CARs for HIV

James (Jim) L. Riley, PhD

The University of Pennsylvania has
determined that Dr. Riley has a FCOI as
the data presented here has been licensed to
a company (Tmunity) in which he has an equity interest. The
University is actively managing this conflict.

Penn Medicine
Center for Cellular Immunotherapies

HOW HIV AND CANCER COMPARE FROM A CAR T CELL PERSPECTIVE

Same

Durability- the need for long term T cell persistence

Escape

Exhaustion-how to maintain highly functional T cells for the long haul

Ability to promote endogenous immune response

Different

Self v Non-Self

Antigen levels when T cell enter the body

Treatment alternatives

Quality of T cells

Growth/Spread Rate

Disease Sites

HIV can infect T cells and engineered T cells

Investment

The Journal of Clinical Investigation CLINICAL

CCR5-edited CD4⁺ T cells augment HIV-specific immunity to enable post-rebound control of HIV replication

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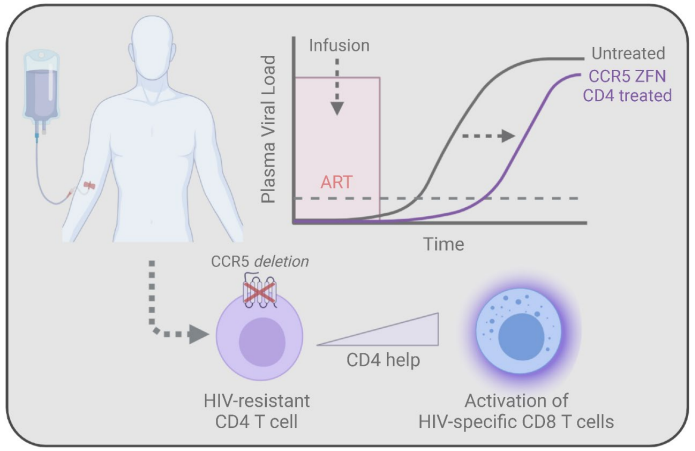
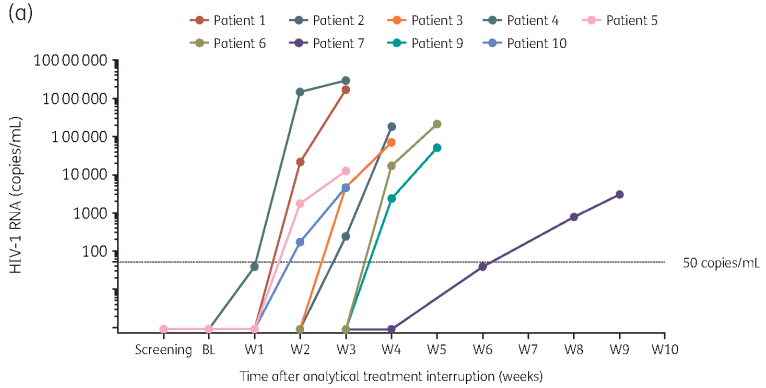
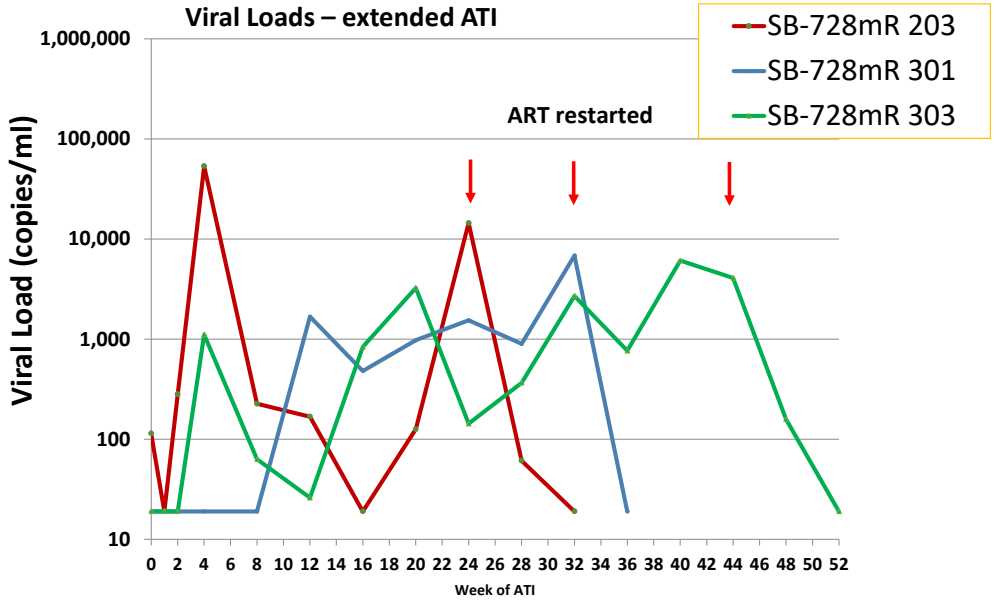
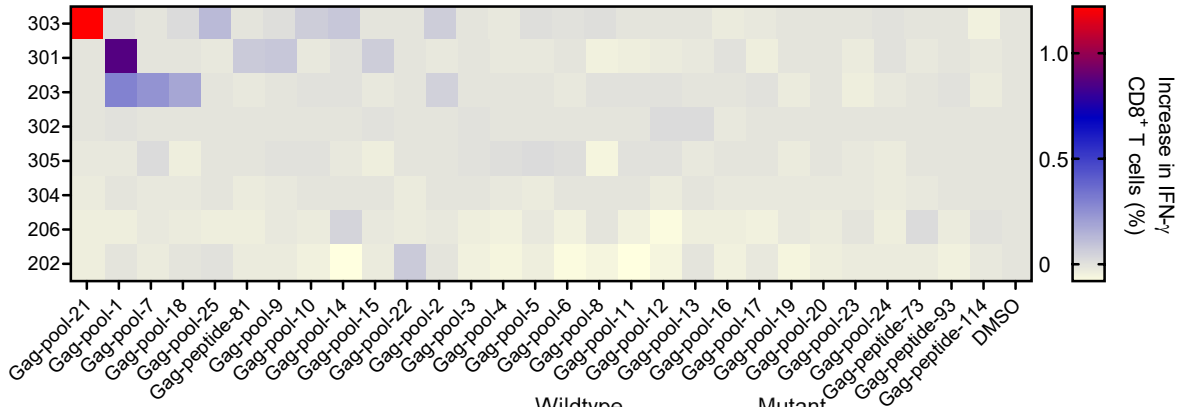
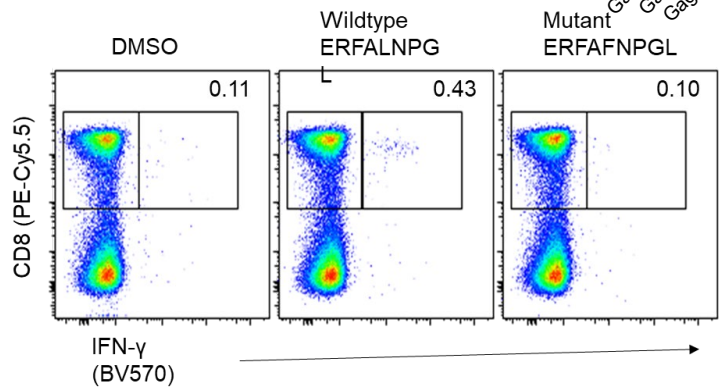




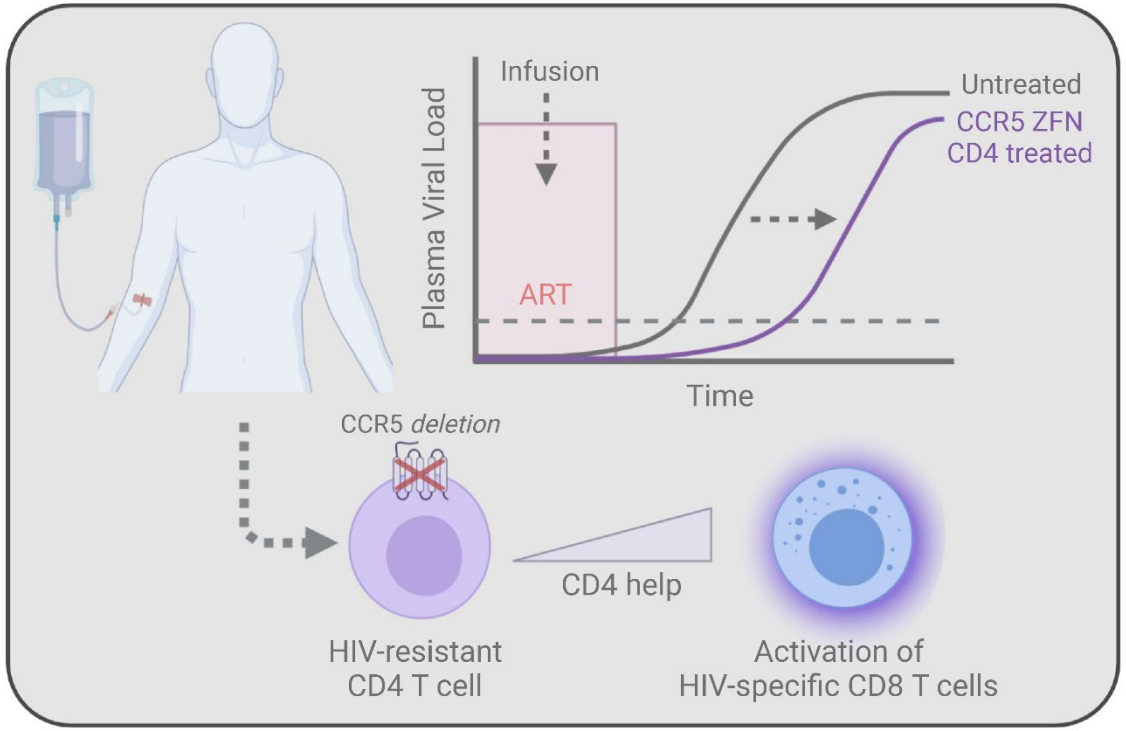






Castagna et al https://doi.org/10.1093/jac/dkz138

SUMMARY OF HOW ENGINEERED T CELLS CAN BOLSTER ENDOGENOUS IMMUNE RESPONSES



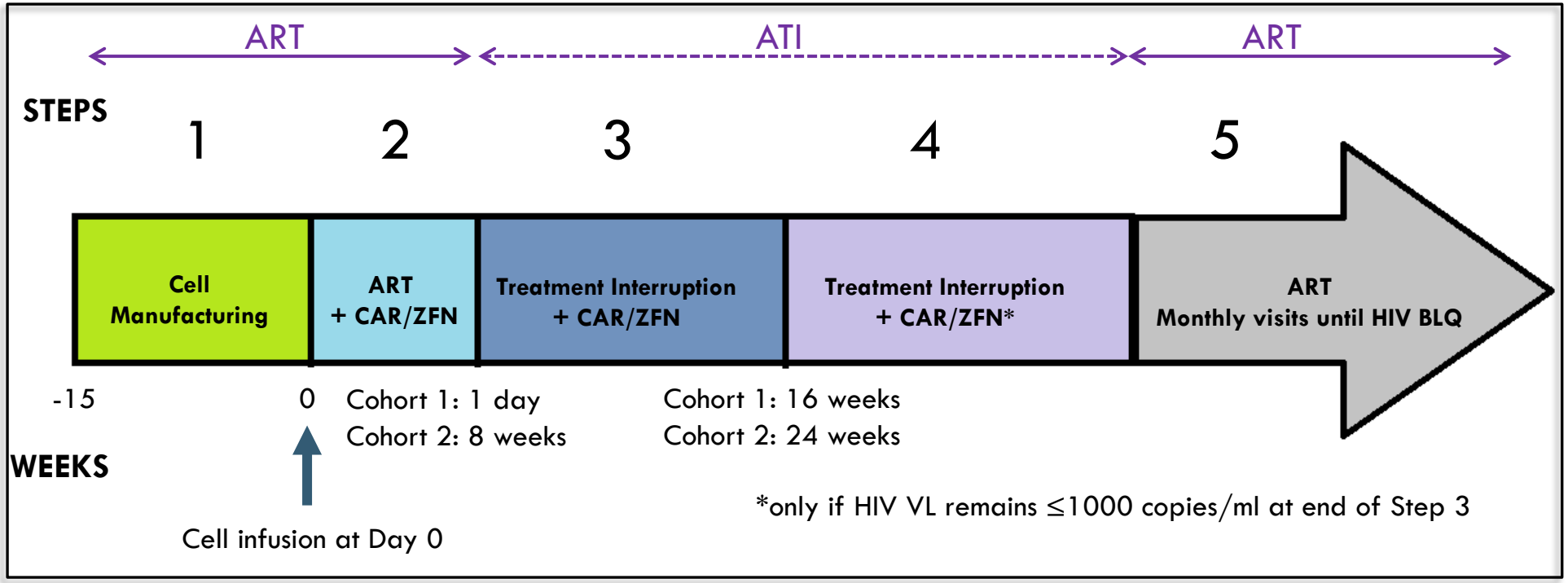
Key Points

Engineered CD4 T cells can bolster endogenous CD8 T cell responses.

How? Maybe these HIV resistant CD4 T cells were able to restore CD4 T cell help to these HIV-specific CD8 T cells

If so, the co-infusion of CCR5 edited HIV-specific CAR CD4 and CD8 T cells should be able to provide potent post rebound control of HIV replication

A PILOT STUDY OF T CELLS GENETICALLY MODIFIED BY ZINC FINGER NUCLEASES SB-728MR, AND CD4 CHIMERIC ANTIGEN RECEPTOR IN HIV-INFECTED SUBJECTS (NCT03617198)



1: To what extent does ongoing HIV replication contribute to the maintenance of the HIV reservoir?

2: Can engineered T cells restore functionality to endogenous HIV-specific T cell populations?

3. Can engineered T cells provide durable control of HIV replication?

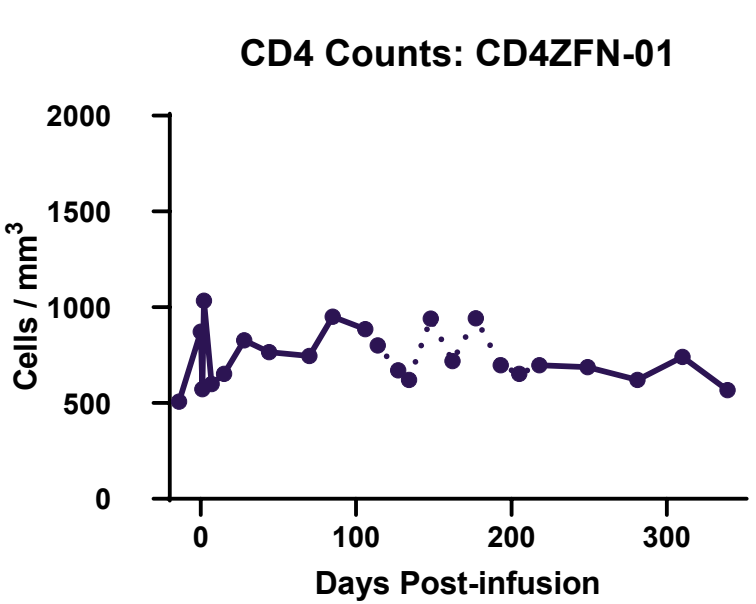
4. When is the best time to do the ATI?

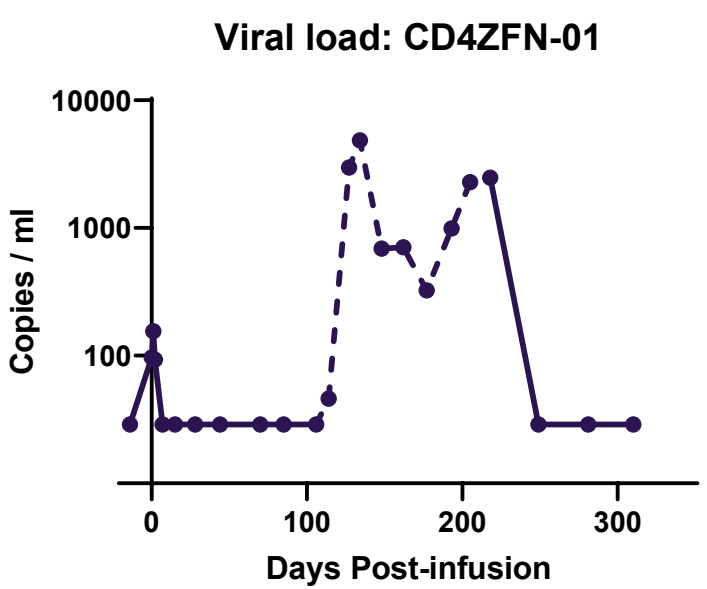
Cohort 1- engraftment (step 2) of 1 day before ATI
Cohort 2- engraftment (step 2) 8 weeks before ATI

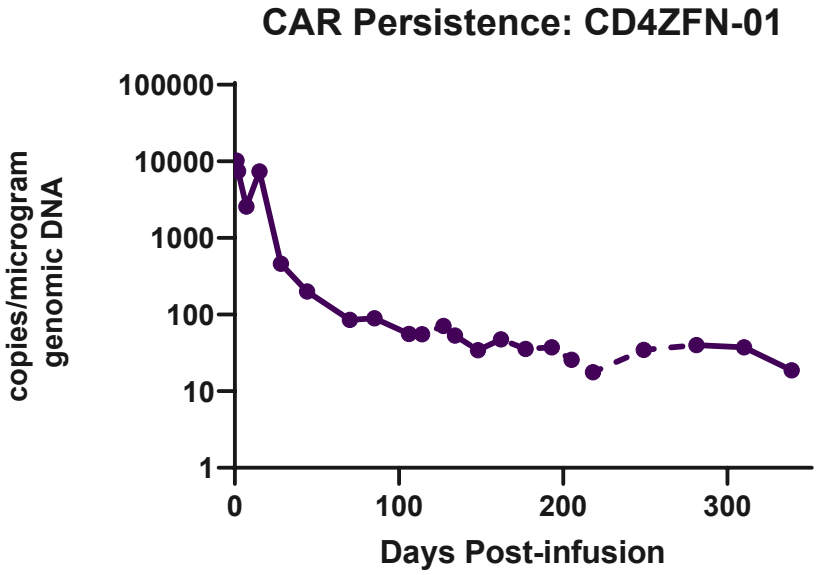
PATIENT DEMOGRAPHICS

Study ID#	Sex	Race	Age at Screening	Consent Date	Years HIV infection (at the time of enrollment)	Screening CD4 abs (cells/uL)	Viral Load Set Point	% CD4 CAR
CD4CAR-ZFN-01	M	African American	21	08/23/2019	4	681	104,750	65.8%
CD4CAR-ZFN-02	M	Caucasian	58	09/05/2019	10	1785	165,810	46.9%
CD4CAR-ZFN-03	M	African American	47	02/17/2020	9	1430	126,500	70.6%
CD4CAR-ZFN-05	M	African American	56	07/17/2020	10	780	12,198	53.6%
CD4CAR-ZFN-06	M	African American	38	08/18/2020	8	559	57,799	63.4%
CD4CAR-ZFN-07	M	Caucasian	58	02/09/2021	3	677	177,178	
CD4CAR-ZFN-08	M	African American	41	2/26/2021			147,000	

CD4 ZFN-01 (COHORT 2…COVID EXTENDED)

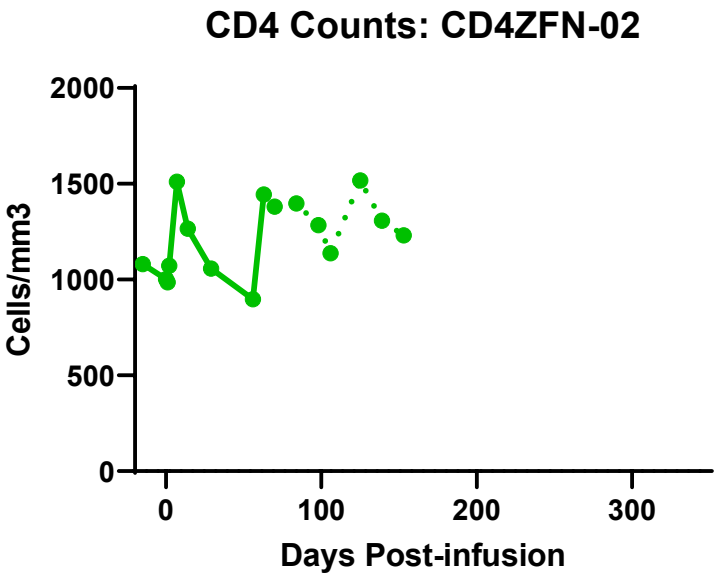




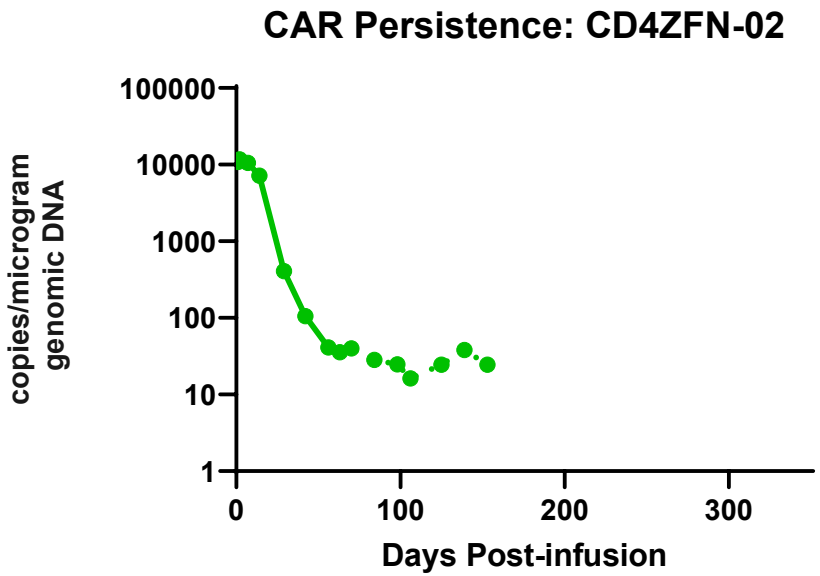


ATI lasted 112 days (16 weeks)

CD4ZFN-02 COHORT 2

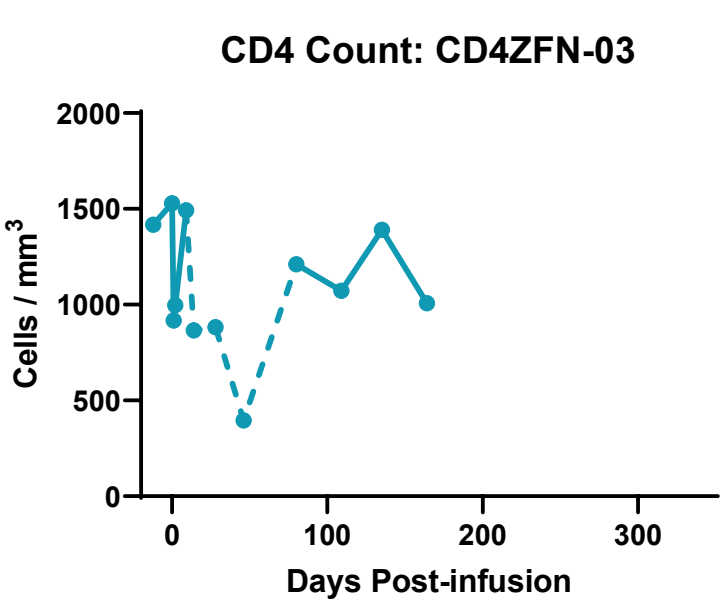


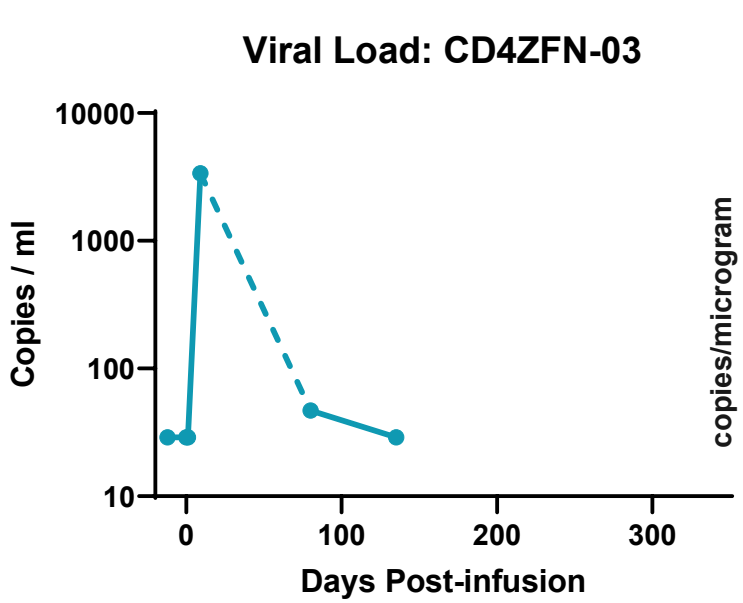
CD4CAR-ZFN-02	VL (copies/ml)	CD4
Safety 8/24/20	<30	1,081
2R 9/8/20	<30	1,002
3R+1W 11/10/20	<30	1,444
3R+2W 11/17/20	<30	1,380
3R+4W 12/1/20	<30	1,397
3R+6W 12/15/20	3,932	1,284
3R+8W 12/23/20	689	1,138
3R+10W 1/11/21	57	1,518
3R+12W 1/25/21	145	1,308
3R+14W 2/8/21	444	1,231
3R+16W 2/22/21	223	1,136
4R 3/8/21	111	1,277
4R+2W 3/22/21	108	1,166
4R+4W 4/05/21	65	1,163

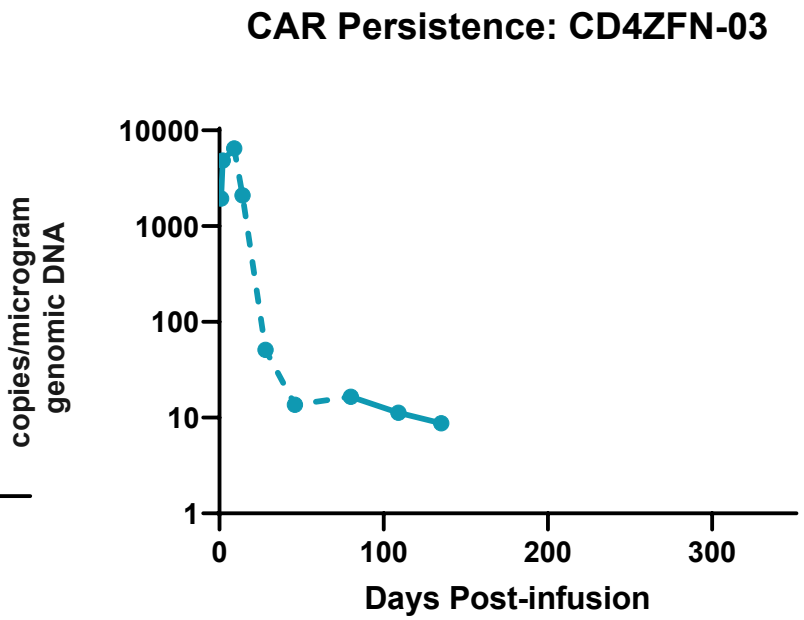


ATI is greater than 180 days

CD4 ZFN-03 (COHORT 1)







ATI lasted 48 days

THE FUTURE: DUAL CAR T CELLS

nature medicine

ARTICLES

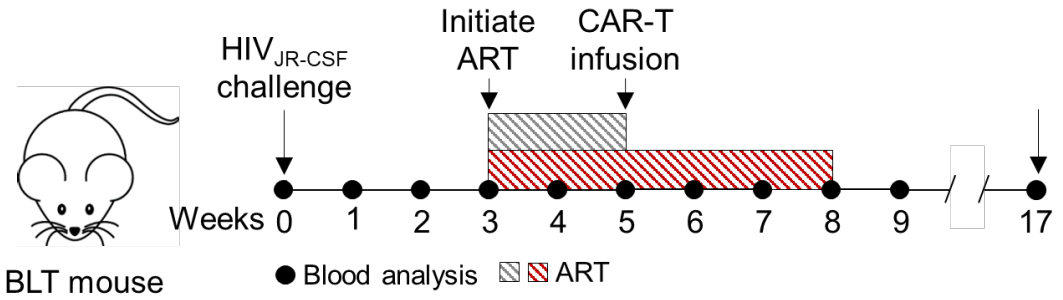
https://doi.org/10.1038/s41591-020-1039-5

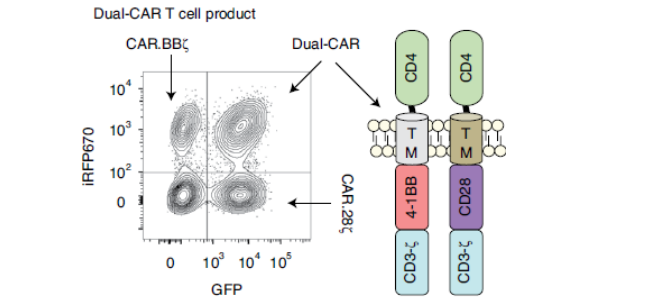
Check for updates

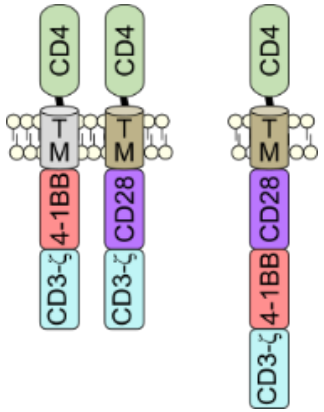
Dual CD4-based CAR T cells with distinct costimulatory domains mitigate HIV pathogenesis in vivo

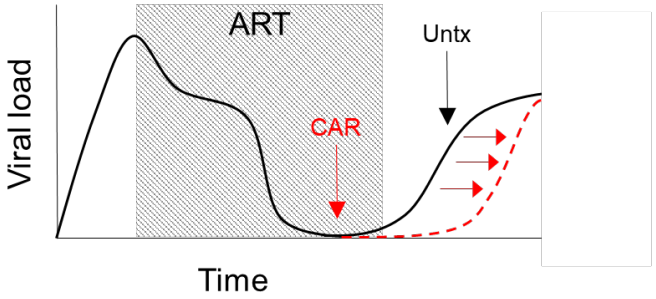
Colby R. Maldini[1,6], Daniel T. Claiborne[2,6], Ken Okawa[2], Tao Chen[2], Derrick L. Dopkin[3], Xiaochuan Shan[3], Karen A. Power[2], Radiana T. Trifonova[2], Katharine Krupp[2], Meredith Phelps[2], Vladimir D. Vrbanac[2,4], Serah Tanno[2,4], Timothy Bateson[2], George J. Leslie[5], James A. Hoxie[5], Christian L. Boutwell[2], James L. Riley[1,7] ✉ and Todd M. Allen[2,7] ✉

Dual-CAR 3G-CAR







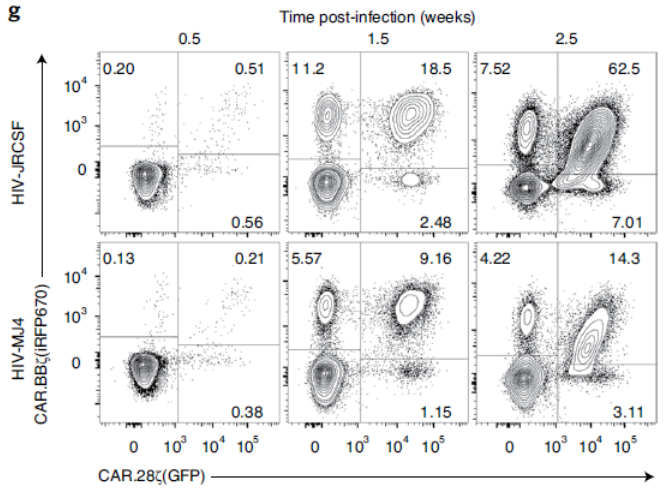


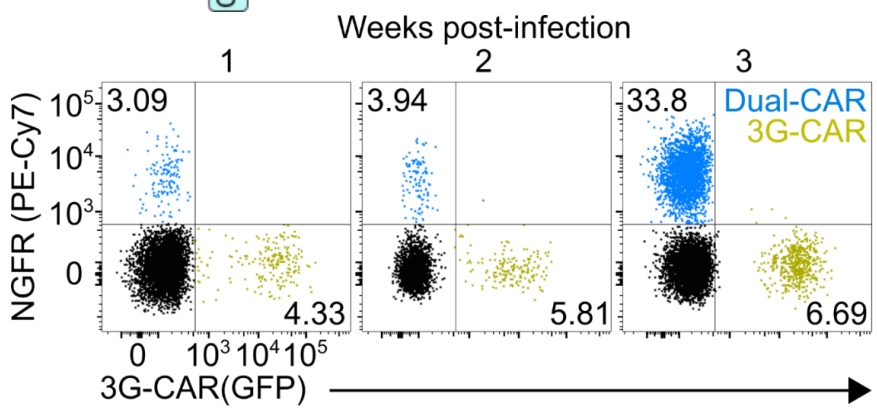
Mitigate HIV pathogenesis

① Delay HIV rebound

② Exert post-rebound control

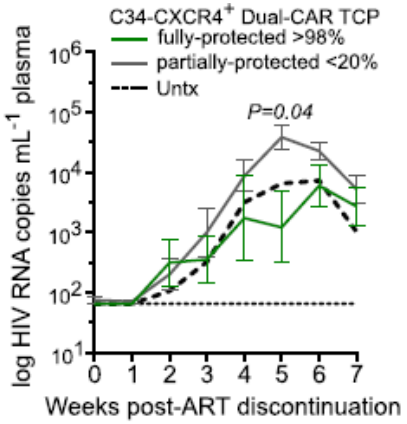
③ Prevent CD4⁺ T cell depletion

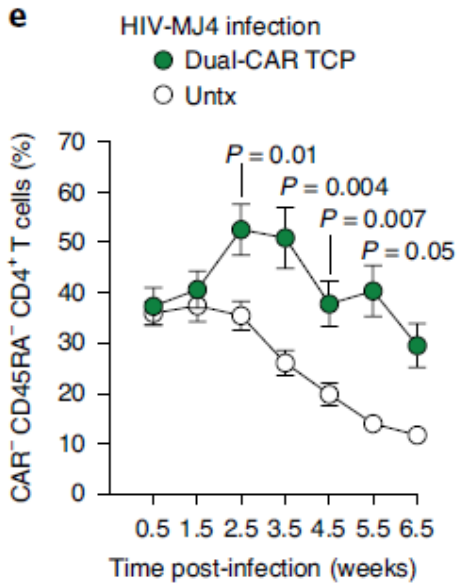


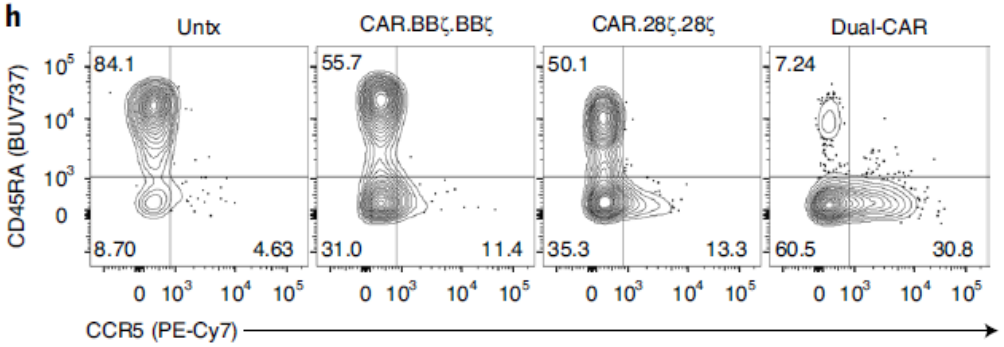


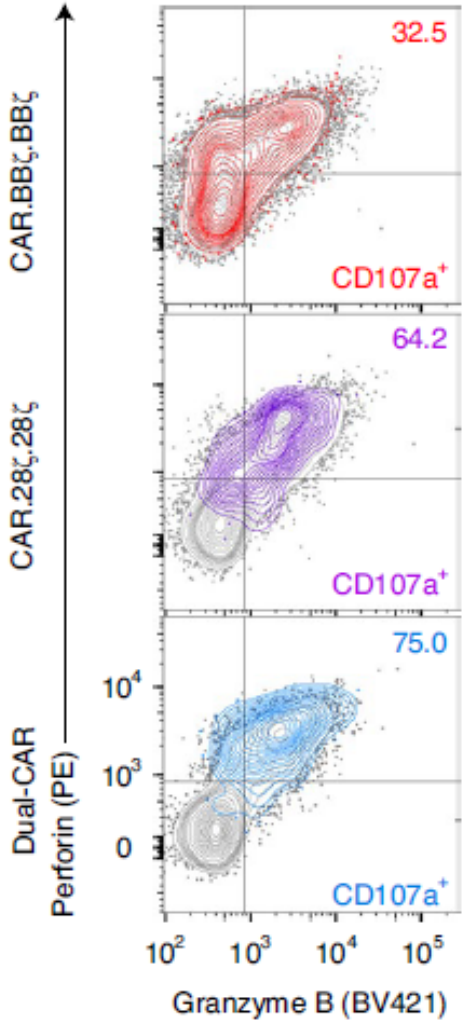
Improved In Vivo Expansion

HIV MAY PROVE A BETTER APPROACH TO TESTING NEW CAR DESIGNS









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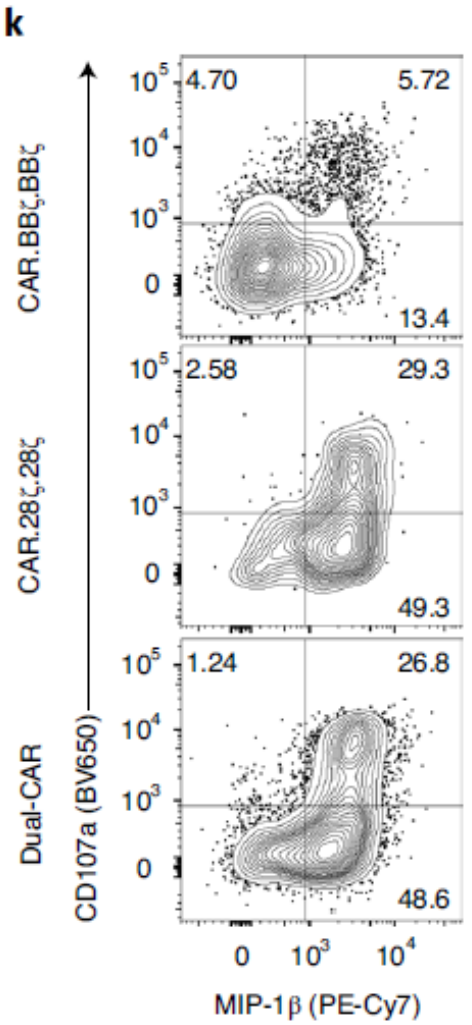
Granzyme B+ Perforin+ of



8 weeks

Improved and Sustained In Vivo Function

Acknowledgements

Riley Lab

- **Colby Maldini**
- Yuqi Zhou
- Rachel Leibman
- Max Richardson
- Kevin Gayoff
- Hong Kong

Human Immunology Core

- Hong Kong
- Vincent Cooper
- Meizan Lai

CFAR Center for AIDS Research
University of Pennsylvania
Children's Hospital of Philadelphia
The Wistar Institute

Simon Lacey and Carl June

Penn Medicine
Center for Cellular Immunotherapies

Funding:
NIAID U19 Engineering Durable Control of HIV:
NIAID U19: Beyond HAART
NIAID U19 GET HIV CURE

BEAT-HIV DELANEY COLLABORATORY

Luis Montaner
Beth Peterson

Todd Allen
John Wherry
Hans-Peter Kiem
Chris Peterson
Jim Hoxie
Rick Bushman
Pablo Tebas
Julie Jadlowsky
Pam Shaw
Mike Betts

CFAR HARVARD UNIVERSITY CENTER FOR AIDS RESEARCH

Dan Claiborne
Ken Okawa
Tao Chen

TMUNITY