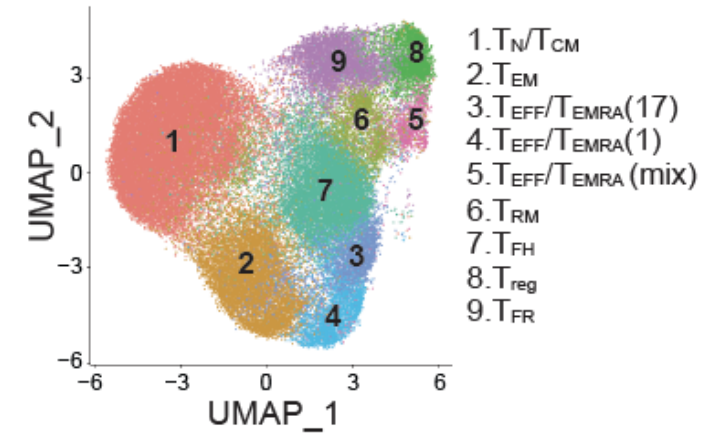
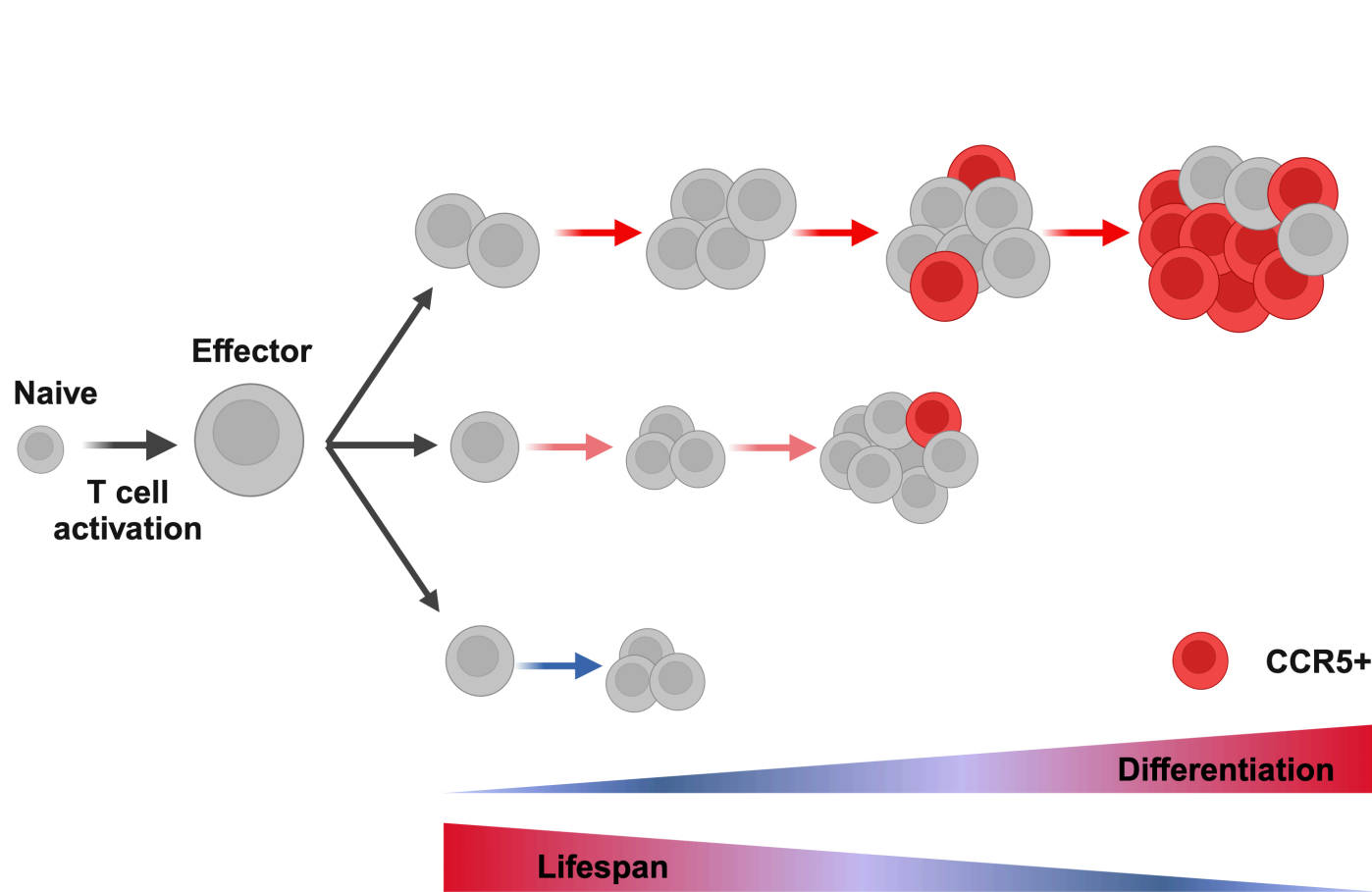


# Differentiation of CCR5<sup>+</sup> T cells



Gao H *et al.* Unpublished

# Differentiation of CCR5<sup>+</sup> T cells requires commitment to TEMRA?

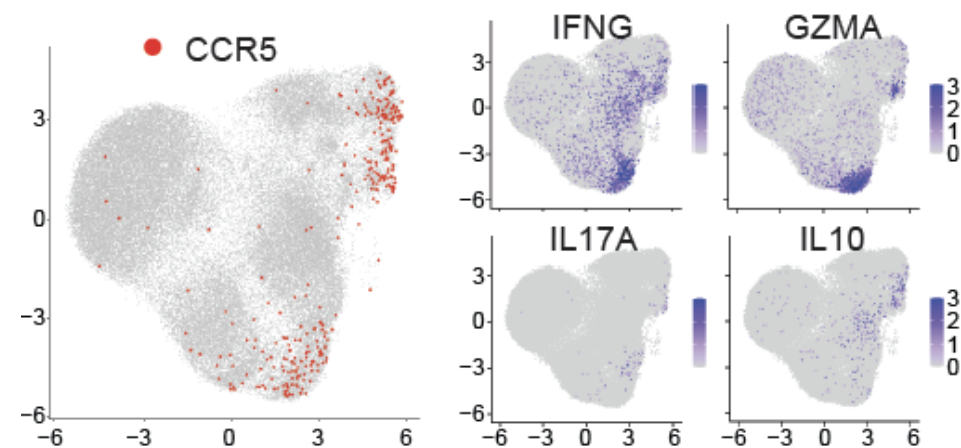
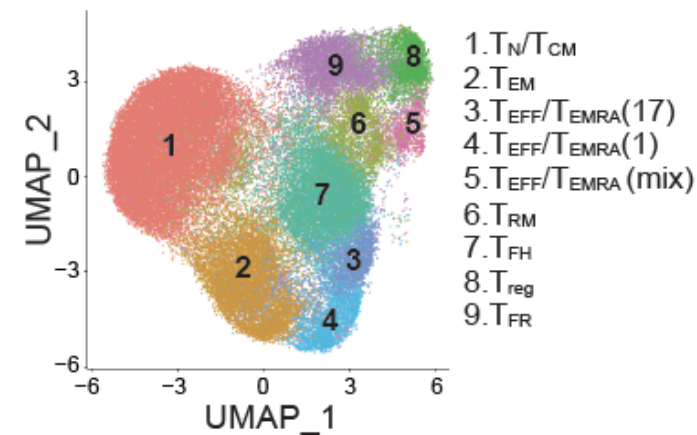


Gao H *et al.* Unpublished

# Differentiation of CCR5<sup>+</sup> T cells requires commitment to TEMRA?

Phenotypic characterization of HIVp24<sup>+</sup> or RNA<sup>+</sup> cells (viremic):

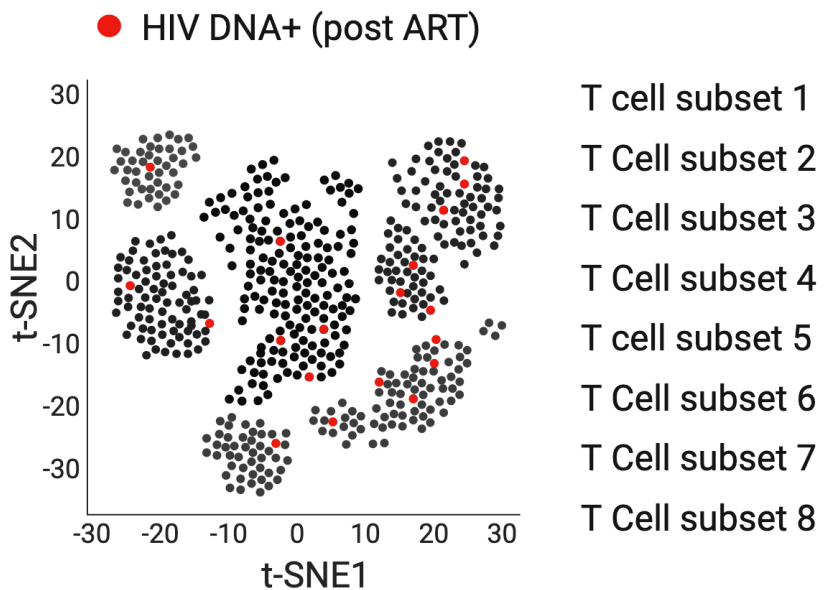
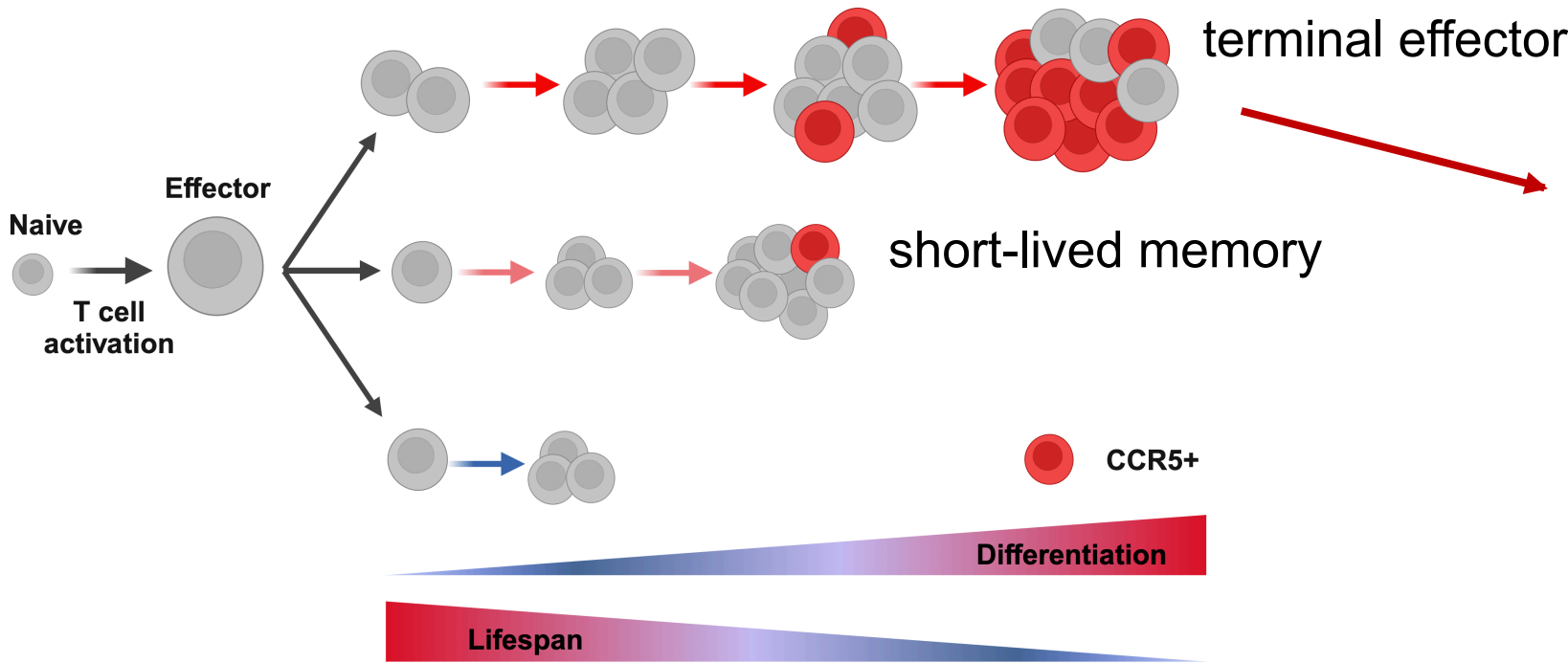
- CCR5<sup>+</sup>
- High activation/exhaustion markers
- Active production of effector molecules (Th1, Th17, etc)



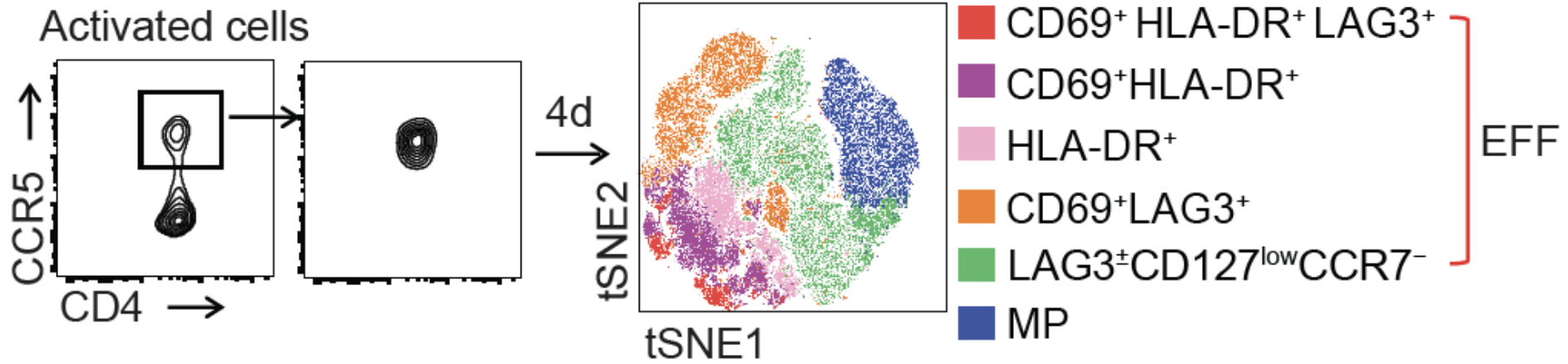
Gao H *et al.* Unpublished

# The HIV reservoir progenitors

- Susceptible (CCR5+)
- Long-lived (abort ongoing TEMa differentiation)
- Differentiation potential (plasticity)

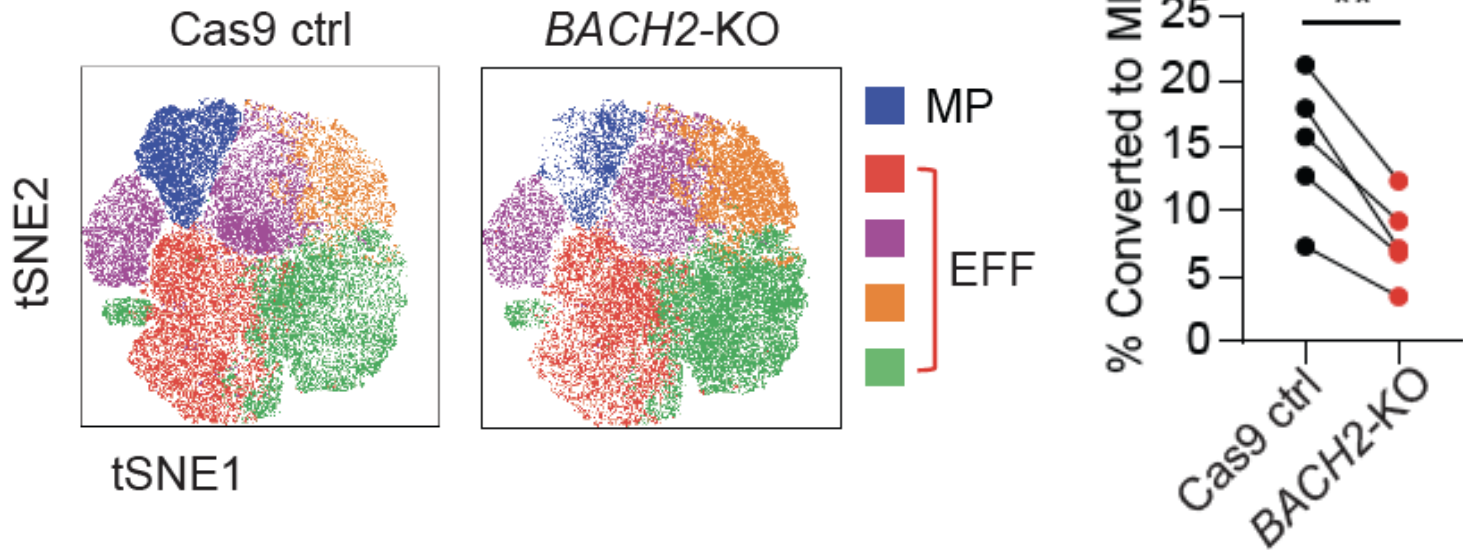


# Heterogeneity and plasticity of CCR5-expressing CD4<sup>+</sup> T cells



Gao H *et al.* Unpublished

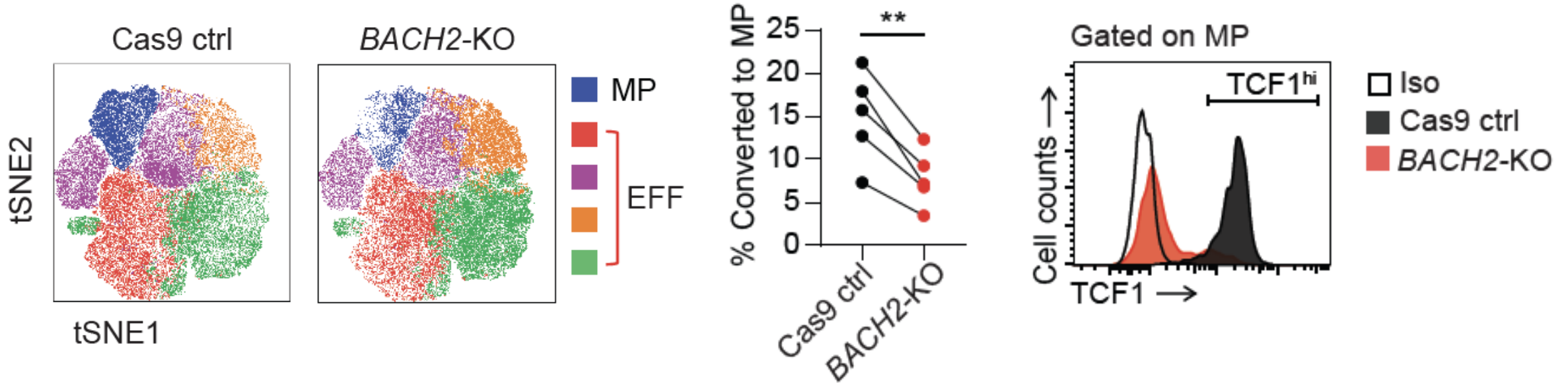
# BACH2 is essential to the **quantity** of HIV reservoir progenitors



Gao H *et al.* Unpublished



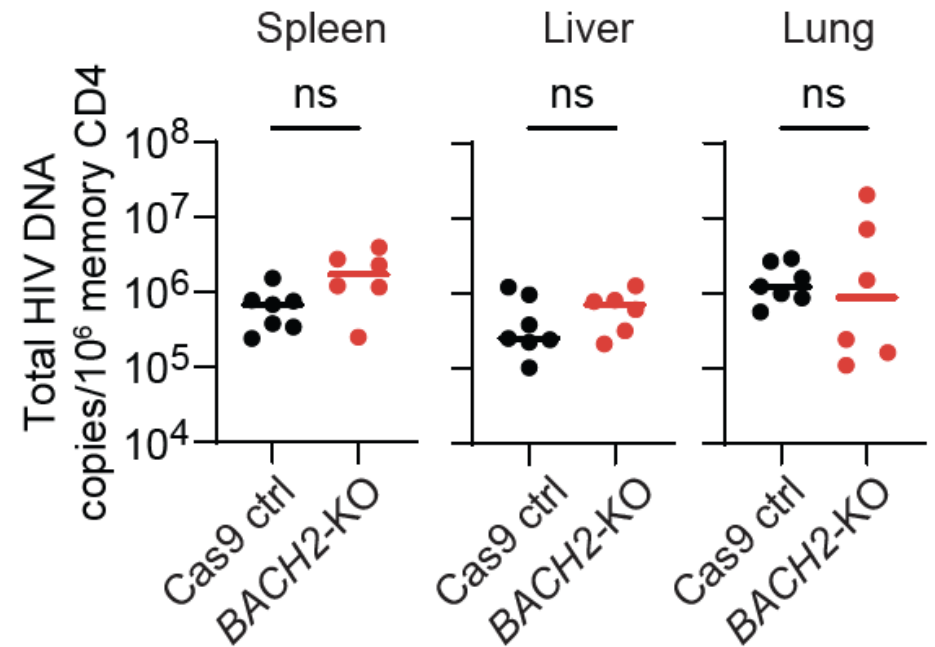
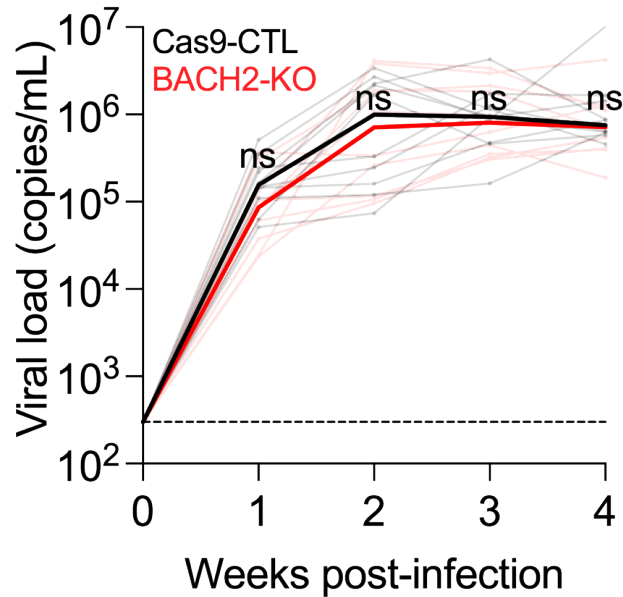
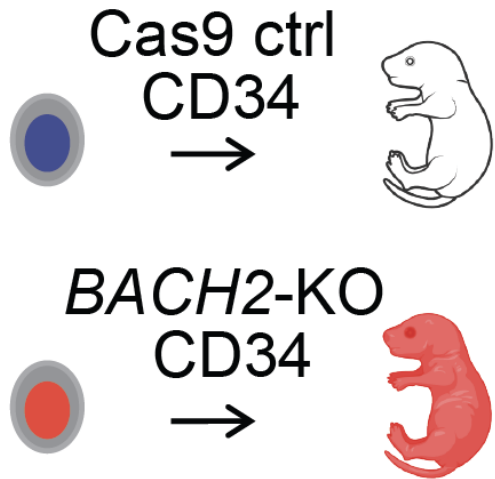
# BACH2 is essential to the **quantity** and **quality** of HIV reservoir progenitors



Gao H *et al.* Unpublished

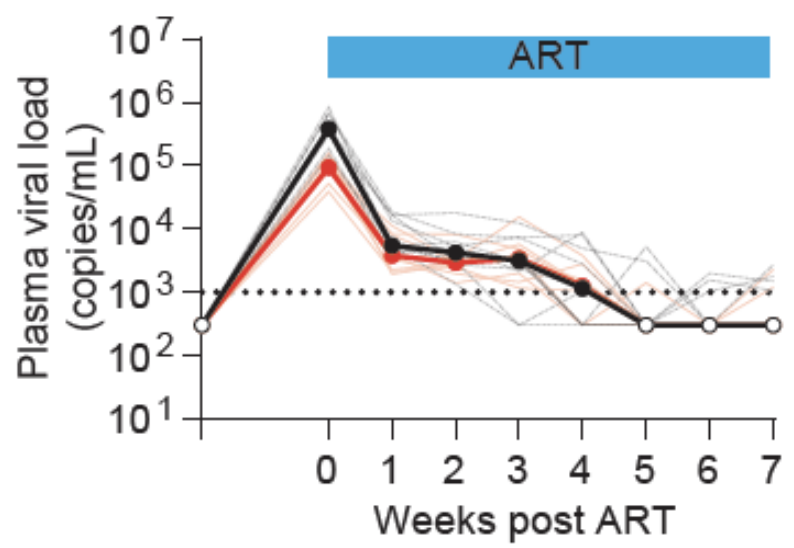


# Generation of humanized mice with a BACH2-deficient immune system



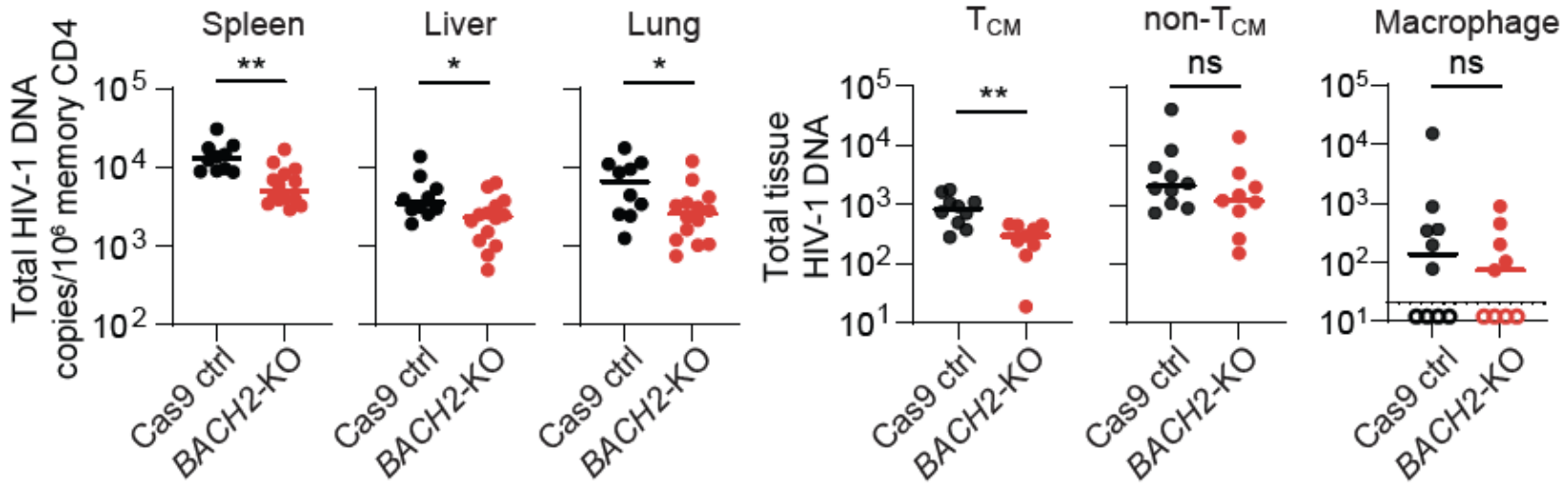
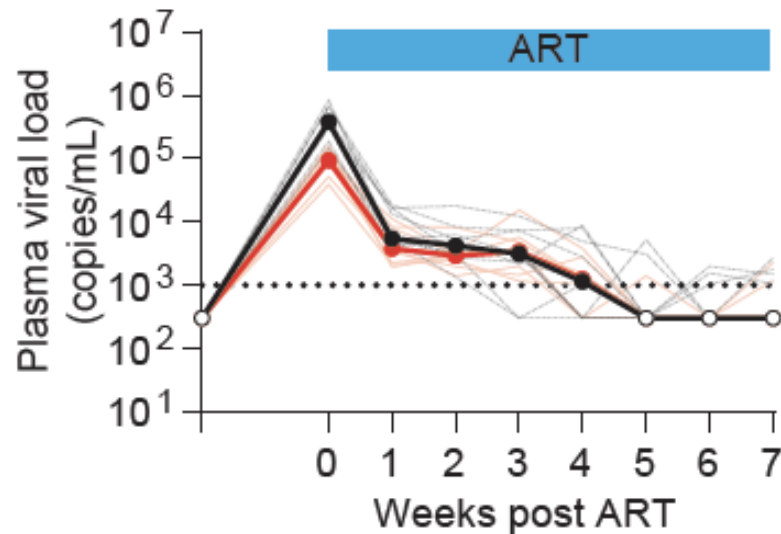
Gao H *et al.* Unpublished

# Reduced HIV reservoir in T<sub>CM</sub> cells in mice with a BACH2-KO immune system



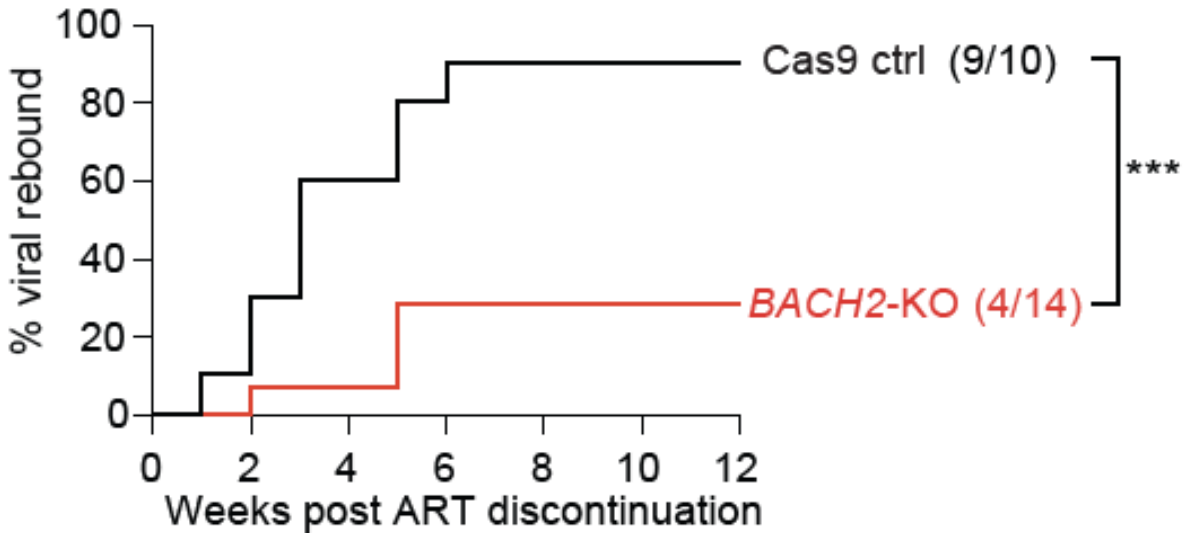
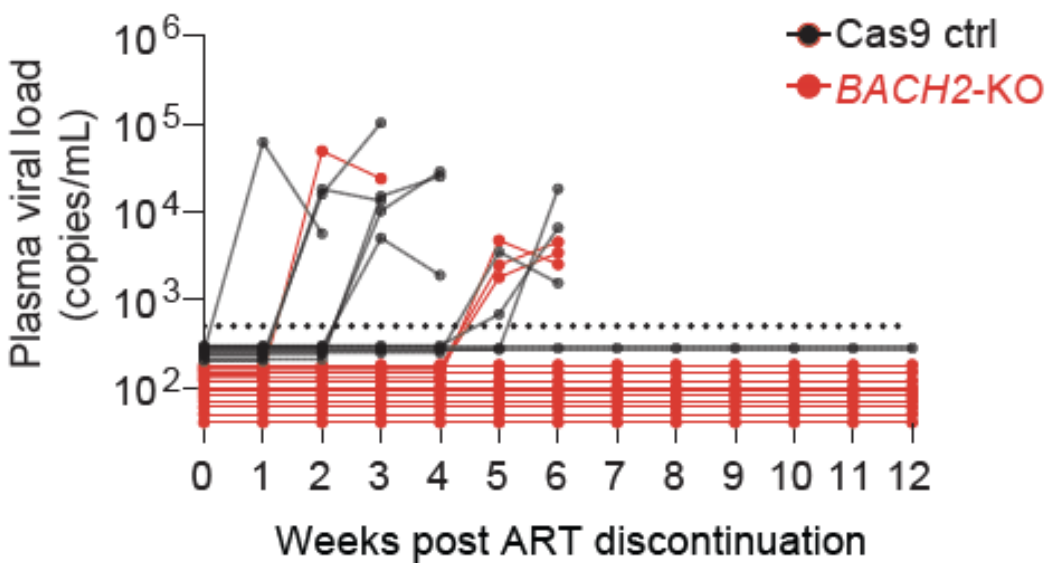
Gao H *et al.* Unpublished

# Reduced HIV reservoir in T<sub>CM</sub> cells in mice with a BACH2-KO immune system



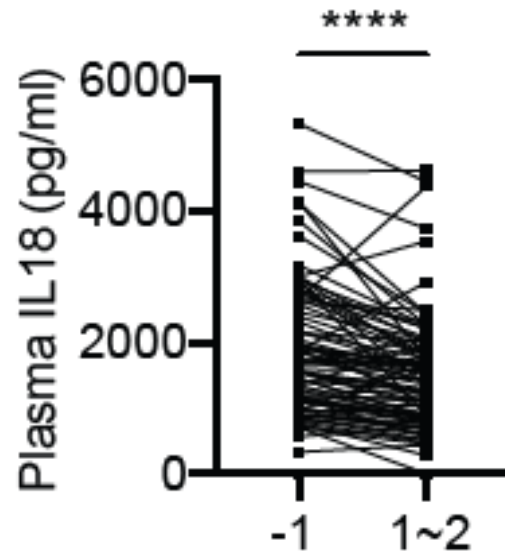
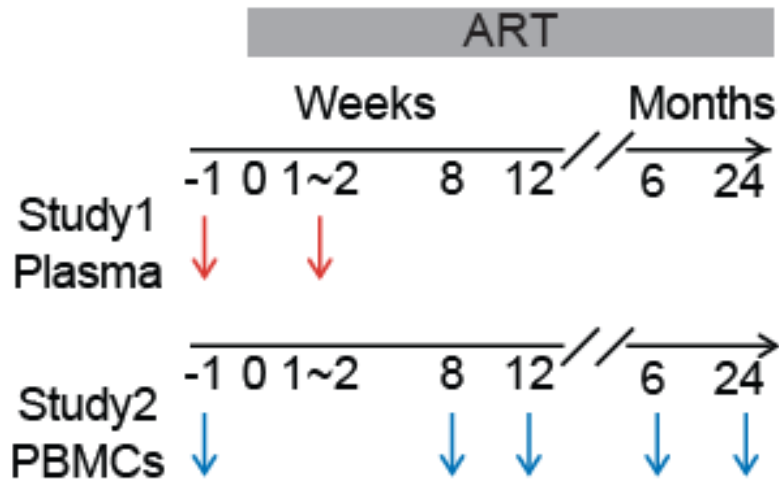
Gao H *et al.* Unpublished

# Delayed or no HIV rebound post ATI in mice with a BACH2-KO immune system



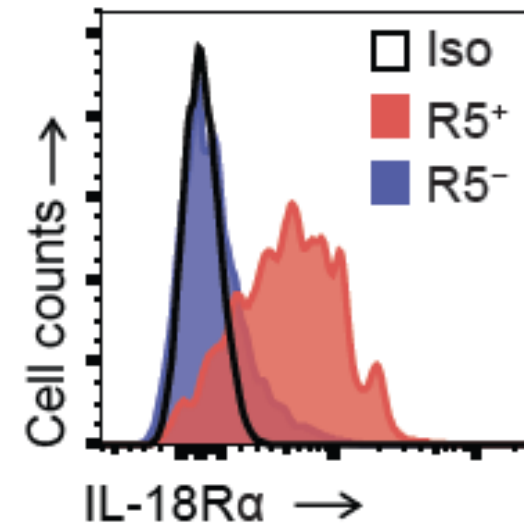
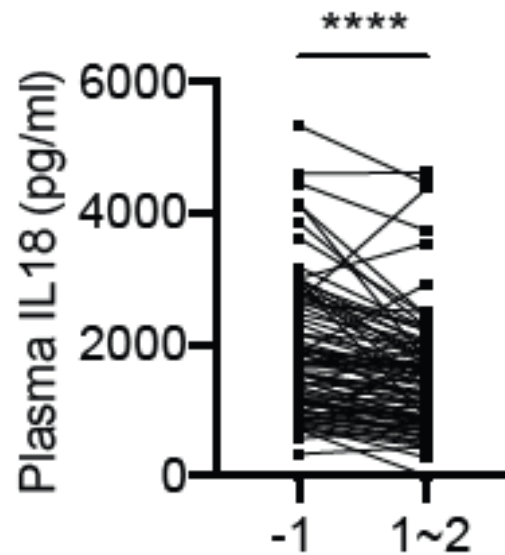
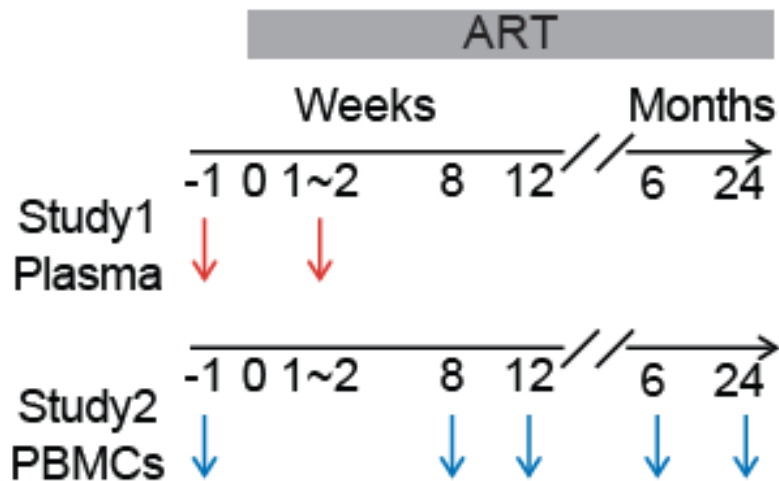
Gao H *et al.* Unpublished

# The role of ART in BACH2-mediated HIV reservoir seeding



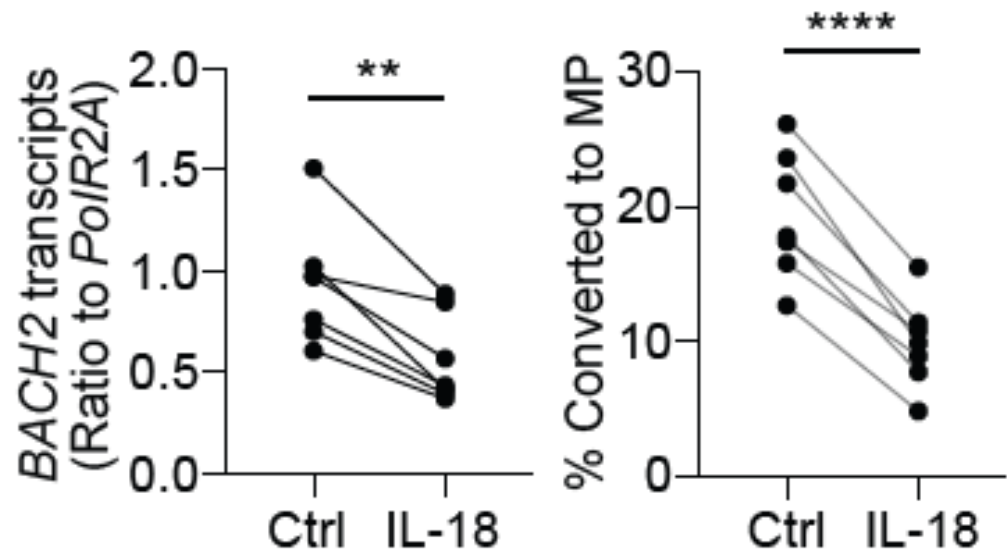
Gao H *et al.* Unpublished

# The role of ART in BACH2-mediated HIV reservoir seeding



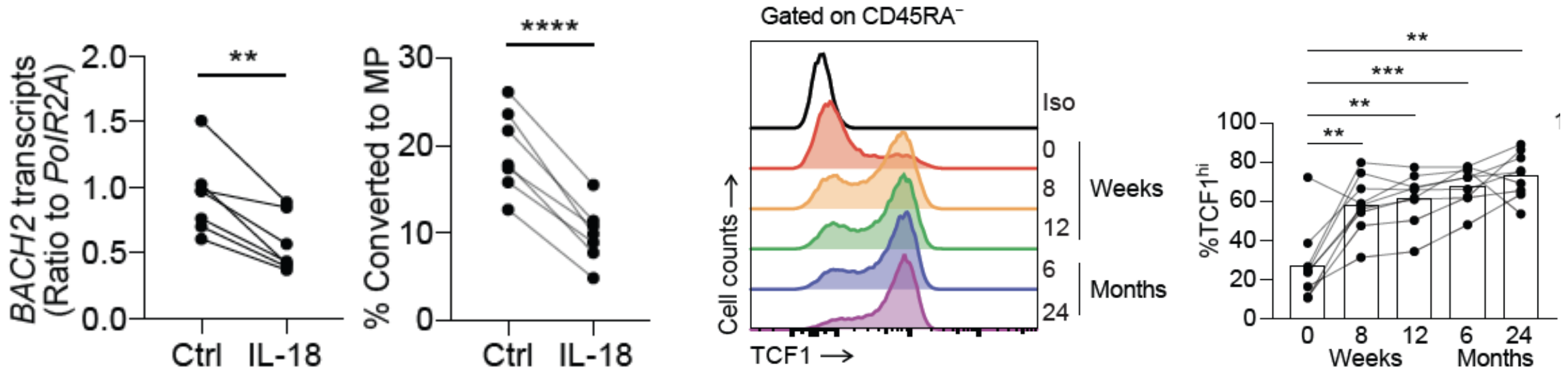
Gao H *et al.* Unpublished

# The role of ART in BACH2-mediated HIV reservoir seeding



Gao H *et al.* Unpublished

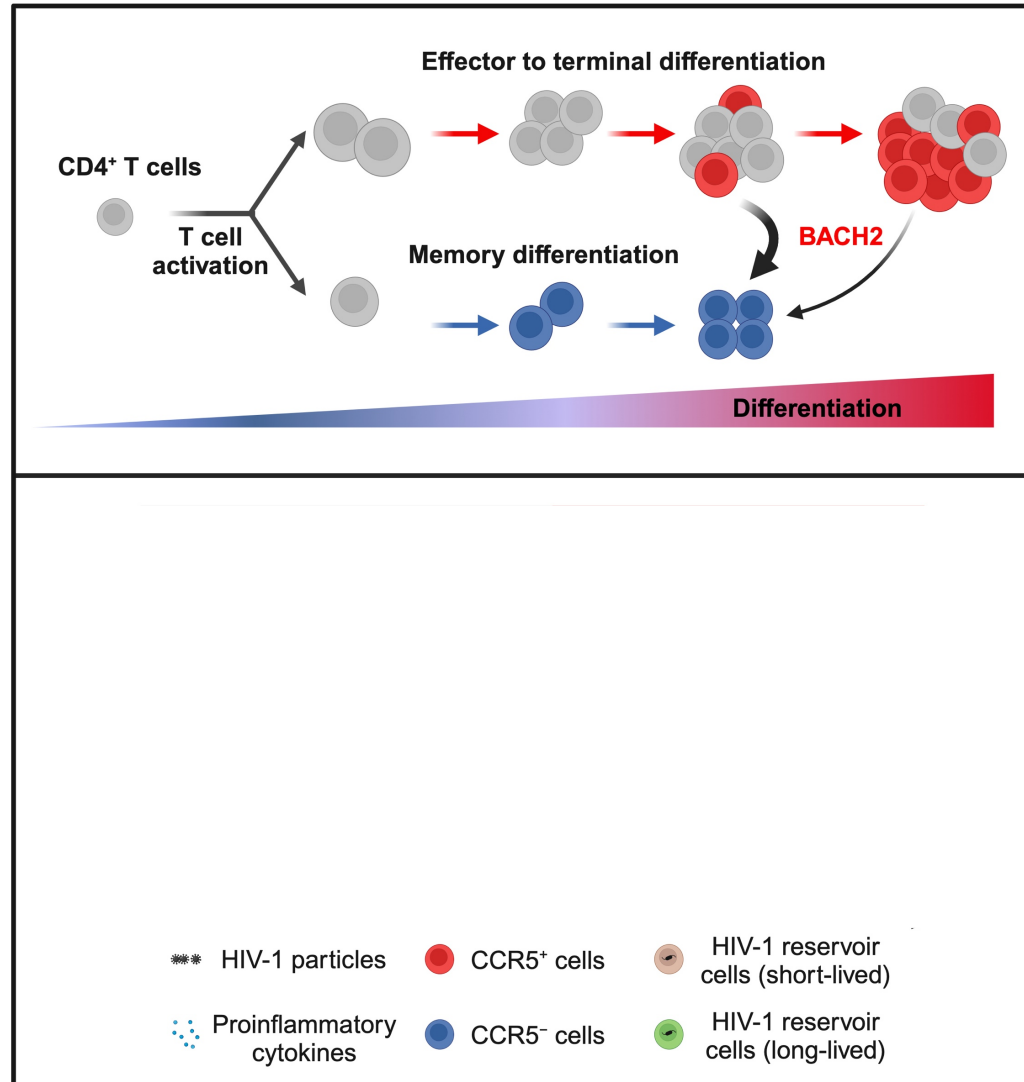
# The role of ART in BACH2-mediated HIV reservoir seeding



Gao H *et al.* Unpublished

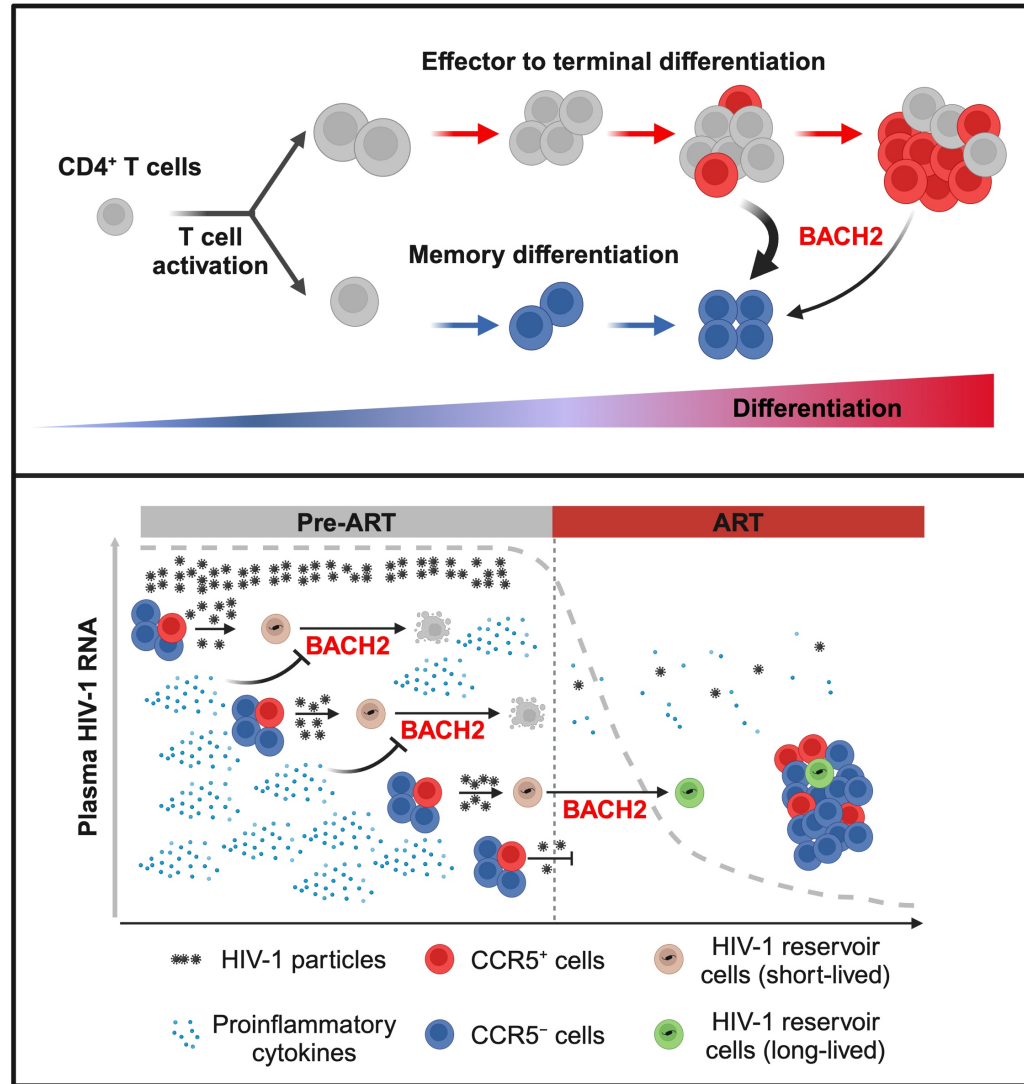


# Conclusions:



Gao H *et al.* Unpublished

# Conclusions:



Gao H *et al.* Unpublished

# Acknowledgments

Shan Lab  
**Hongbo Gao**  
**Ritu Tiwari**  
**Marilia Pinzone**  
Priya Pal  
Qiankun Wang  
Kolin Clark  
Shuai Gao  
Xiwen Qin  
Toni Sherlinski  
Elizabeth Denn  
Sara Nicholson  
Hilary Weisburd



## WUSTL ID-CRU/ACTU

Rachel Presti  
Mike Klebert  
Lisa Kessels  
**All study participants**



Midwest Developmental  
Center for AIDS Research

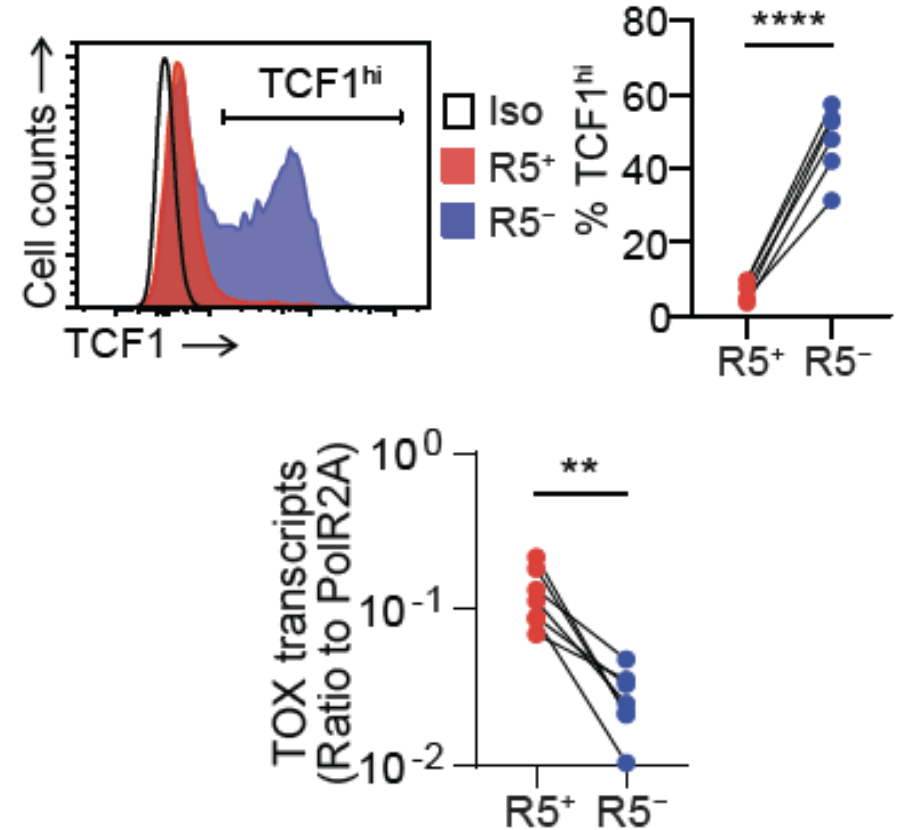
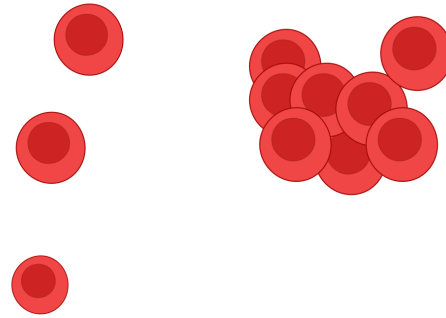
**Washington Univ**  
Sebla Kutluay  
Christian Mugisha  
Keanu Davis  
  
Wayne Yokoyama  
Can Sungur  
  
Marco Colonna  
Marina Cella  
  
**Emory Univ**  
Guido Silvestri  
Steven Bosinger  
Nagarajan Raju  
Gregory Tharp  
  
**Univ of Penn**  
Beatrice Hahn  
Fred Bibollet-Ruche

**Temple Univ**  
Tricia Burdo  
Kamel Khalili  
Rafal Kaminski  
  
**NIH**  
Irin Sereti  
  
**Johns Hopkins**  
Francesco Simonetti  
Mark Marzinke  
  
**UCSF**  
Peter Hunt  
  
**Ulm Univ**  
Frank Kirchhoff  
Rayhane Nchioua  
  
**ACTG A5142**



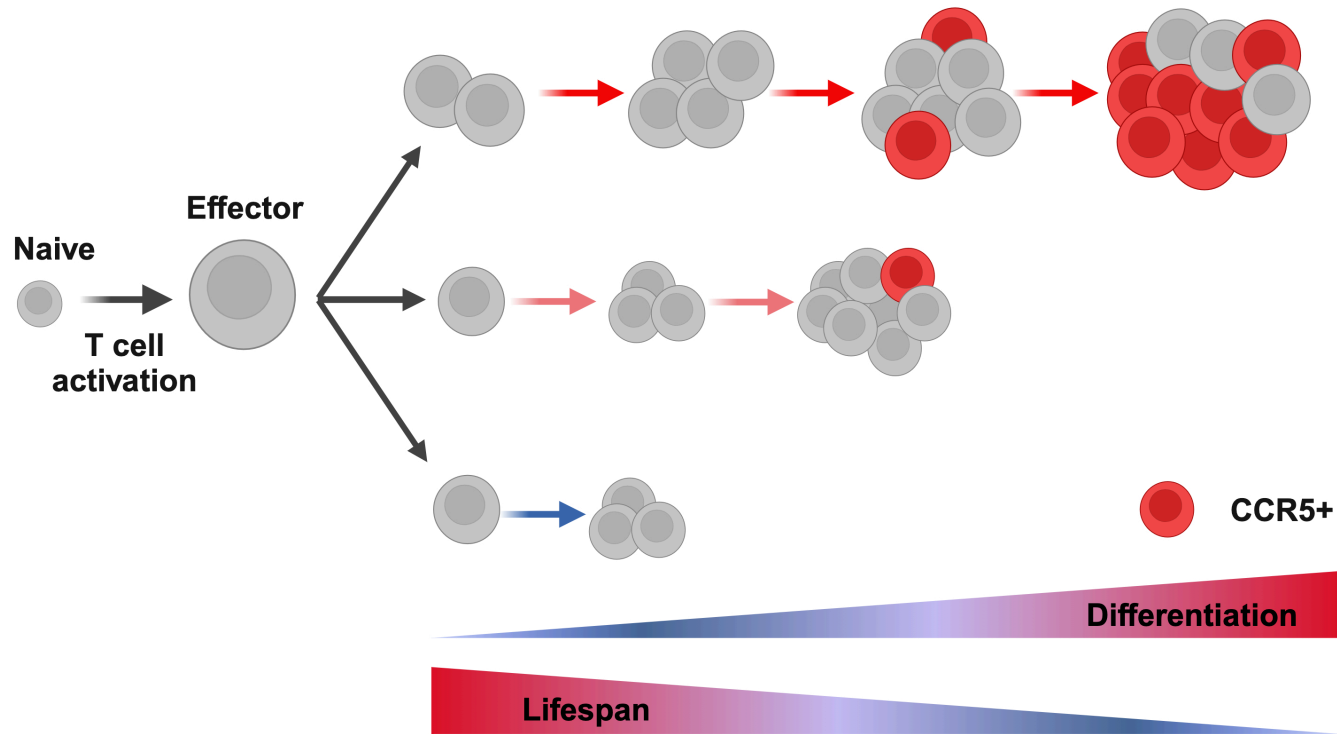
# Functional characterization of CCR5<sup>+</sup> T cells

- Upregulated in cells completed multiple rounds of proliferation
- Low proliferation capacity
- High activation/exhaustion
- Mitochondrial damage



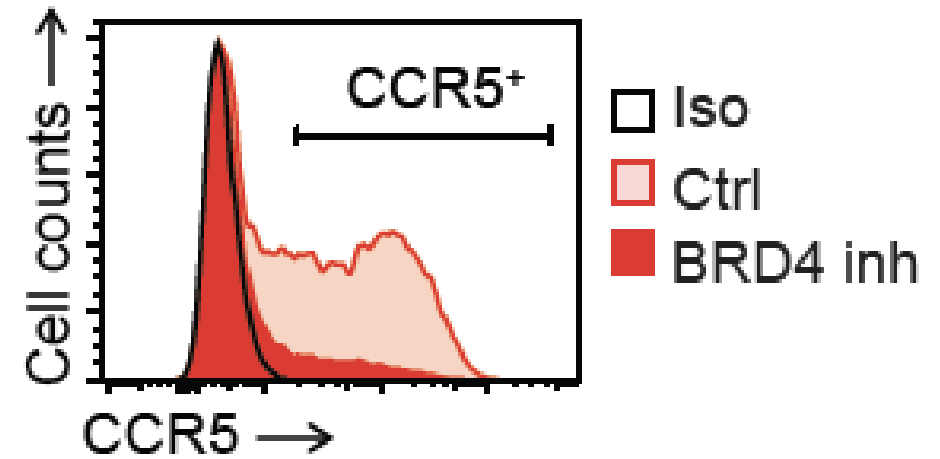
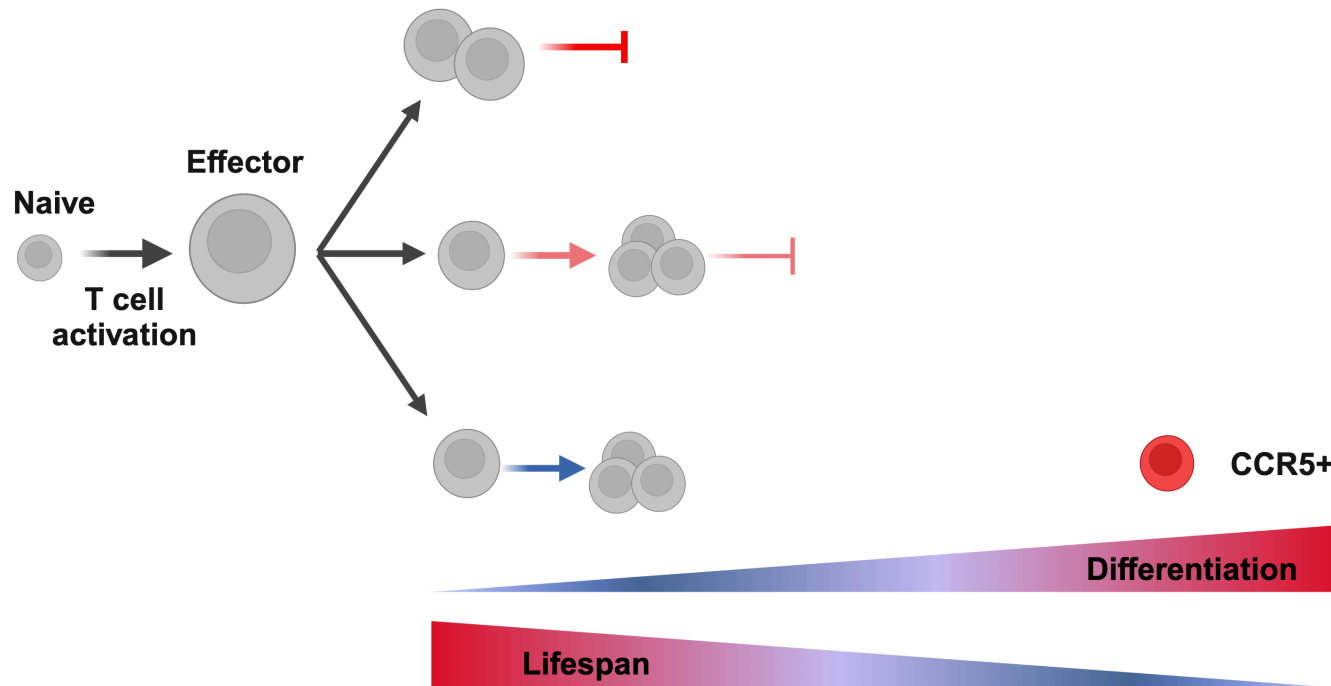
Gao H *et al.* Unpublished

# Blocking effector/terminal T cell differentiation aborts differentiation of CCR5<sup>+</sup> cells



Gao H *et al.* Unpublished

# Blocking effector/terminal T cell differentiation aborts differentiation of CCR5<sup>+</sup> cells



Gao H *et al.* Unpublished