

# SHIV Reservoirs Persist Following CAR T Cell-Mediated Depletion of B Cell Follicles in Nonhuman Primates

Chris Peterson

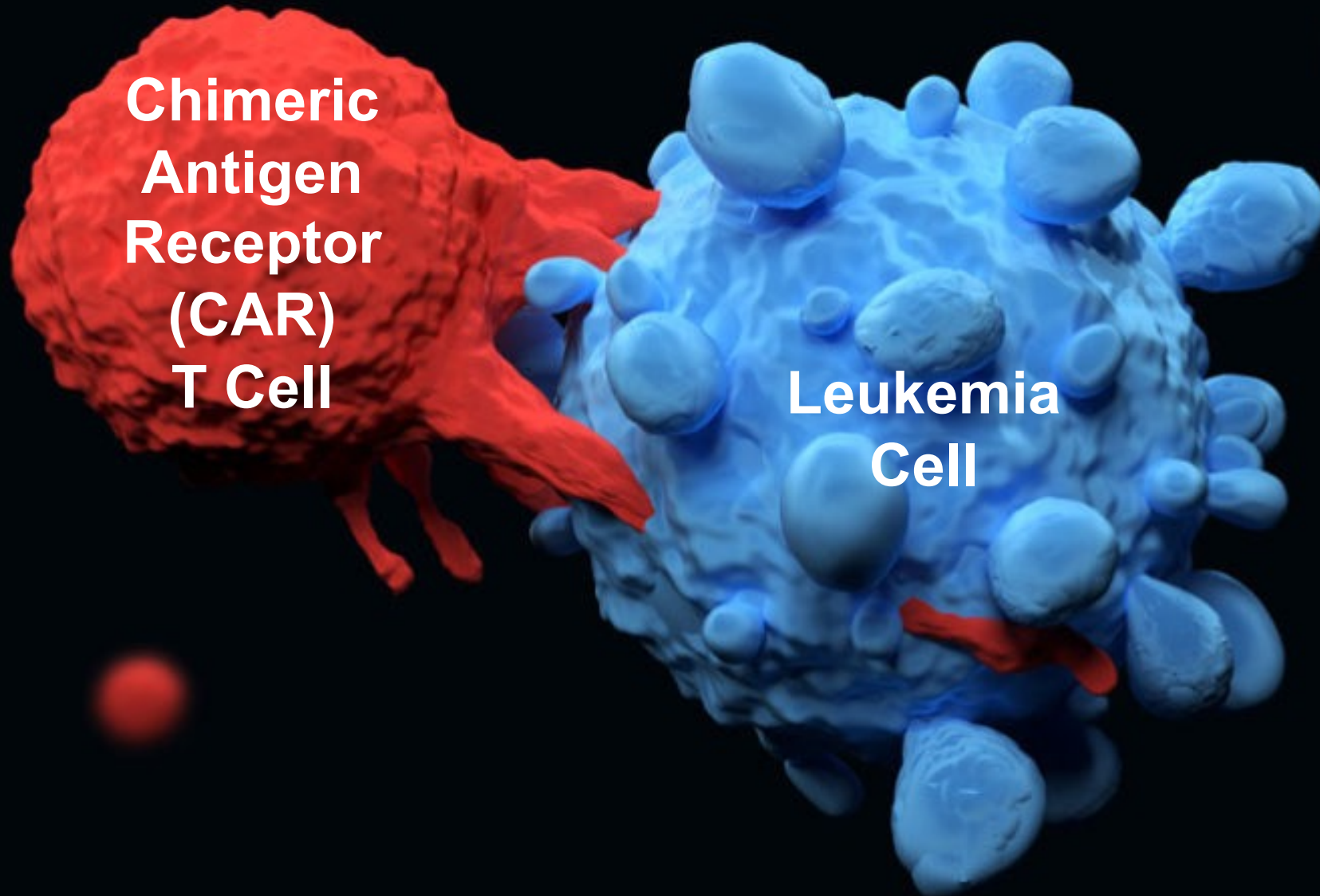
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CURES START HERE™





**Chimeric  
Antigen  
Receptor  
(CAR)  
T Cell**

**Leukemia  
Cell**

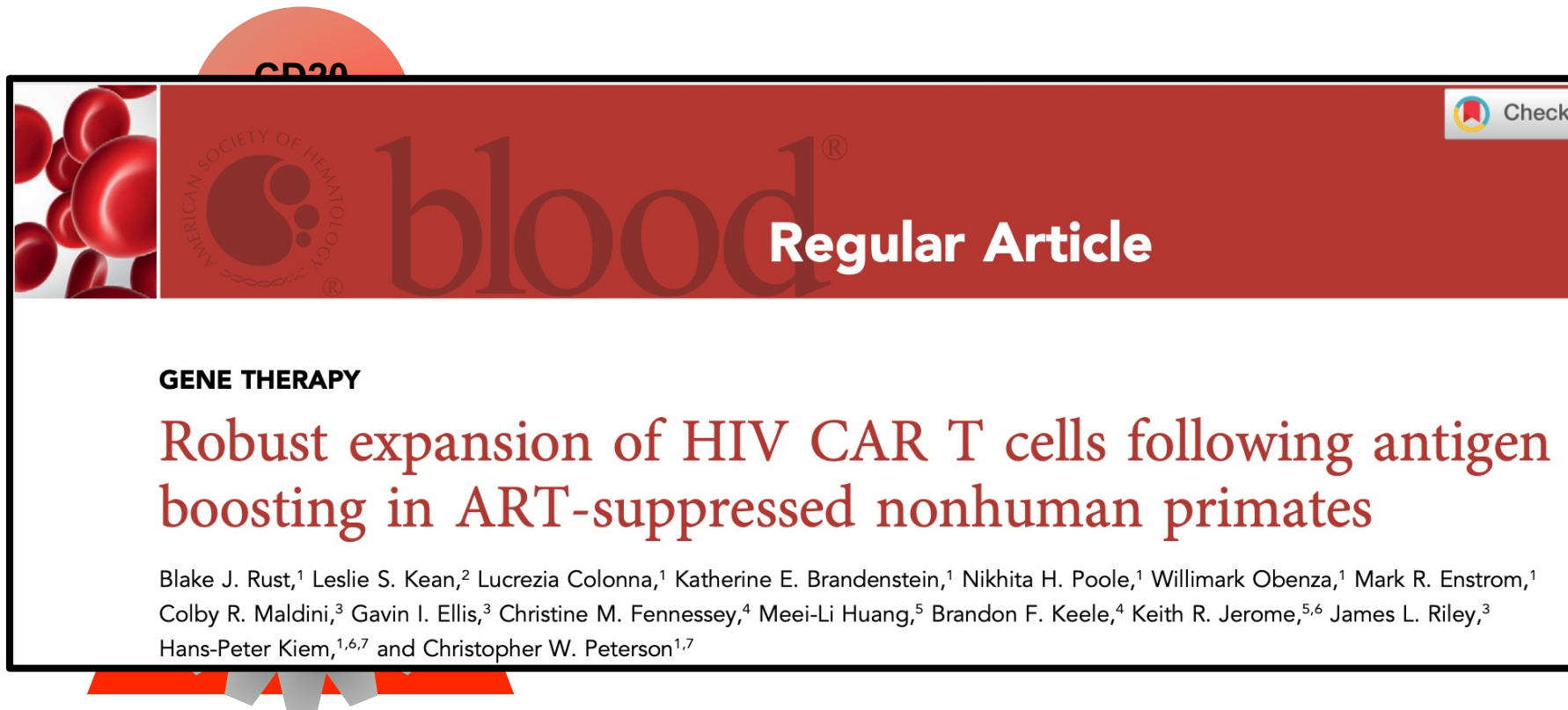


A 3D digital illustration showing a red, irregularly shaped cell on the left, labeled 'Chimeric Antigen Receptor (CAR) T Cell'. It is interacting with a larger, blue, spherical cell on the right, labeled 'HIV-Infected Cell'. The blue cell is covered in numerous small, rounded protrusions. The background is black with several blurred, out-of-focus cells in red and blue, suggesting a cellular environment.

**Chimeric  
Antigen  
Receptor  
(CAR)  
T Cell**

**HIV-Infected  
Cell**

# Cell-Associated Viral Antigen Can Supplement and Augment Virus-Specific CAR T Cells



+++++

+++++

Target antigen levels  
CAR-T killing efficiency



# Assessing HIV Cure Approaches in People Living with HIV and Cancer



Timothy Brown



Adam Castillejo

Berlin/London HIV<sup>+</sup> Malignancy Patients

HLA-matched, **CCR5 $\Delta$ 32/ $\Delta$ 32**  
bone marrow donor

Conditioning Regimen

Allogeneic **CCR5 $\Delta$ 32/ $\Delta$ 32** stem cell transplant

Withdrawal of ART

Sustained ART-free  
HIV remission

Düssel-  
dorf  
Patient

City of  
Hope  
Patient

New  
York  
Patient



Gary Steinkohl



Boston/Minneapolis HIV<sup>+</sup> Malignancy Patients

HLA-matched, **CCR5<sup>wt/wt</sup>**  
bone marrow donor

Conditioning Regimen

Allogeneic **CCR5<sup>wt/wt</sup>** stem cell transplant

Withdrawal of ART

HIV-free for 12/32/41 weeks,  
followed by viral rebound

## Persistence of Virus Reservoirs in ART-Treated SHIV-Infected Rhesus Macaques after Autologous Hematopoietic Stem Cell Transplant

Maud Mavigner<sup>1,3</sup>, Benjamin Watkins<sup>2,3</sup>, Benton Lawson<sup>1</sup>, S. Thera Lee<sup>1</sup>, Ann Chahroudi<sup>1,3,4</sup>, Leslie Kean<sup>2,3</sup>, Guido Silvestri<sup>1,3\*</sup>

<sup>1</sup> Emory  
Center  
Childre  
of Med

### ARTICLE

DOI: 10.1038/s41467-018-06736-7

OPEN

Evidence for persistence of the SHIV reservoir early after MHC haploidentical hematopoietic stem cell

hev<sup>1</sup>,  
no<sup>5</sup>,  
el<sup>5</sup>,  
h<sup>5</sup>,  
an<sup>1,2,4,12</sup>

## Correlates of Durable HIV-1 Remission

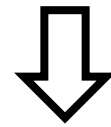
- ~~1) Conditioning Regimen: Depleting the reservoir~~
- ~~2) Allogeneic graft-versus reservoir effect~~
- 3) Infection-resistant hematopoietic cells**

February 2017

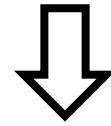
## Loss of immune homeostasis dictates SHIV rebound after stem-cell transplantation

Christopher W. Peterson,<sup>1,2</sup> Clarisse Benne,<sup>3</sup> Patricia Polacino,<sup>4</sup> Jasbir Kaur,<sup>1</sup> Cristina E. McAllister,<sup>1</sup> Abdelali Filali-Mouhim,<sup>3</sup> Willi Obenza,<sup>1</sup> Tiffany A. Pecor,<sup>4</sup> Meei-Li Huang,<sup>5</sup> Audrey Baldessari,<sup>4</sup> Robert D. Murnane,<sup>4</sup> Ann E. Woolfrey,<sup>1,2</sup> Keith R. Jerome,<sup>5,6</sup> Shiu-Lok Hu,<sup>4,7</sup> Nichole R. Klatt,<sup>4,7</sup> Stephen DeRosa,<sup>5</sup> Rafick P. Sékaly,<sup>3</sup> and Hans-Peter Kiem<sup>1,2,8</sup>

How Does B Cell Depletion  
(e.g. for B Cell Leukemia) Impact HIV Persistence?

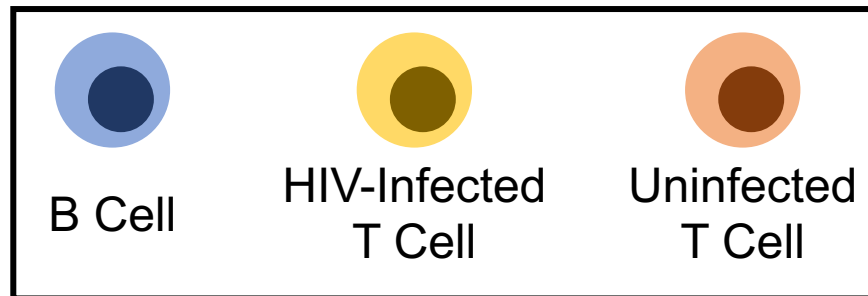
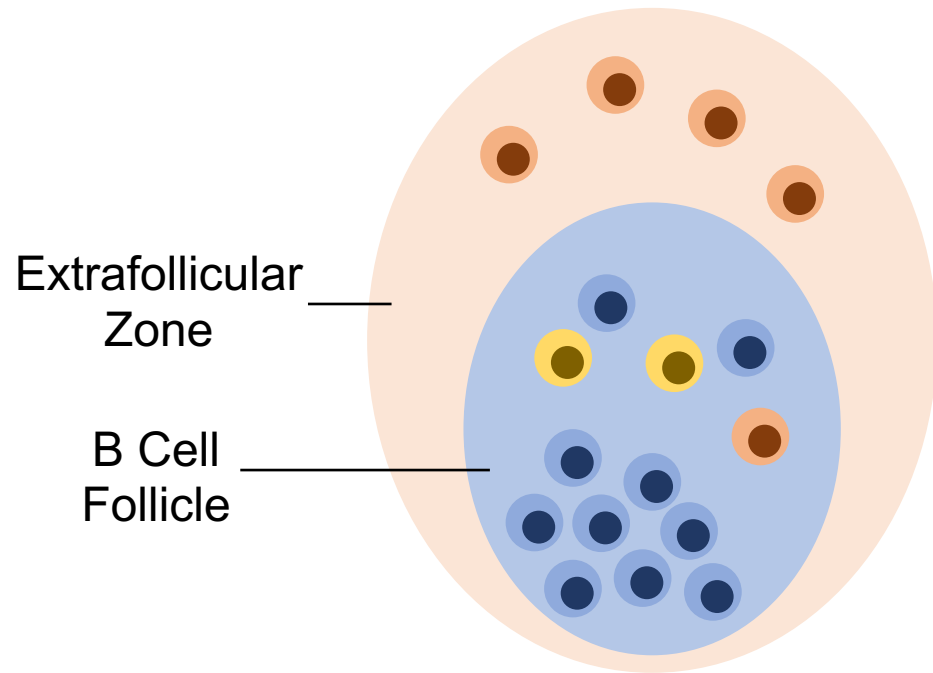


B Cell-Targeted CAR T Cells



Nonhuman Primate Model  
of HIV Persistence

# B Cell Follicles are a Sanctuary for the Persisting HIV Reservoir



**Elizabeth  
Connick**



**Pamela  
Skinner**



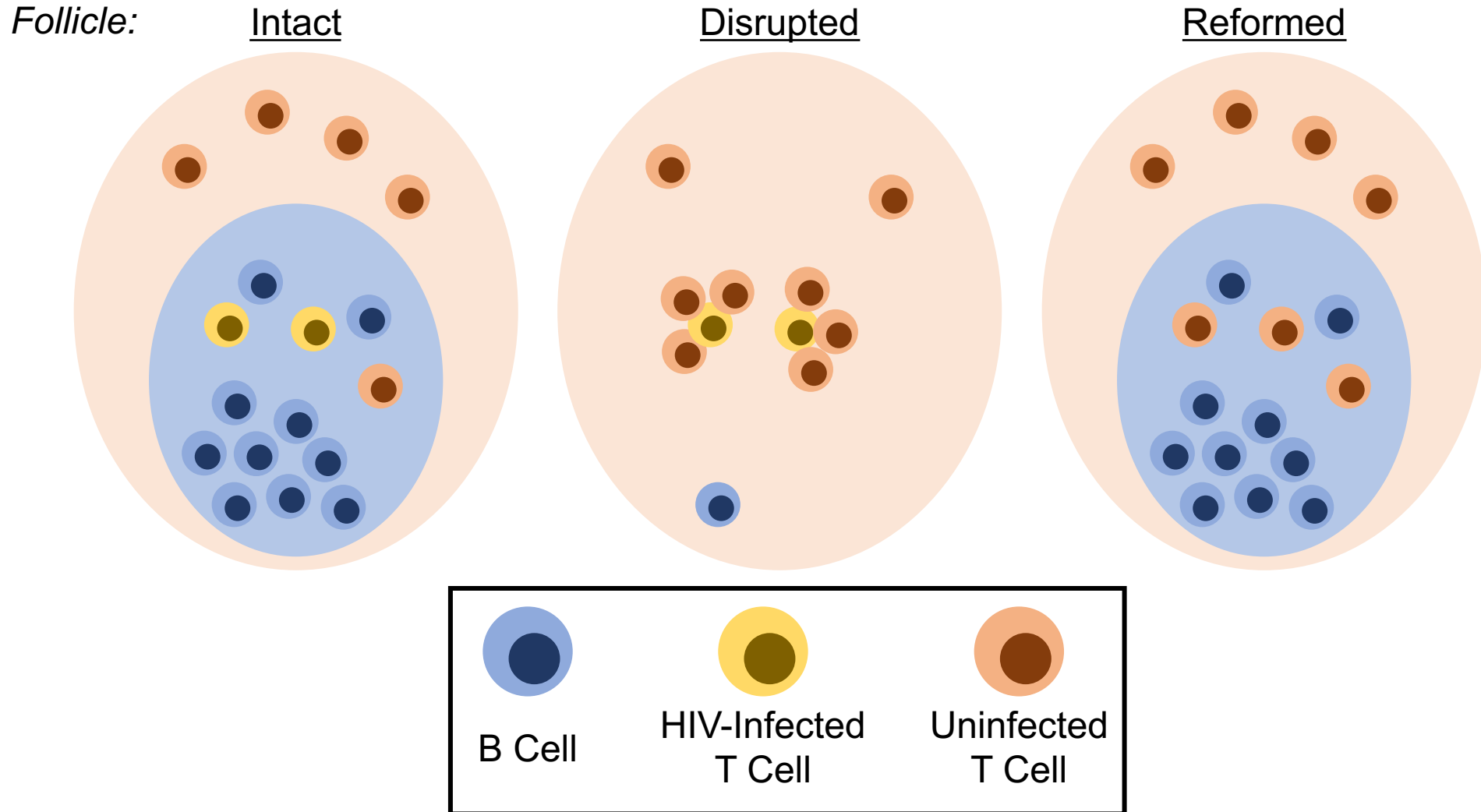
**Afam  
Okoye**



**Louis  
Picker**



# Hypothesis: B Cell Depletion Disrupts B Cell Follicles and Facilitates Immune Clearance of HIV<sup>+</sup> Targets

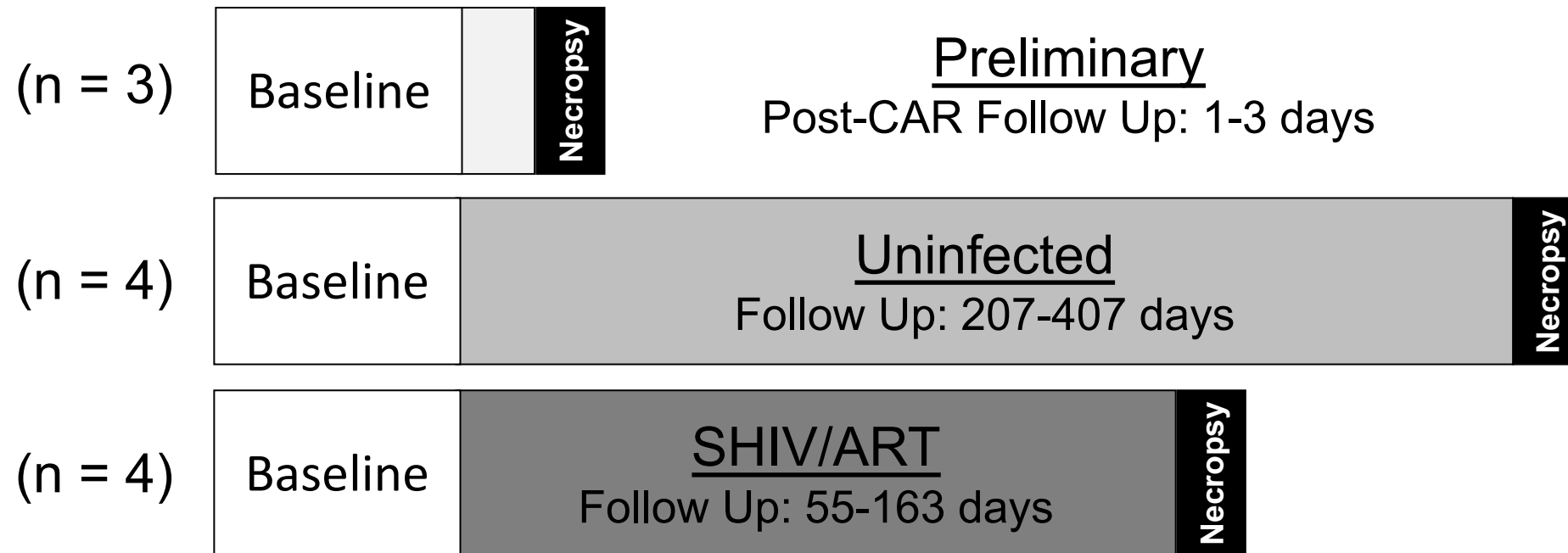


John Bui, MD

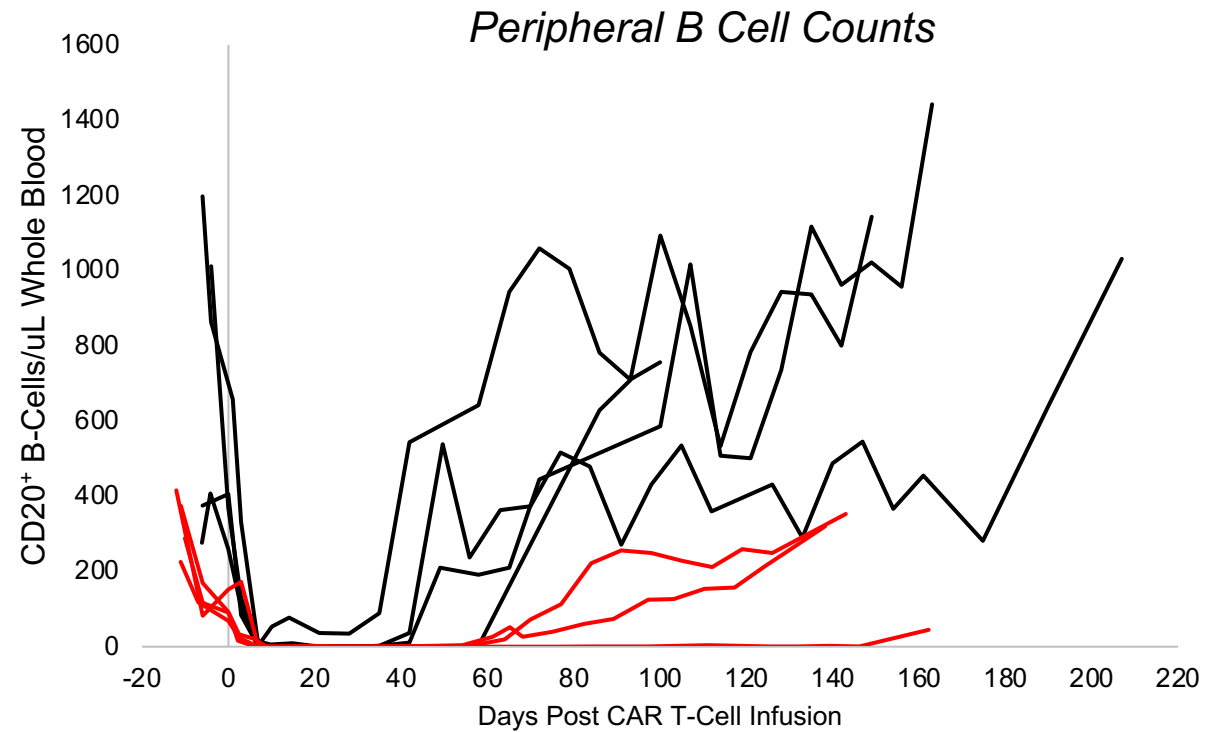
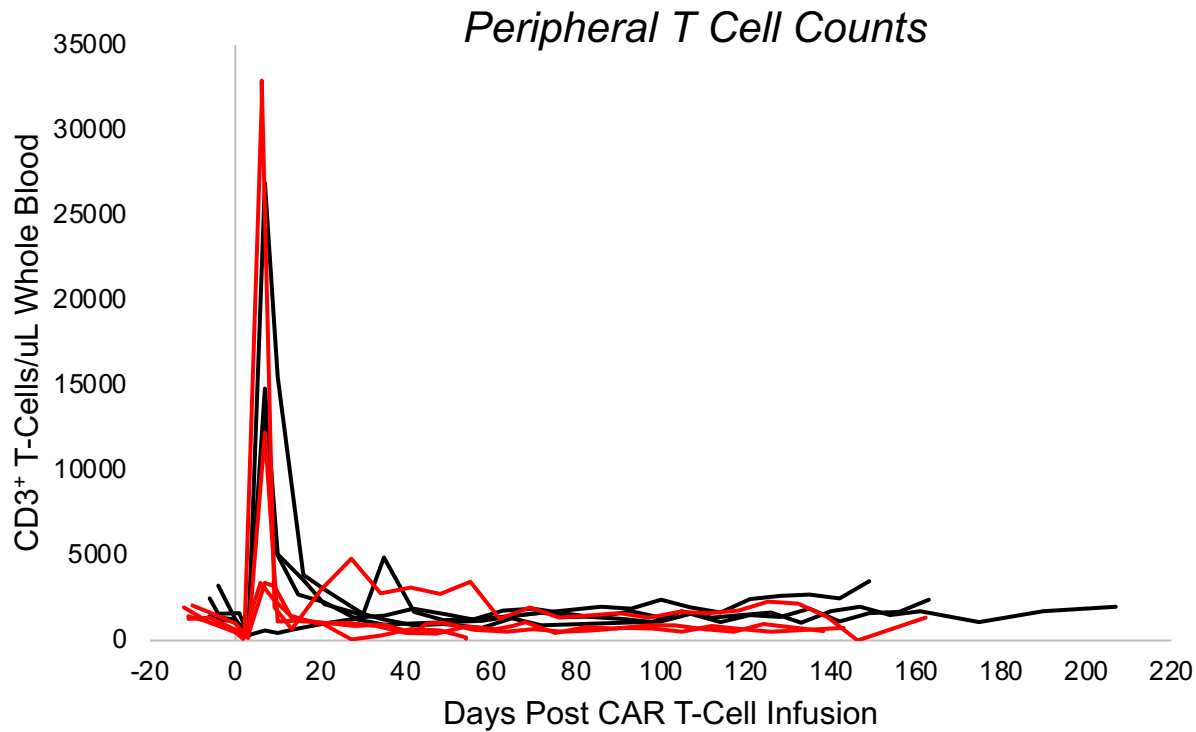


Carly Starke, PhD

# Quantifying CD20 CAR T Cell Function and Trafficking in Naïve and SHIV-Infected, ART-Suppressed Macaques

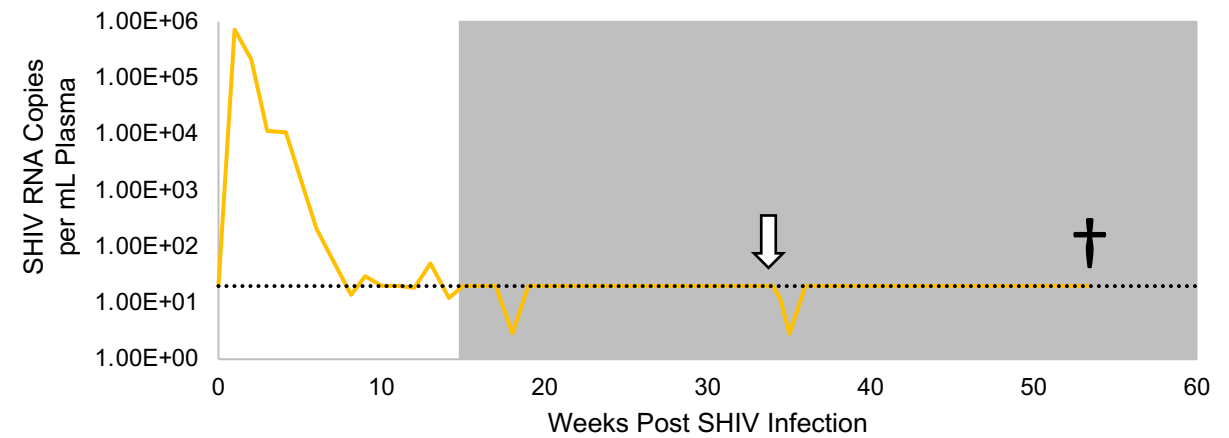
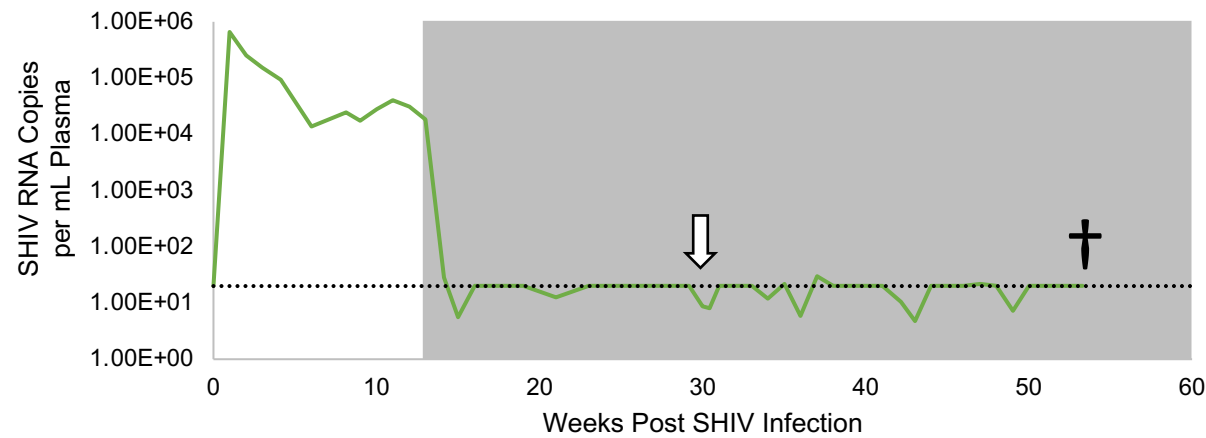
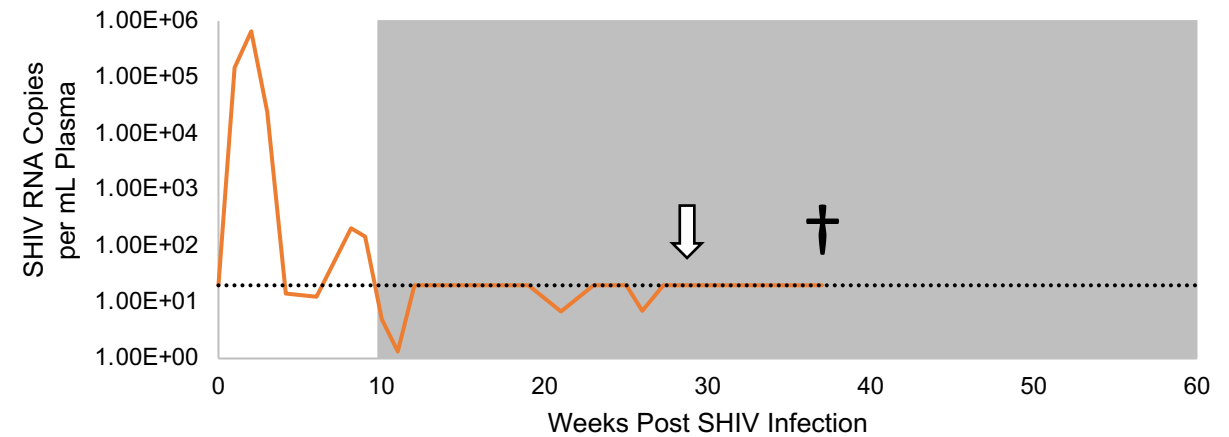
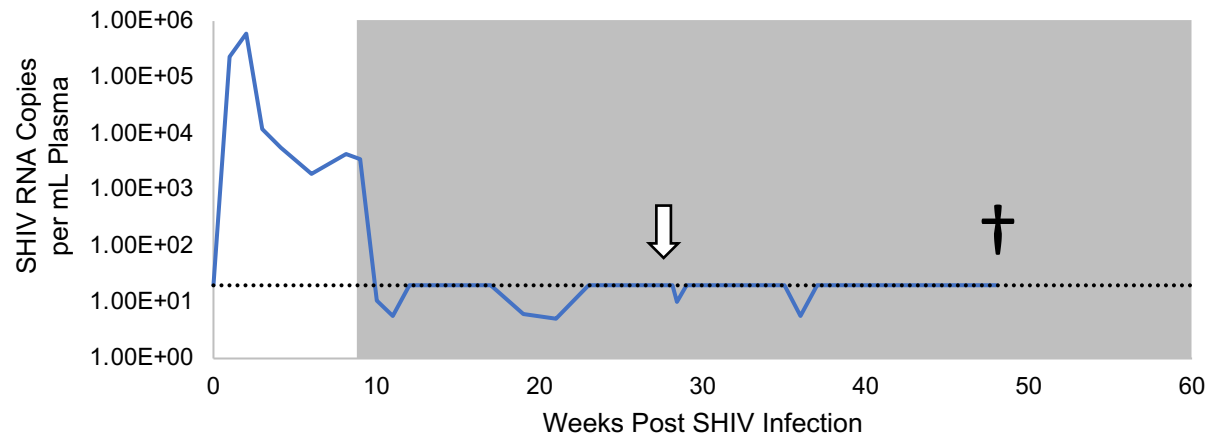


# CD20 CAR T Cells Maintain Function of While Recovery of CD20<sup>+</sup> Targets is Impaired in SHIV-Infected, ART-Suppressed NHP



Uninfected NHP (n = 4)  
SHIV-Infected, ART-Suppressed NHP (n = 4)

# ART Suppression is Maintained Following Infusion of CD20 CAR T Cells



..... Plasma Viral Load Limit of Quantification    ■ Daily ART    ↓ CD20 CAR T Cell Infusion    † Necropsy

**CONFIDENTIAL**



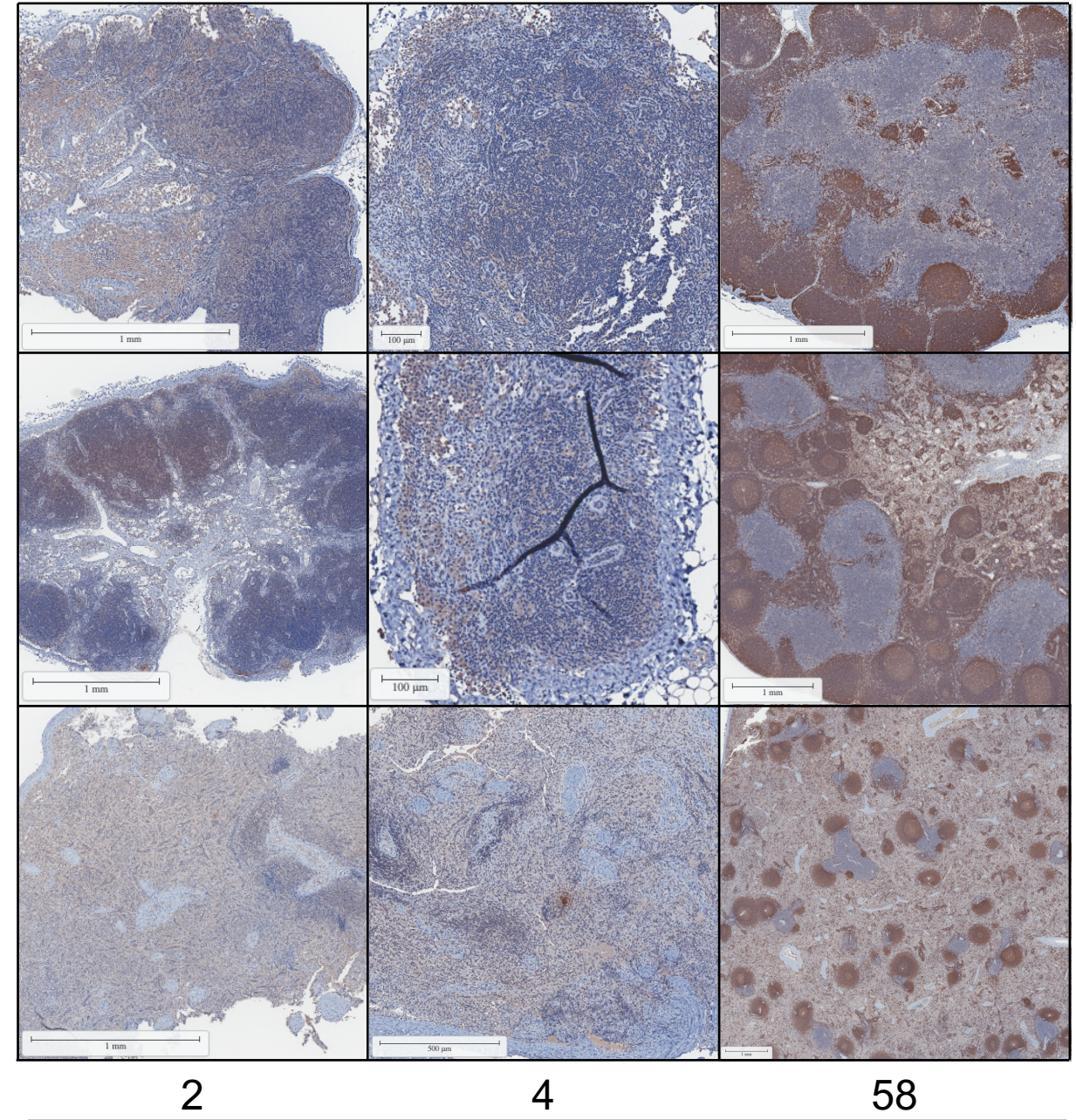
# CD20 CAR T Cells Induce Transient Ablation of B Cell Follicles in Lymph Nodes and Spleen

Peripheral  
Lymph Node

Mesenteric  
Lymph Node

Spleen

## Anti-CD20 Immunohistochemistry



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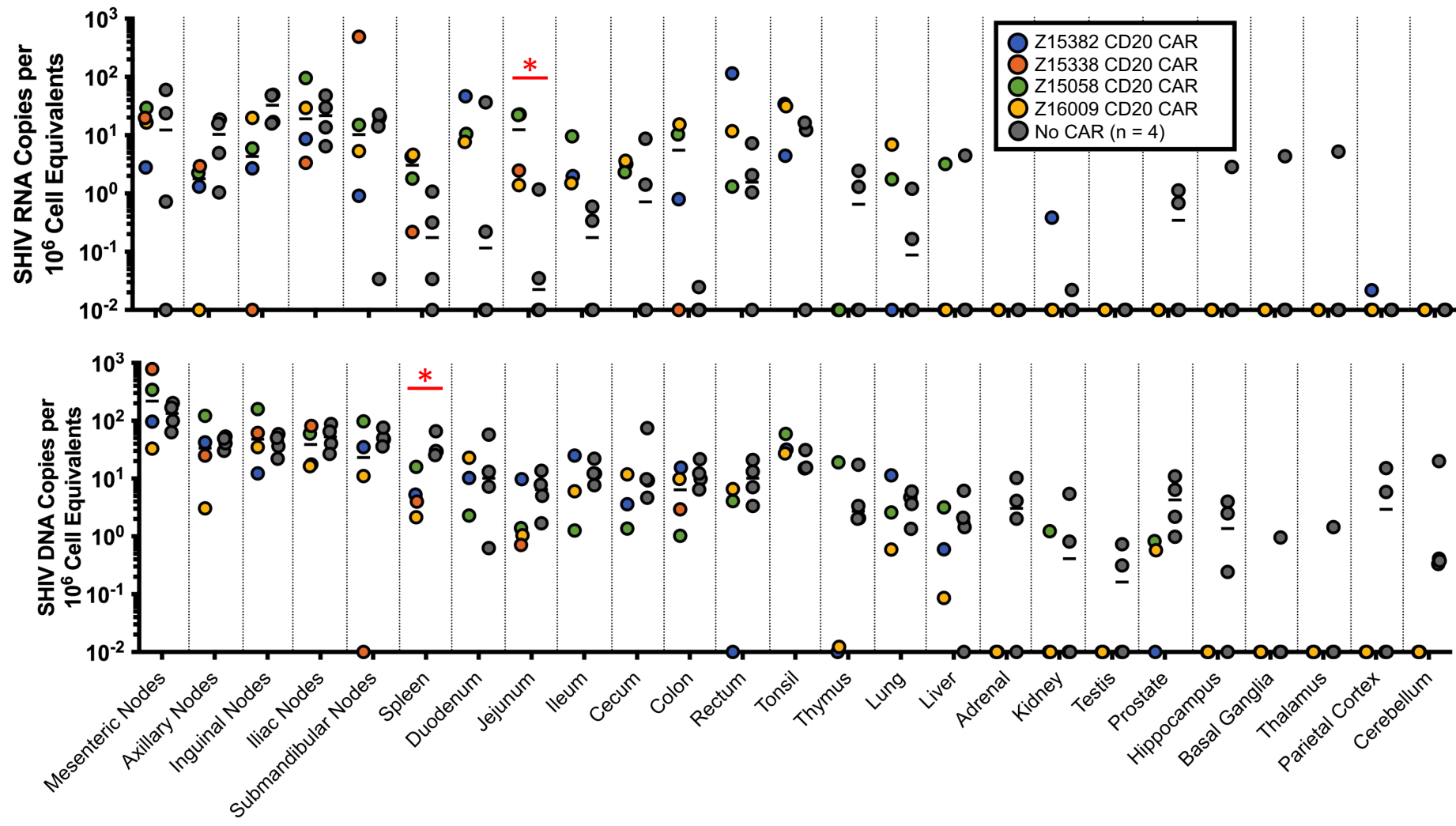
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58

Weeks Post-CD20 CAR T Cell Infusion



# CD20 CAR T Cell Therapy Does Not Systemically Impact SHIV Reservoir Size



# Conclusions

- CD20 CAR T cells function comparably in uninfected and SHIV-infected, ART-suppressed hosts, consistent with clinical data
- SHIV remains well suppressed during CD20 CAR T cell expansion
- Suppressed SHIV infection is associated with impaired B cell recovery following CAR T cell treatment
- No substantial impact of B cell follicle disruption on SHIV persistence within diverse tissue compartments

# Next Steps

- Combine B cell depletion with more potent strategies to recognize and kill persistently-infected target cells
- Continued development and optimization of virus-specific effectors
  - HIV/SIV/SHIV-specific CAR T cells
  - bNAb-engineered B cells
  - Cell based antigen boosting strategies
- How do B cell depletion approaches impact the HIV reservoir in people living with HIV and undergoing treatment for B cell leukemia?

# Community Summary

- What was the key question of this research?

*How can we reveal HIV-infected cells to be killed by the immune system?*

- Key finding(s) and take home message?

*We can temporarily break down structures within tissues that hide HIV-infected cells, but this is not enough to eliminate those cells.*

- How is this related to cure?

*For HIV cure/remission, we will likely need **both** enhanced anti-HIV immunity and strategies to reveal infected cells to the immune system.*

- Why should we be excited?

*We can use CAR T cells not only to find and clear HIV-infected cells, but also as a tool to understand how the persisting virus co-opts other cell types.*