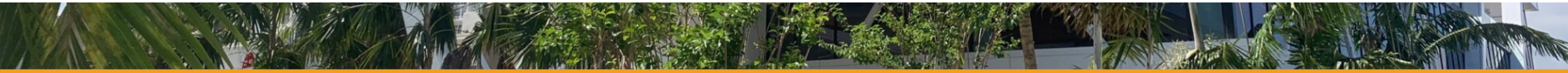
Multivalent CAR T Cell Therapy Shows Superior Potency in Controlling HIV Escape and Replication in BLT Humanized Mice

Federica Severi

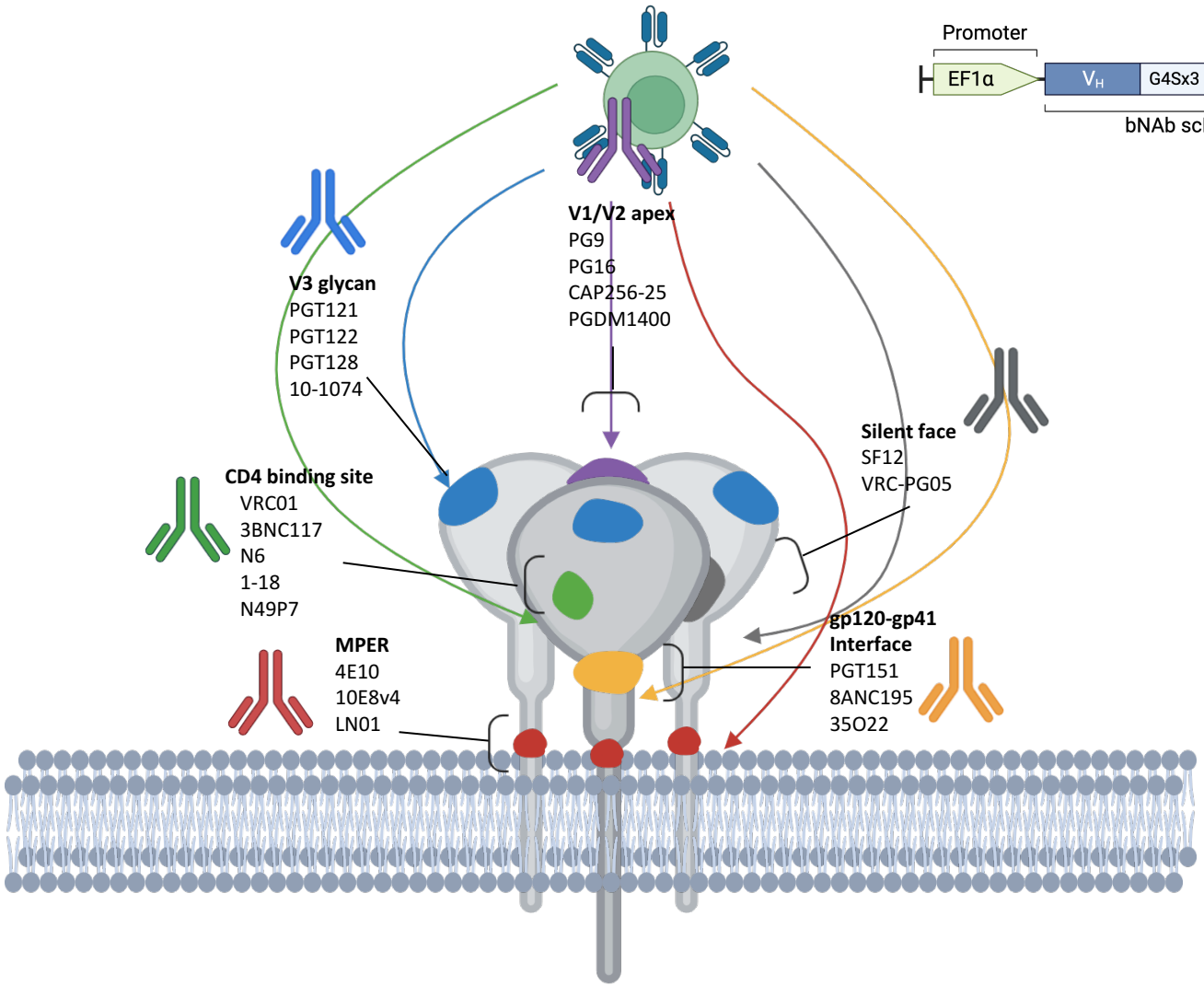
Claiborne Lab – The Wistar Institute

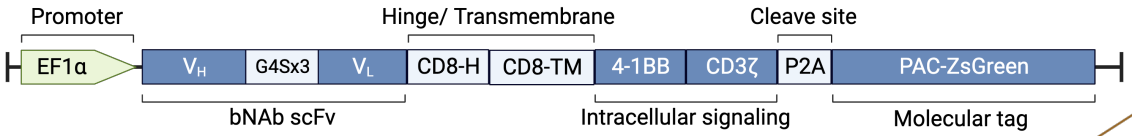


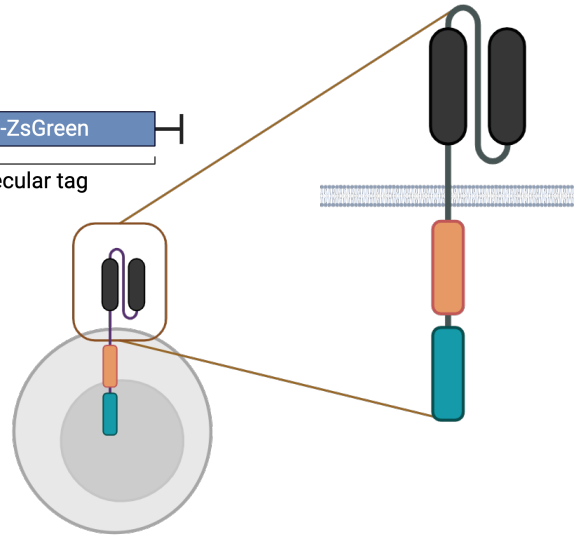
CONFLICTS OF INTEREST

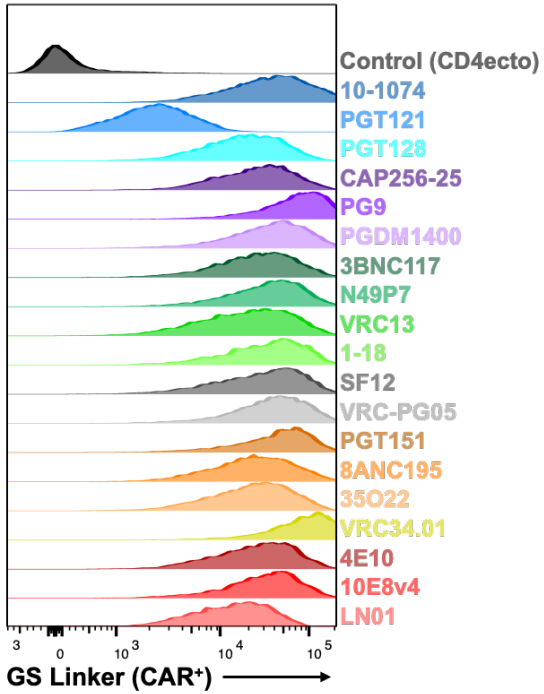
We declare no conflicts of interest

bNAb-based CAR T cells: what to target.. And why?

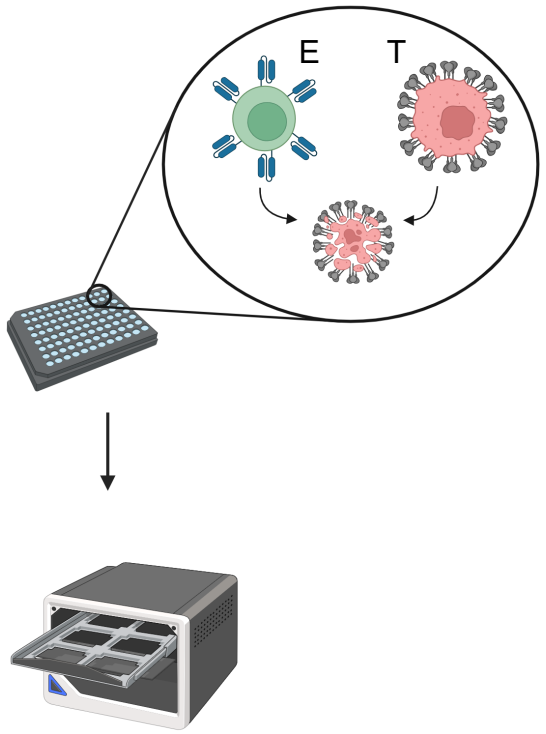


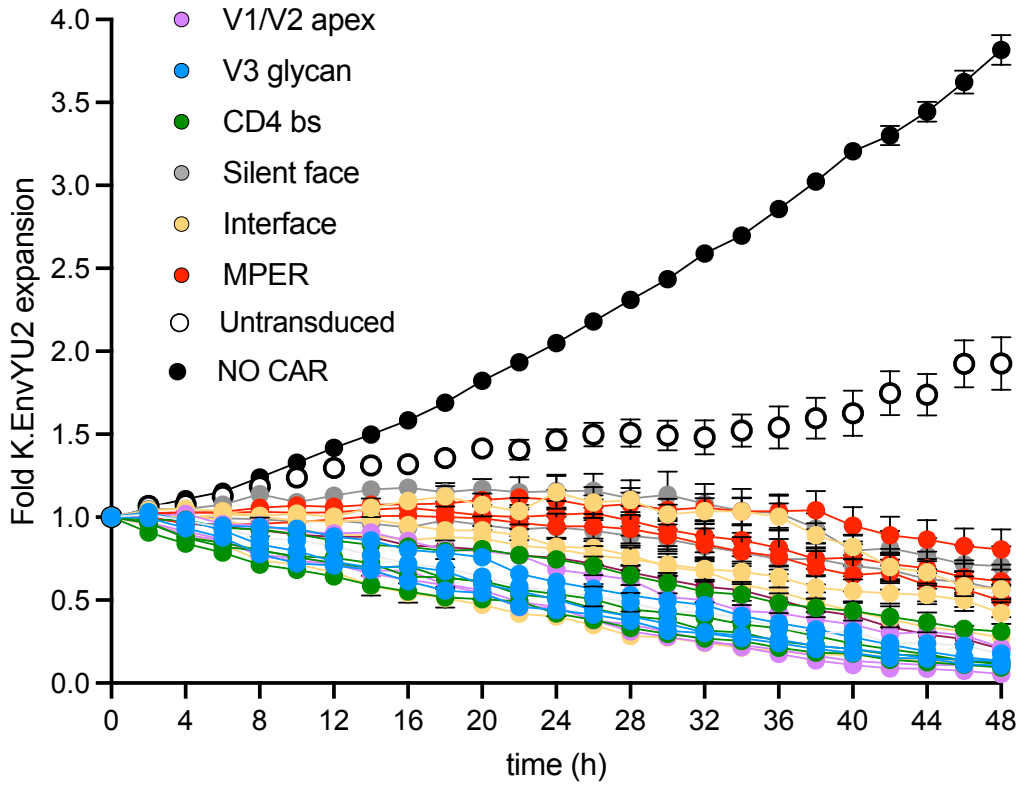


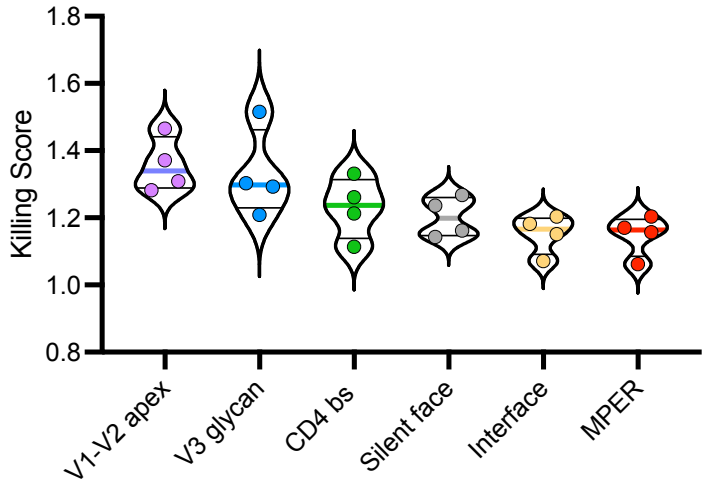


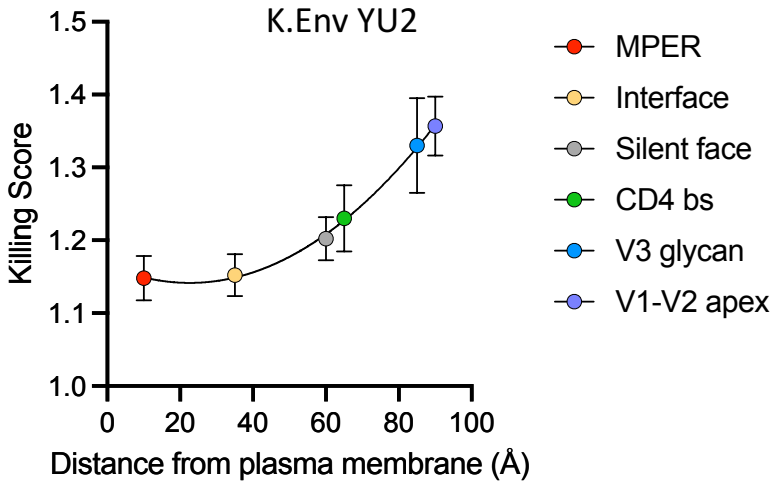


Membrane distal epitopes are associated with greater CAR potency

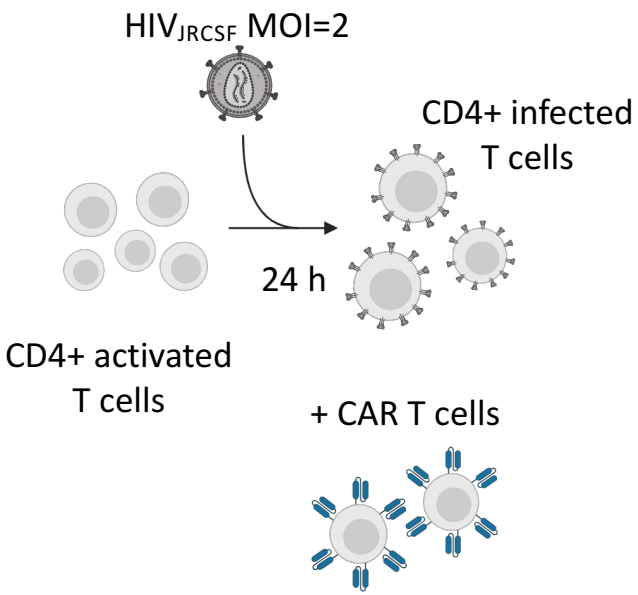


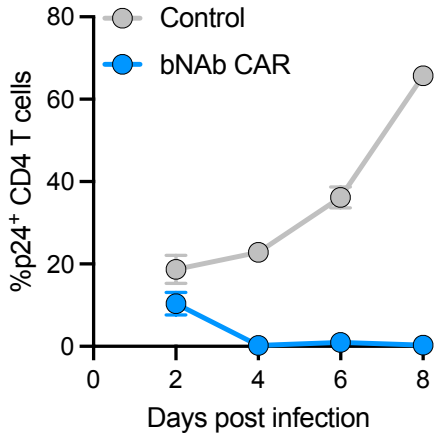


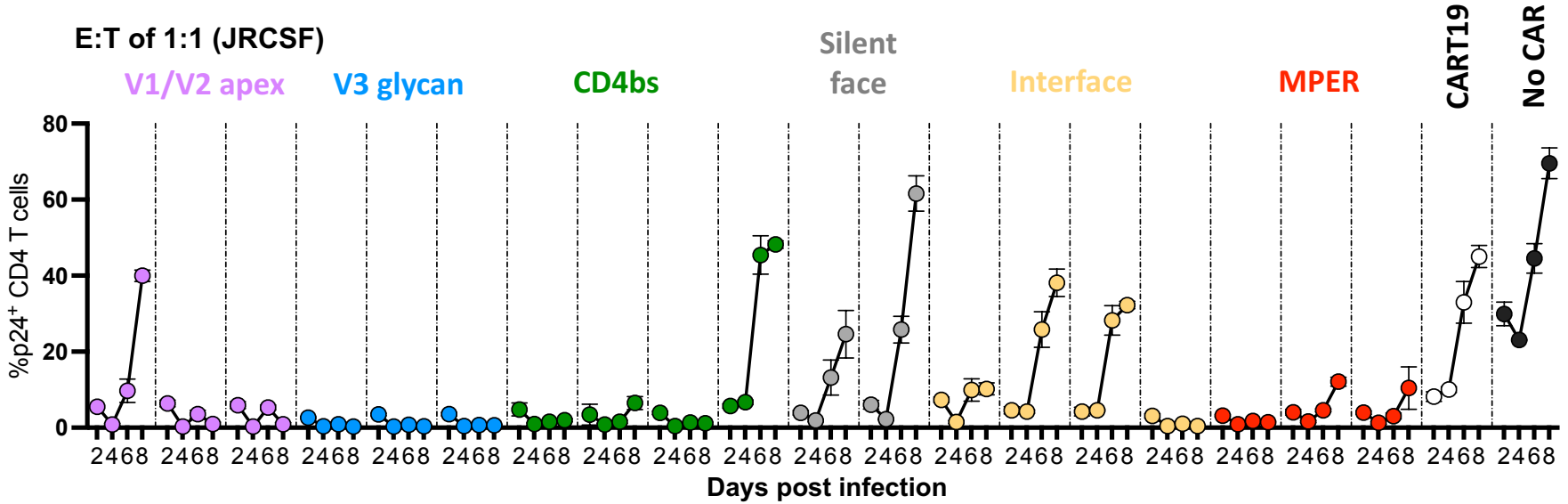


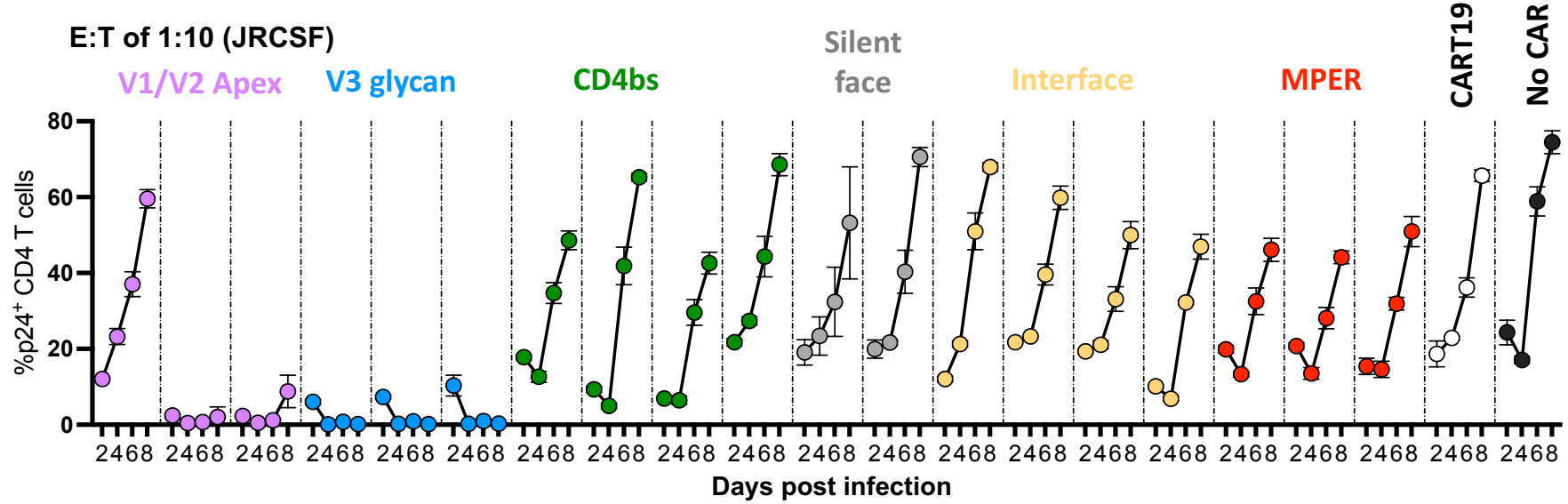


CARs targeting membrane distal epitopes suppress HIV replication

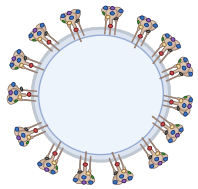


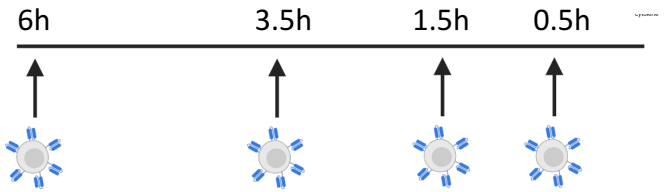


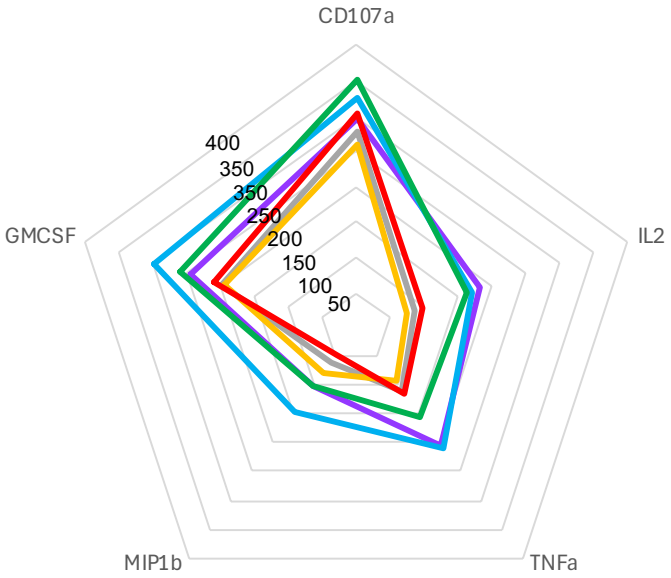


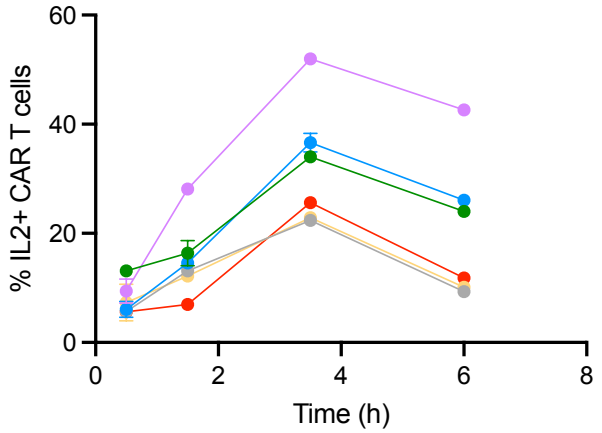


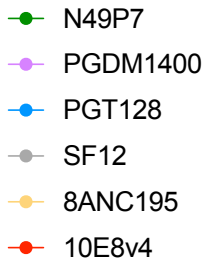
Most accessible epitopes are associated with increased CAR potency

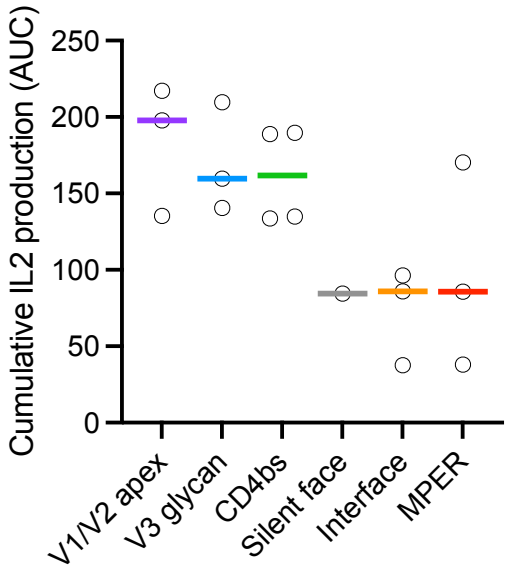


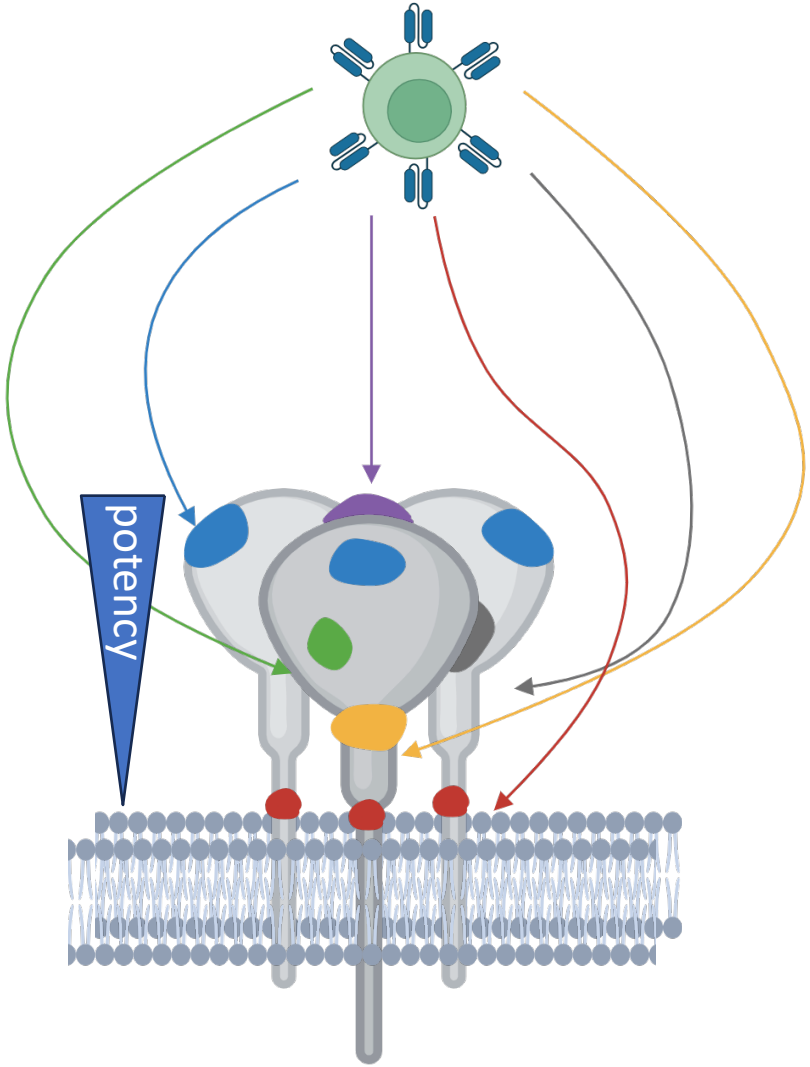




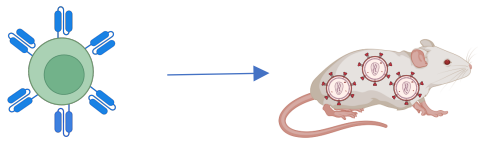




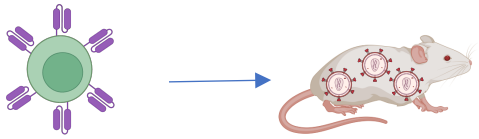




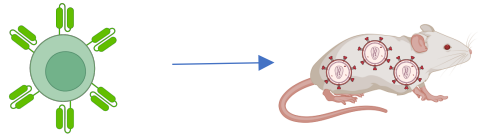
CAR T cell monotherapy drives HIV escape *in vivo* in hBLT mice



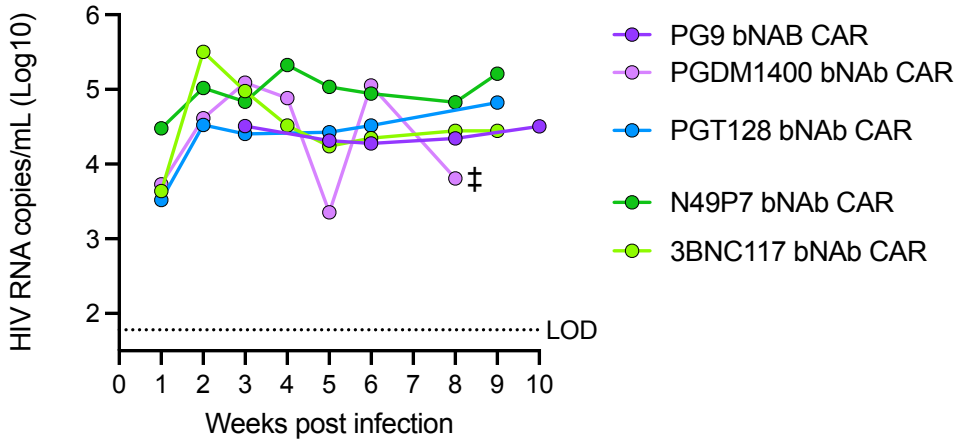
PGT128



PGDM1400
PG9

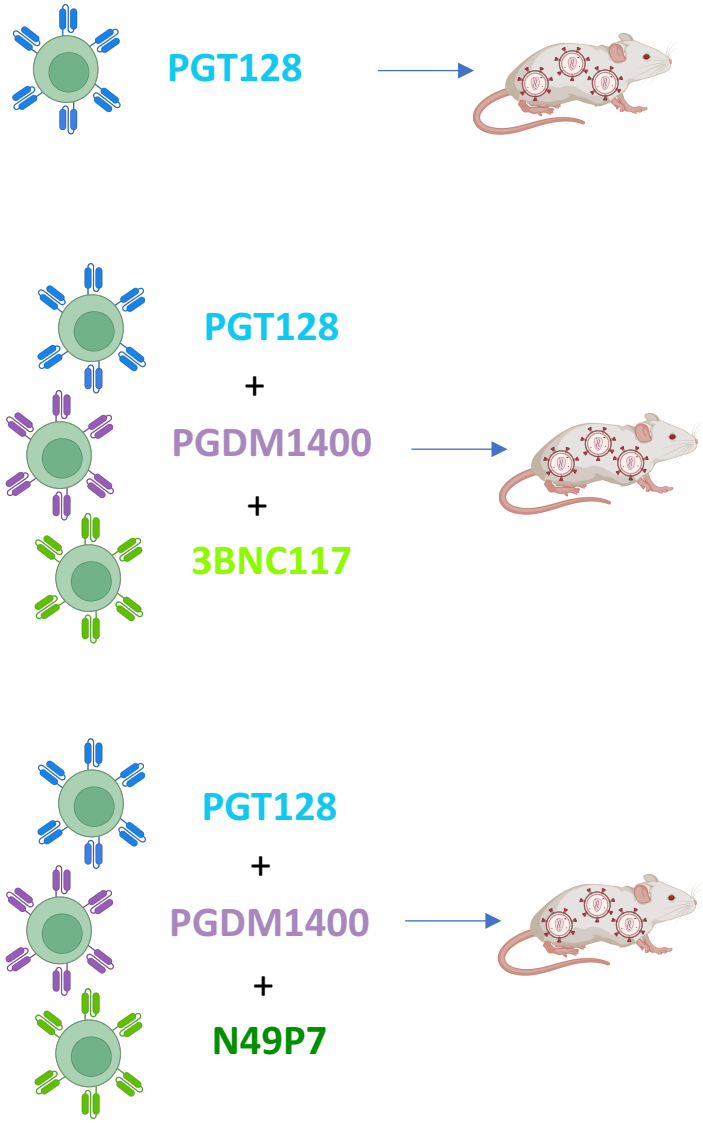


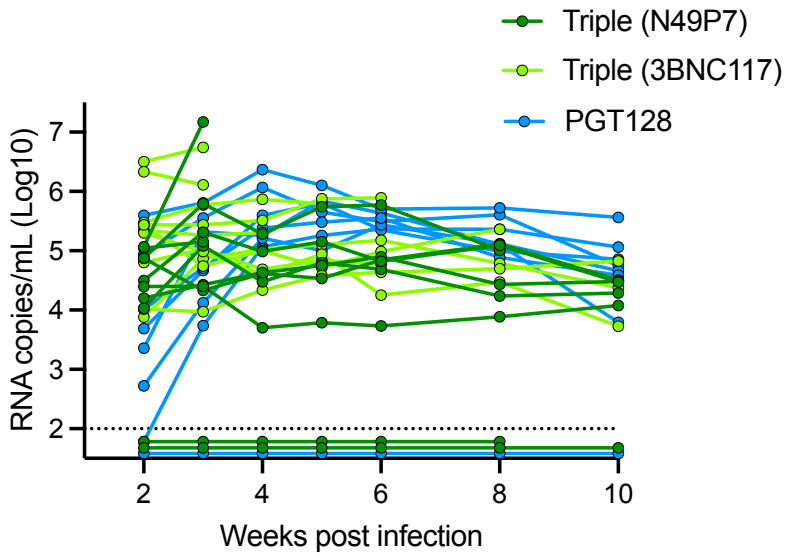
N49P7
3BNC117

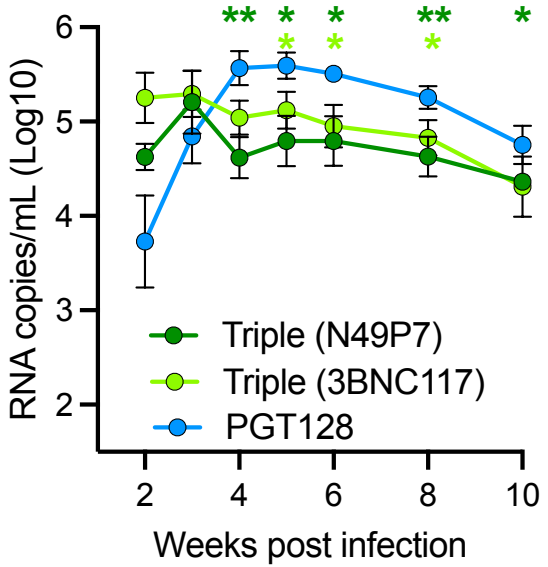


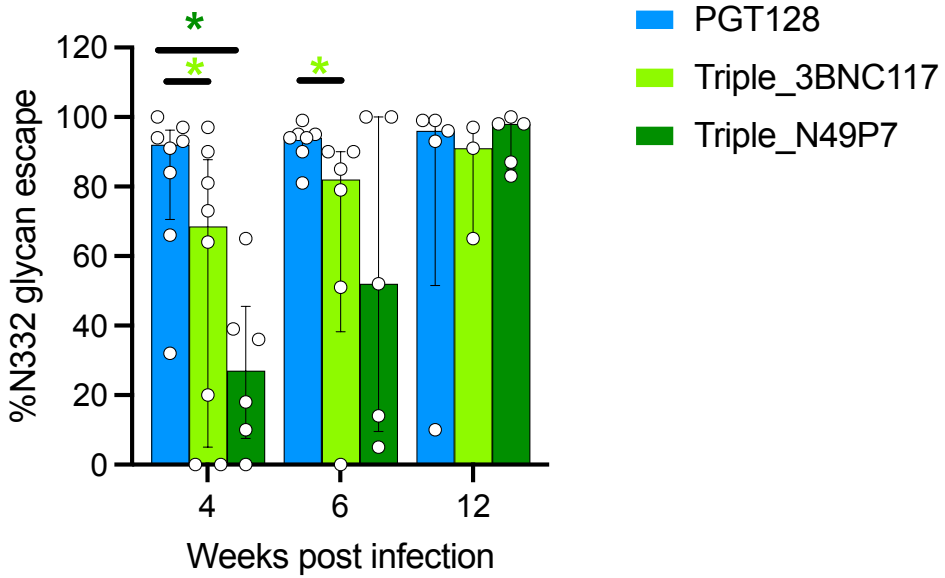
	Mouse ID_Weeks PI	N160 Glycan					%	Loop D								%	"GDIR" motif				%	N332 Glycan					%
	HXB2 #	159	160	161	162	163		275	276	277	278	279	280	281	282		324	325	326	327		331	332	333	334	335	
CAR bNAb	JRCSF AA	F	N	I	T	K		D	N	F	T	D	N	A	K		G	D	I	R		C	N	I	S	R	
PGDM1400	B0144_5-WPI	.	D	.	.	.	99	.	.	.	.	.	.	.	.	0	.	.	.	.	0		.	.	.	0	
PG9	1817_6-WPI		D	.	.		43	.	.		.	.	.	.	.	0	.	.	.	.	0	.	.	.	.	.	0
3BNC117	9805_12-WPI	.	.	.	.	.	0	.	D	.	.	.	.	.	.	77	.	.	.	.	0		.	.	.	0	
3BNC117	9693_12-WPI	.	.	.	.	.	0	.	D	.	.	.	.	.	.	13	.	.	.	.	0		.	.	.	0	
N49P7	86_6-WPI	.	.	.	.	.	0	.	.	.	.	E	.	.	.	99	.	.	.	.	0		.	.	.	0	
N49P7	B0142_9-WPI	.	.	.	.	.	0	.	.	.	.	E	.	.	.	49	.	.	.	.	0		.	.	.	0	
PGT128	87_9-WPI	.	.	.	.	.	0	.	.		.	.	.	.	.	0	.	.	.	.	0	.	.	.	N	.	99
PGT128	B0613_6-WPI	.	.	.	.	.	0	.	.		.	.	.	.	.	0	.	.	.	.	0	.	D	.	.	.	99

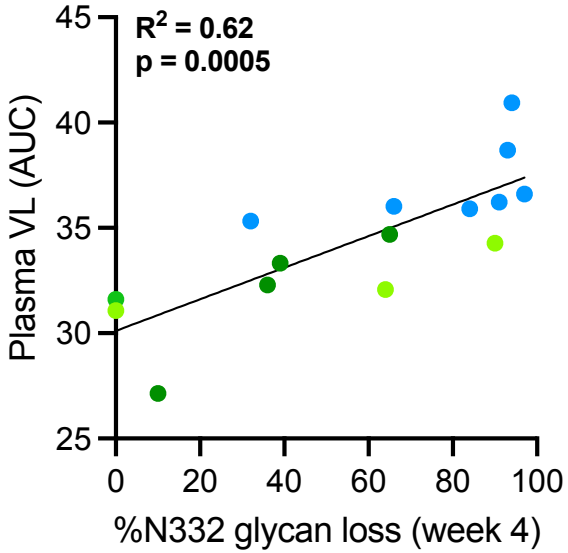
Combination CAR T cell therapy improves control of HIV in hBLT mice



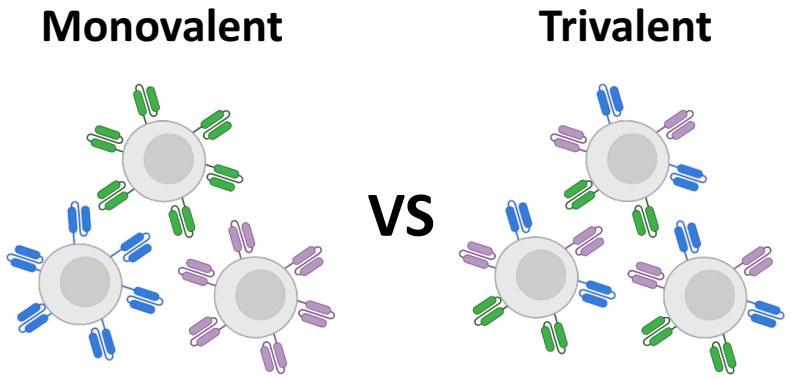


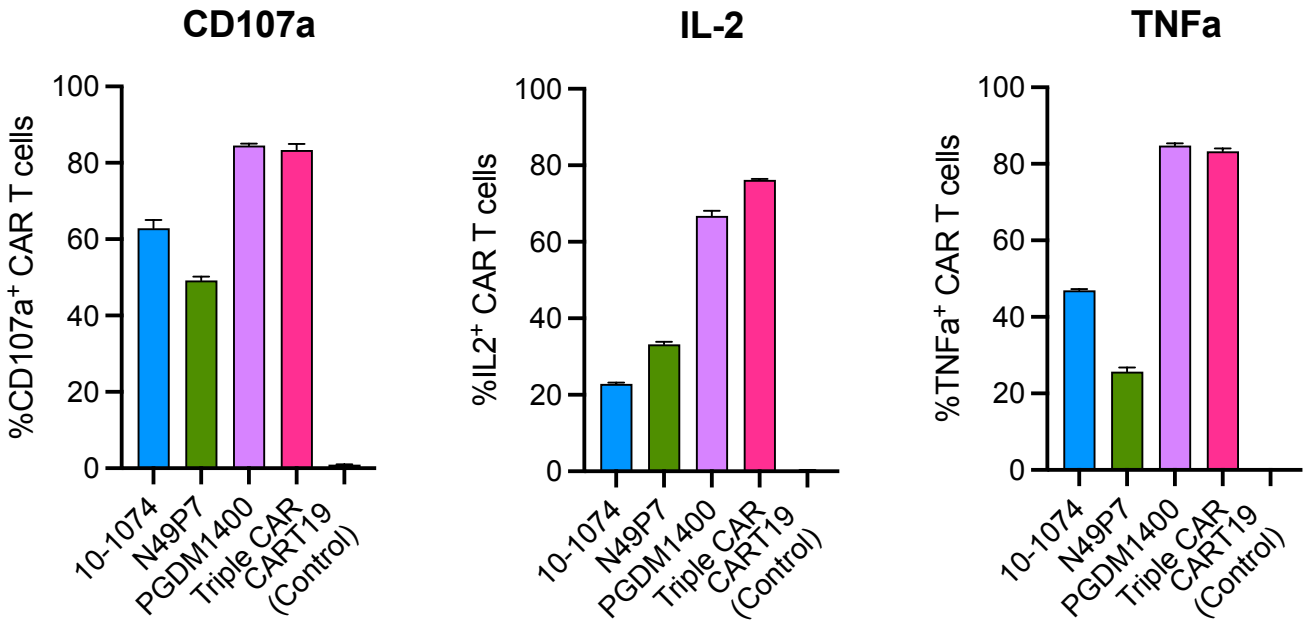


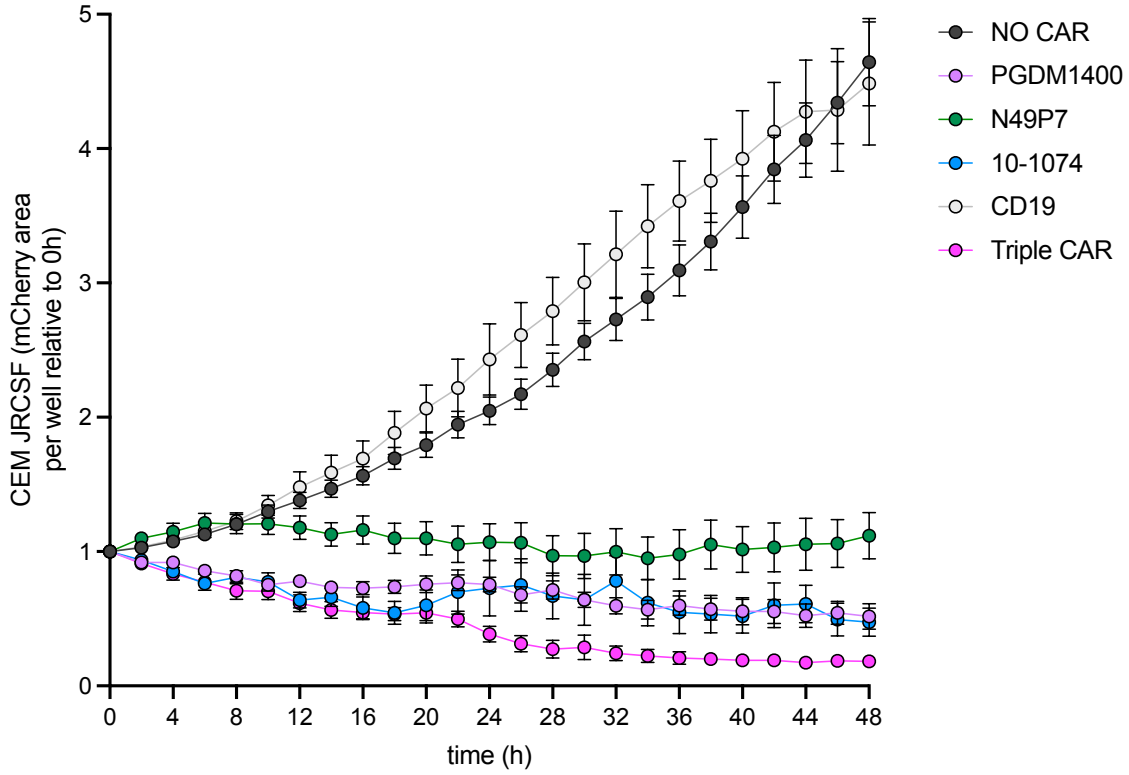




Trivalent CAR T cells demonstrate significant potency *in vitro*

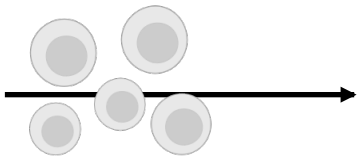


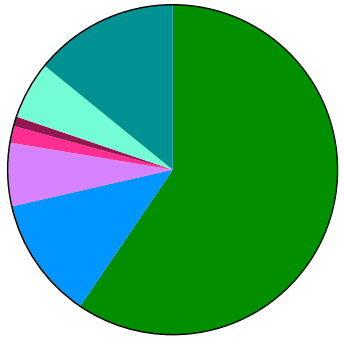




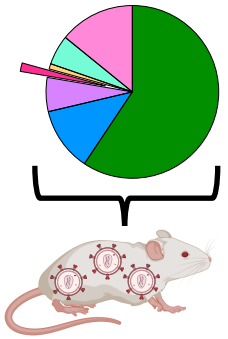
Multivalent CAR demonstrate superior *in vivo* expansion

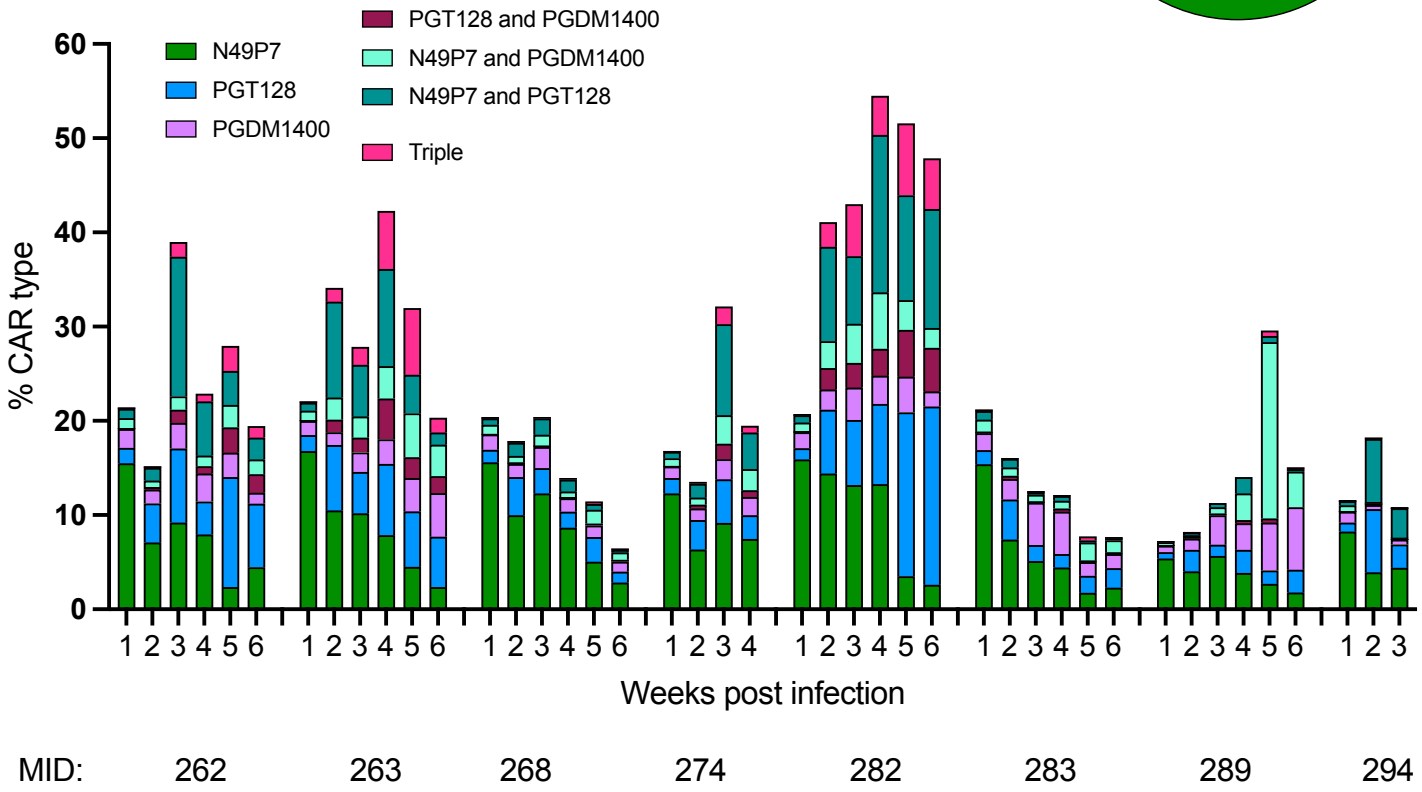
PGT128-EGFR
PGDM1400-eGFP
N49P7-NGFR



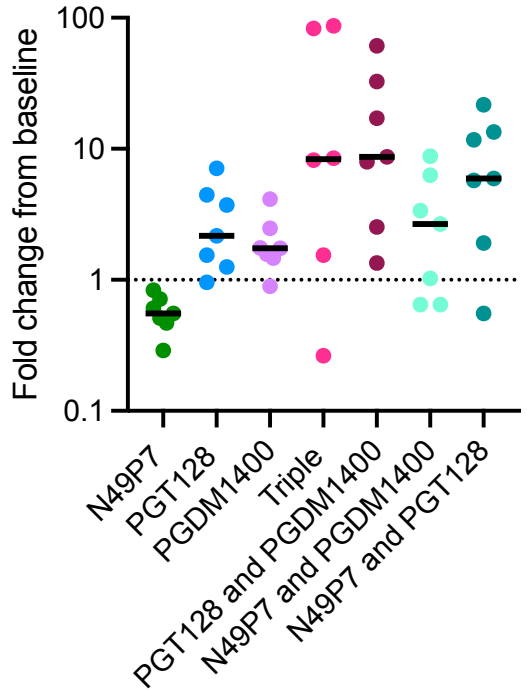


Triple Lenti CAR Mix

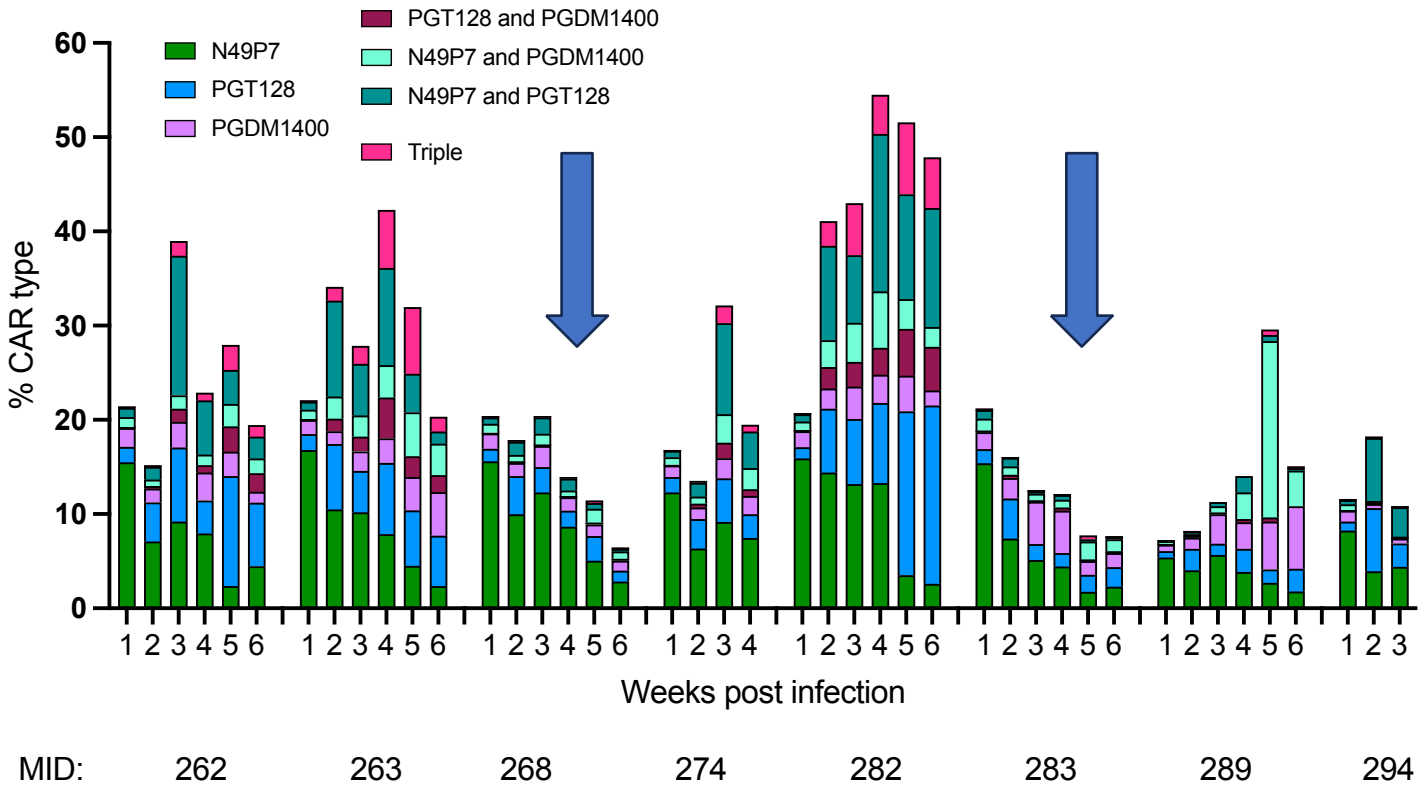


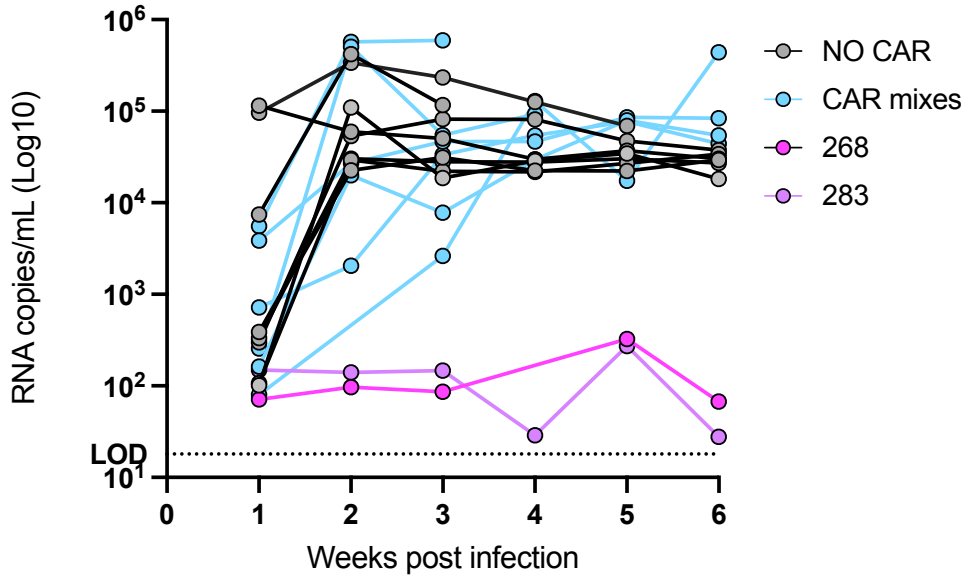


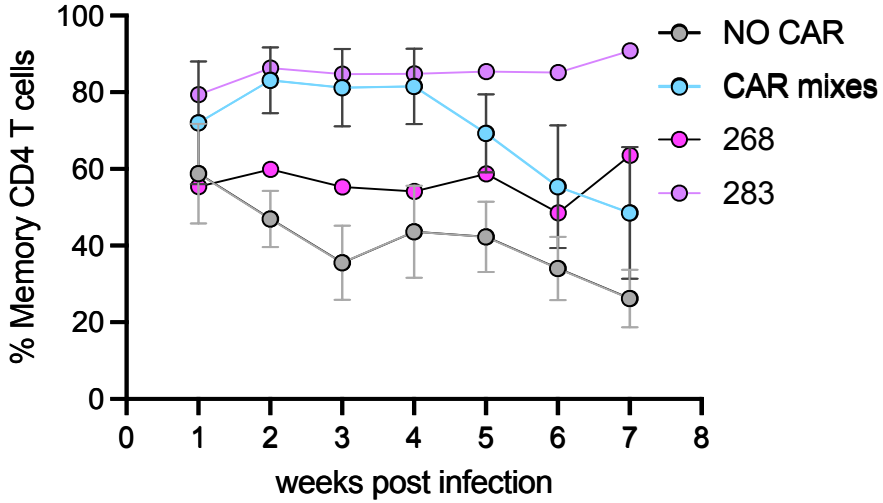
Fold in CAR expansion week 4



Multivalent CAR control viral load and prevent from memory cell loss

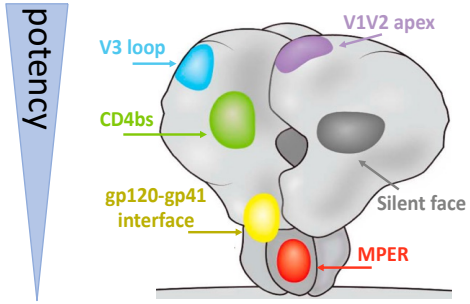






Summary and future directions

- Distal epitopes are associated with superior CAR potency;



- Restricting HIV escape through combinations of potent CARs selecting for orthogonal escape mutations may be a viable strategy to achieve long-term suppression of viral loads;

- Trivalent CAR products demonstrate the potential for greater functional potency;

- Determine escape mutations in the non-controlling mice with high triple CAR expansion

- Administrate pure trivalent CAR products to test their ability to restrict escape and control plasma viral loads *in vivo*.

Acknowledgments

Claiborne Lab

Daniel Claiborne

Francesco Pennino

Nur Izzah Ismail

Reyes Acosta

Ally Criswell

Tyler Yang

Dalia Bercow

Kristina Stallings

Alice Li

Flow cytometry facility

Bioinformatics core

Humanized mice core

BEAT-HIV DELANEY COLLABORATORY

amfAR MAKING AIDS HISTORY

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

NIH NIAID

VACCINE & IMMUNOTHERAPY CENTER THE WISTAR INSTITUTE

ALMA MATER STUDIORUM UNIVERSITA DI BOLOGNA A.D. 1088

THE CAMPBELL FOUNDATION Supporting Innovative HIV/AIDS Research Since 1995