

Future Prospects for Cell Therapy in Solid Tumors

Ned Waller, MD, PhD, FACP
ewaller@emory.edu

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Disclosures

Consultant/Advisory Boards

- Sanofi
- Novartis
- Biolinerx
- Allogene

Equity

- Cambium Medical Technologies (founder)
- Cambium Oncology (founder)
- Doximetry

Outline of the talk

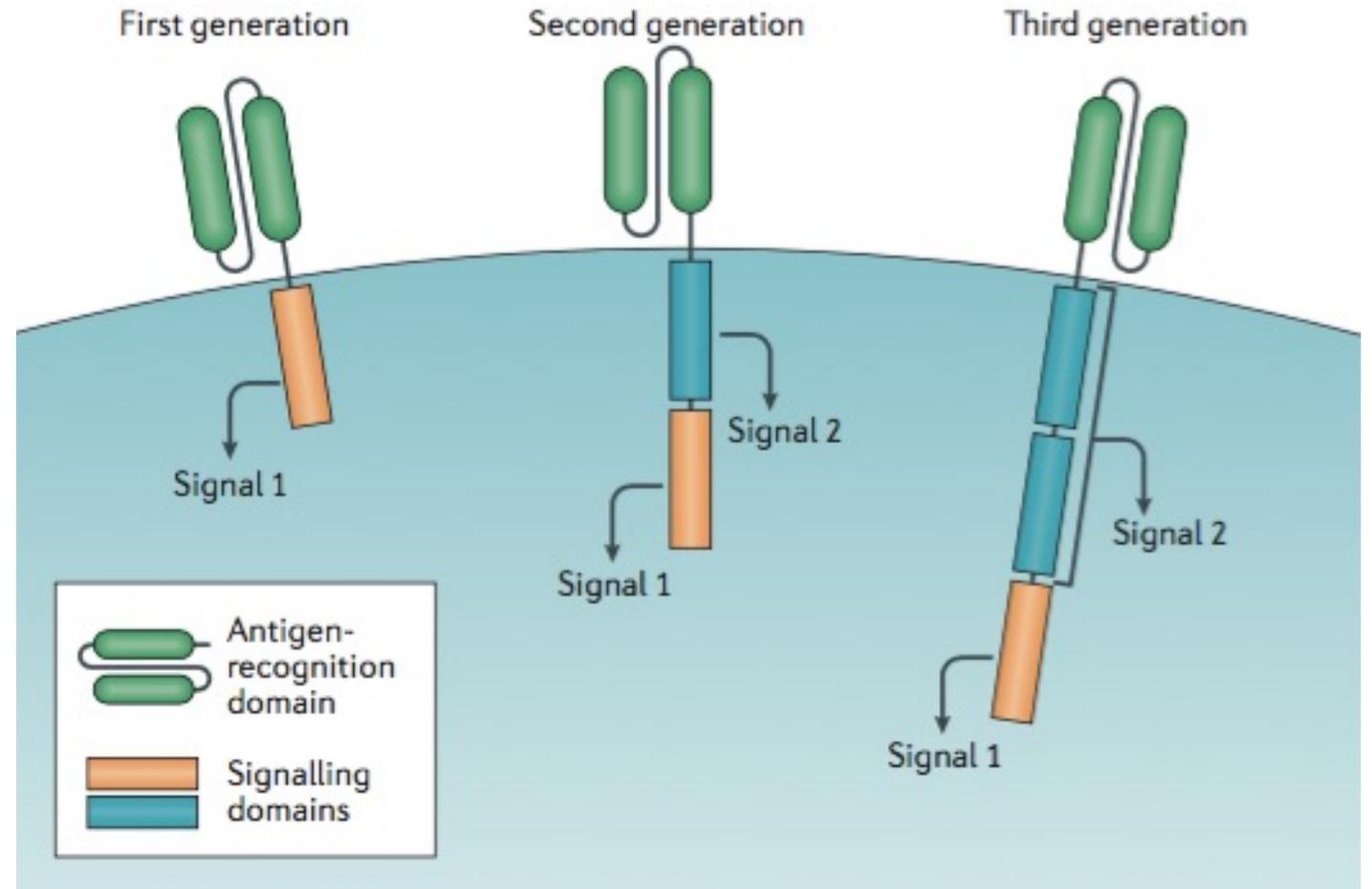
1. Refresher on CART
2. Limitations of CART for solid tumors
3. Synthetic Biology Advances in CART
4. Targeting the VIP pathway to enhance anti-cancer immunity
5. Combining VIP receptor antagonists and Pi3K inhibitors to expand T Cells
6. CD26^{hi} PI3-kinase inhibited CD4⁺ CART for pancreatic cancer

1. Chimeric Antigen Receptor (CAR) T Cell Therapy

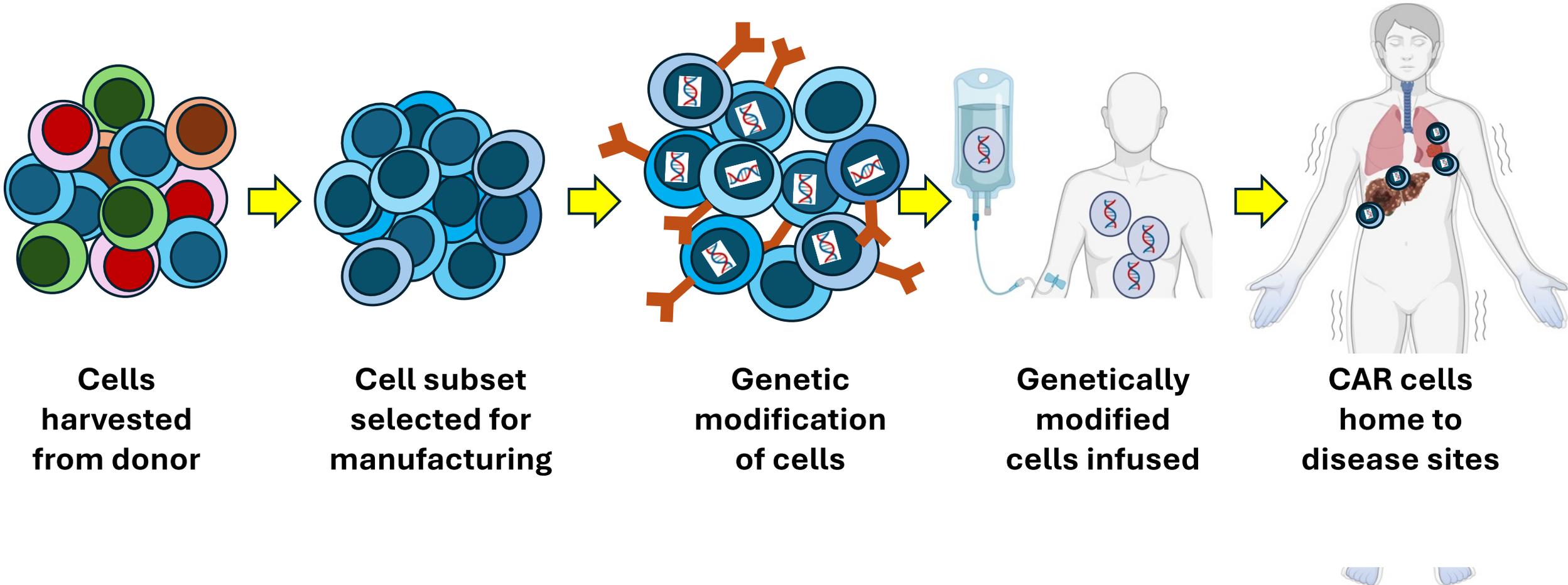
Signal 1 → activation (CD3ζ)
Signal 2 → co-stimulation

2nd gen → 4-1BB or CD28

3rd gen → multiple co-stimulatory signaling



Chimeric Antigen Receptor Cell Technology



Principles of CAR cells

- Target antigen

Physiologic versus ectopic
(cancer) expression
Tissue distribution
Antigen density

- Type of binder

Chimeric antibody
Surface-bound receptor ligand
Physiologic receptor for surface-
bound ligand

- Properties of the cell

Payload and effector function
Cell type: Autologous vs allogeneic
In vivo expansion & persistence
Tissue homing and penetrance

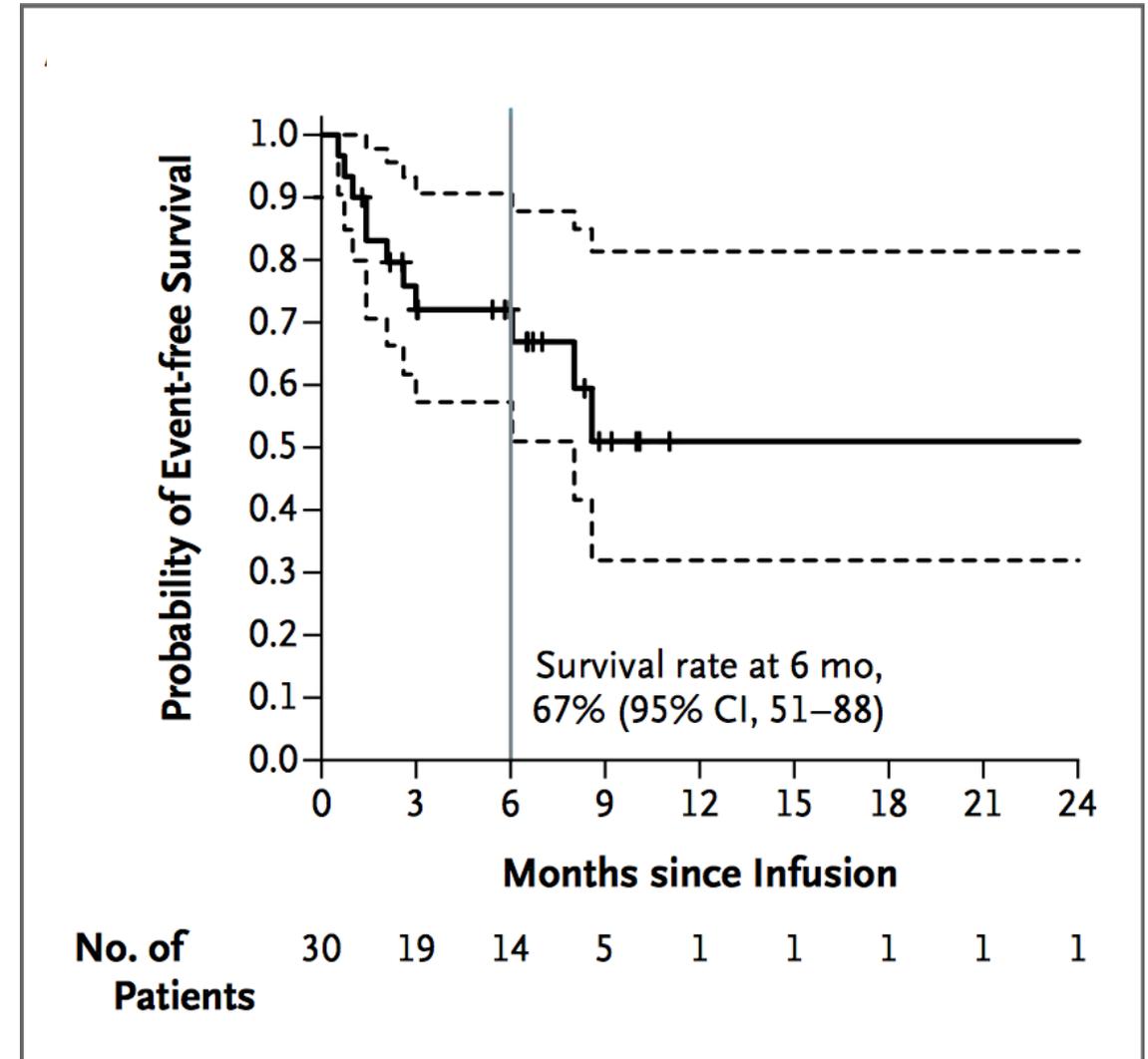
- Efficacy and toxicity

On-target effects
Off-target damage
Systemic effects

CAR T cell therapy cures Pediatric ALL patients

Table 1. Baseline Characteristics of the Patients.*

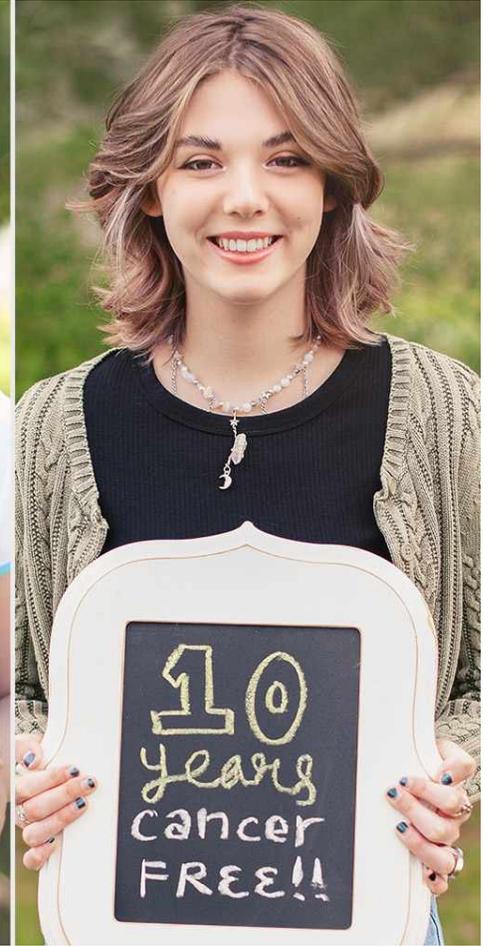
Characteristic	Pediatric Cohort (N=25)	Adult Cohort (N=5)	Total (N=30)
Sex — no. (%)			
Female	11 (44)	1 (20)	12 (40)
Male	14 (56)	4 (80)	18 (60)
Age at infusion — yr			
Median	11	47	14
Range	5–22	26–60	5–60
Allogeneic transplantation — no. (%)	18 (72)	0	18 (60)
Primary refractory disease — no. (%)	0	3 (60)	3 (10)
Relapse — no. (%)			
1	3 (12)	2 (40)	5 (17)
≥2	22 (88)		22 (73)
Baseline burden of acute lymphoblastic leukemia — no. (%)			
Presence of detectable disease†	20 (80)	4 (80)	24 (80)
Morphologic remission‡		1 (20)	1 (3)
Absence of minimal residual disease	5 (20)		5 (17)
High-risk cytogenetic factors — no.			
<i>BCR-ABL1</i>	2		
<i>IKZF1</i> deletion	2		
<i>iAMP21</i>	1		
<i>MLL</i> translocation	1		
Hypodiploidy	2		
CNS status — no.§			
CNS-1	23		
CNS-2	2		



Emily Whitehead- first pediatric ALL patient treated at CHOP with CART



**Dying of leukemia in
CHOP ICU in 2012**

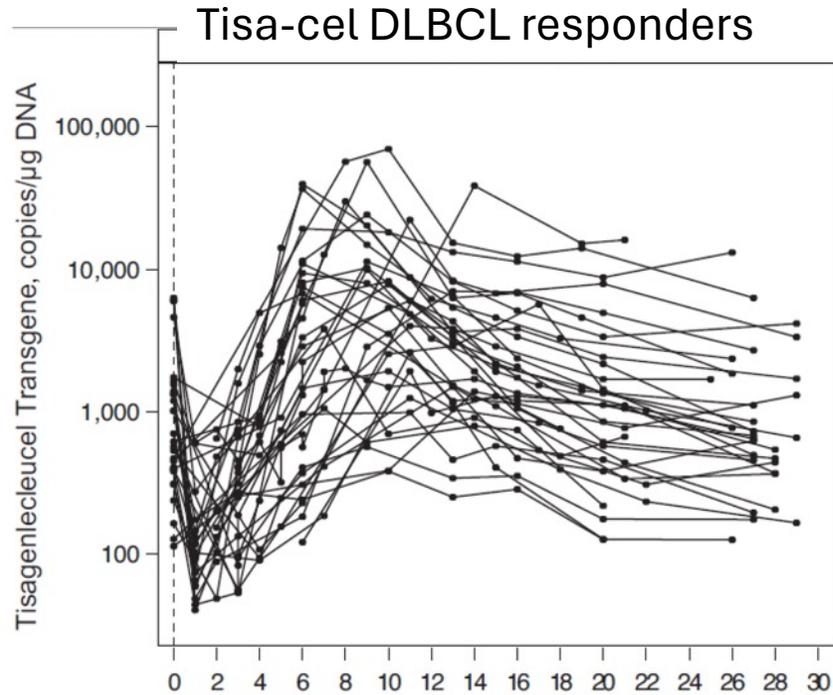


**Freshman at
U Penn 2023**

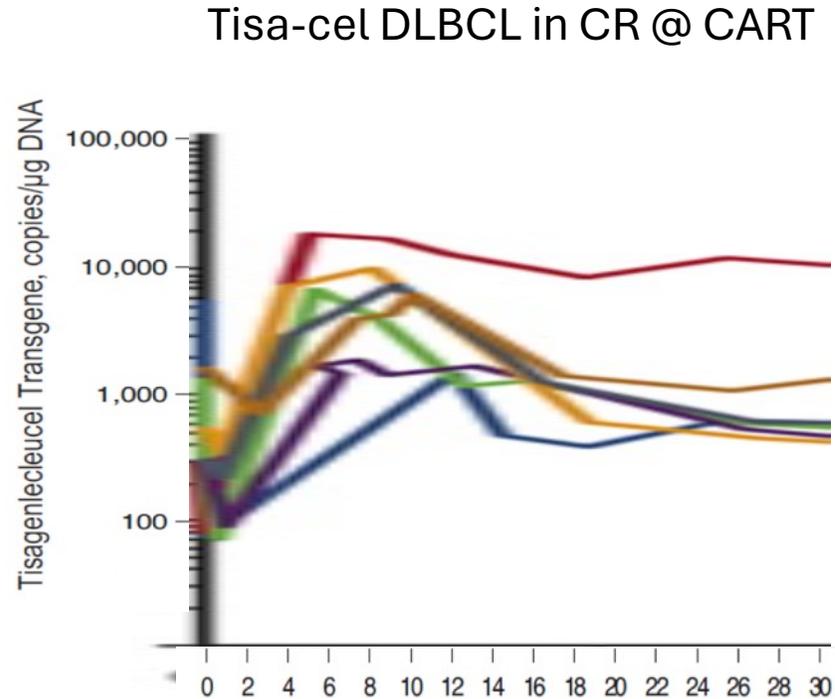
2. Barriers to treating solid tumors with CART

- Lack of tumor-specific cell-surface-associated antigen
- Synthetic Biology approaches to enhance CART for solid tumors
- Immunosuppressive tumor microenvironment
- Tumor-intrinsic resistance to T cell-mediated cytotoxicity

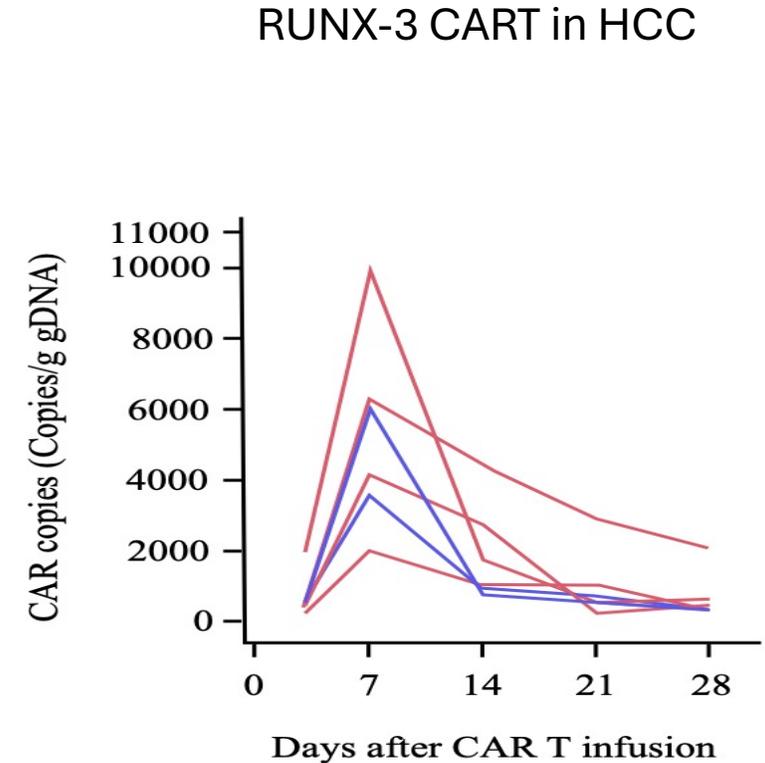
Lower *in vivo* expansion of CART in CR DLBCL patients and in hepatocellular carcinoma patients



Schuster SJ (2019) Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* 2019;380:45-56.

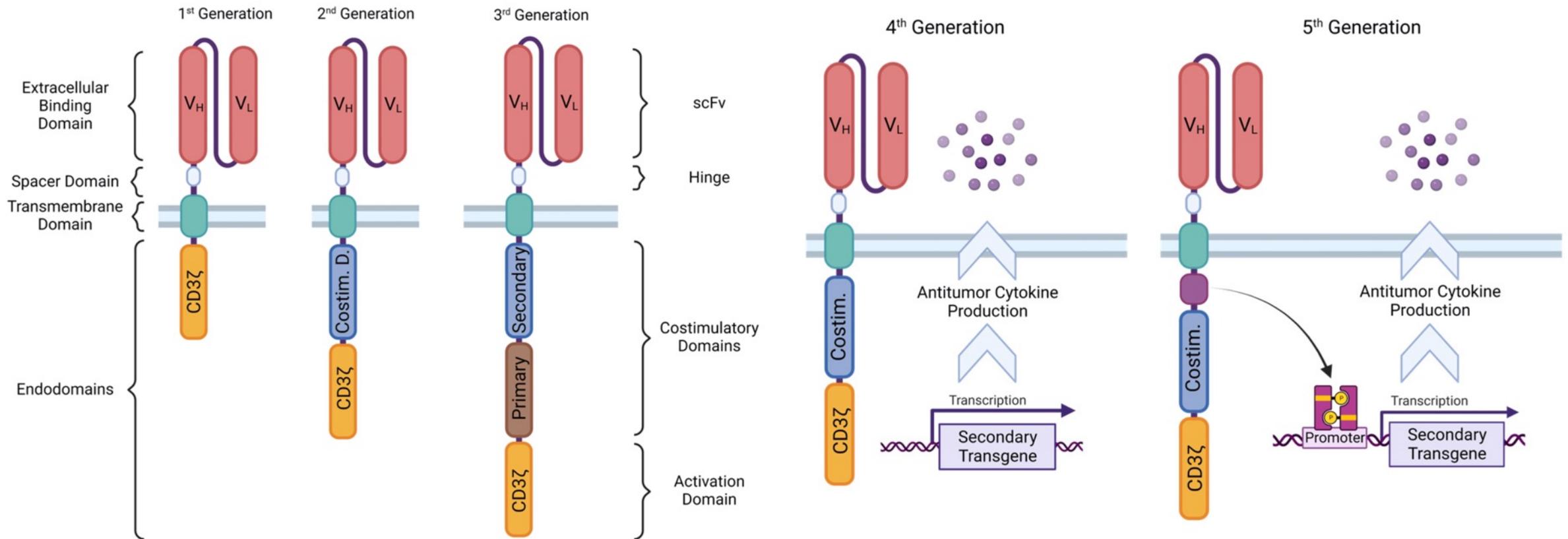


Bishop MR (2019) Tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma patients without measurable disease at infusion *Blood Adv* (2019) 3 (14): 2230-22

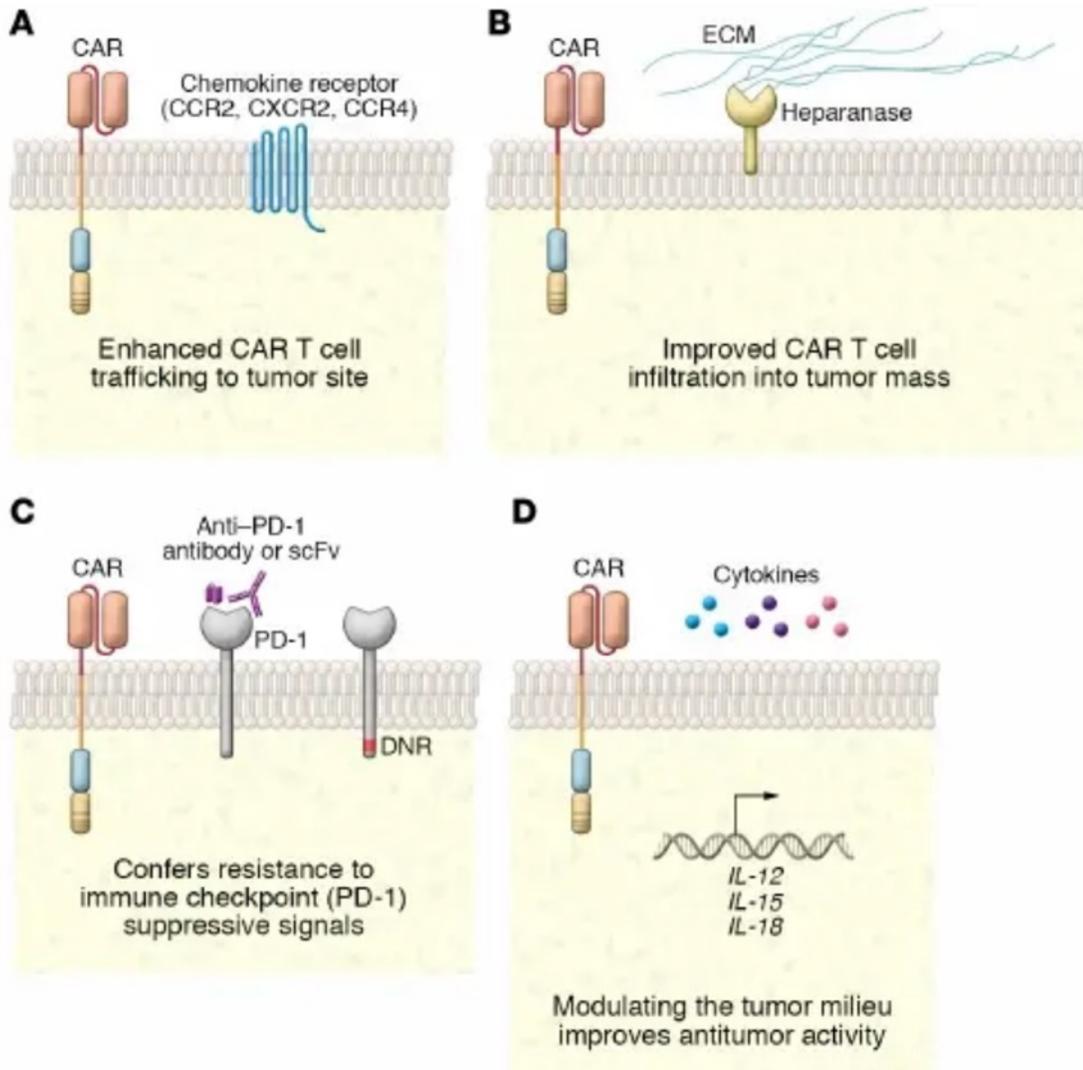


Fu Q (2023) RUNX-3-expressing CAR T cells targeting glypican-3 in patients with heavily pretreated advanced hepatocellular carcinoma: a phase I trial *eClinicalMedicine* 63: 102175

3. Evolution of CART Synthetic Biology

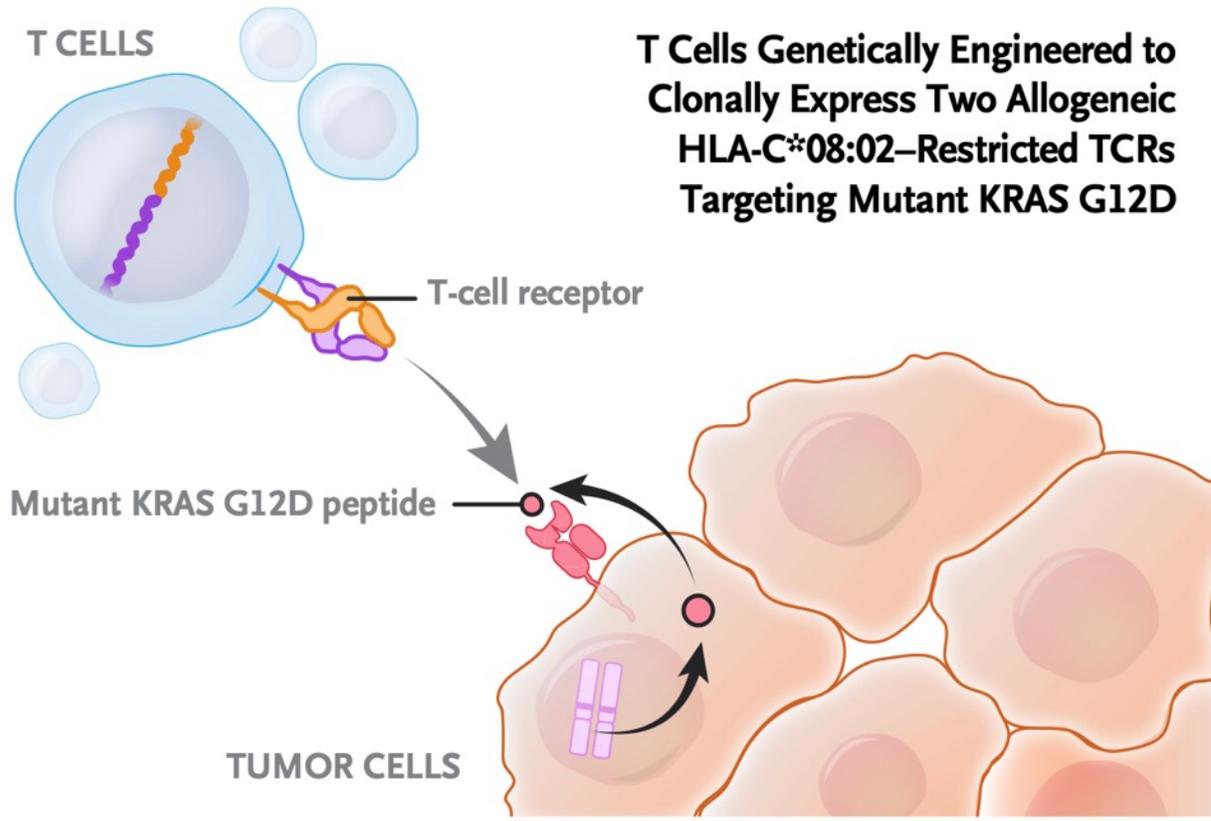


Strategies to enhance the efficacy of CAR T cells against solid tumors

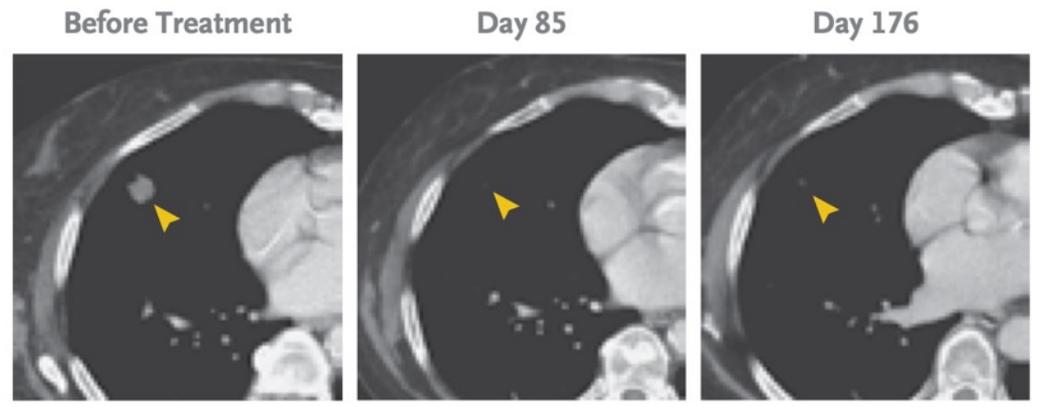


- Target peptide neoantigen with TCR-modified T-cell
- Improve T cell trafficking to the tumor
- Add enzymes that help T cells penetrate the tumor
- Secrete immune check-point drugs
- Secrete cytokines that stimulate the immune system

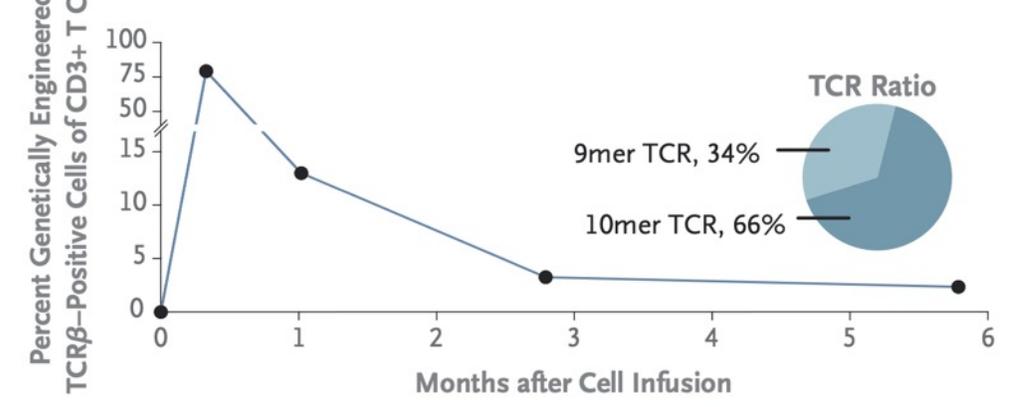
Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer



Computed Tomography of Chest: Lesion 1

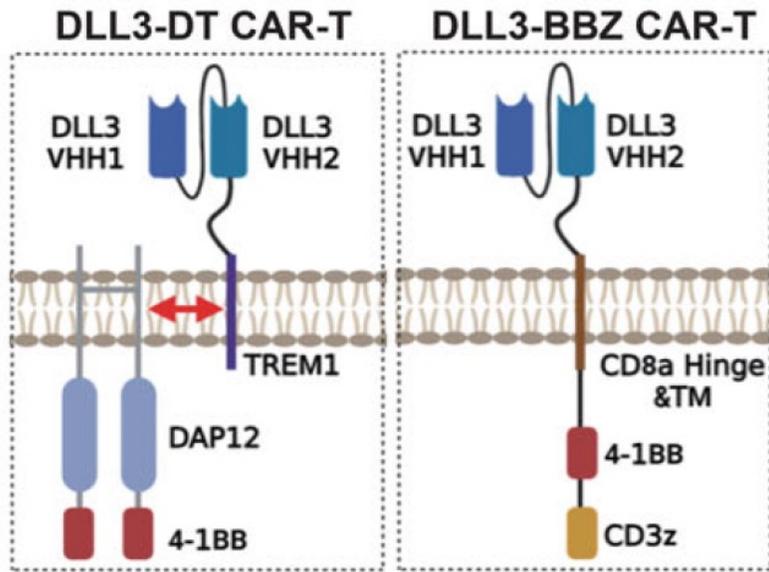


In Vivo Persistence of TCR-Engineered T Cells

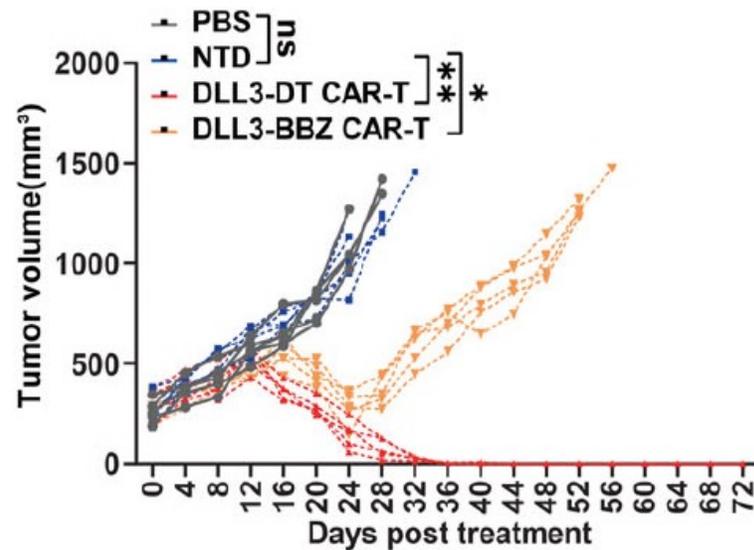
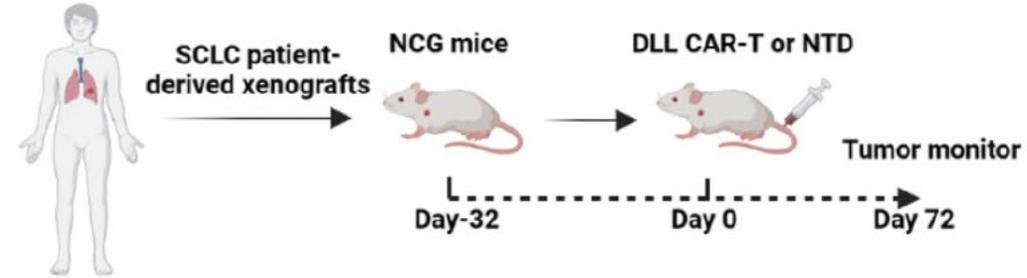


Leidner et al. 2022 NEJM 386:2112-2119

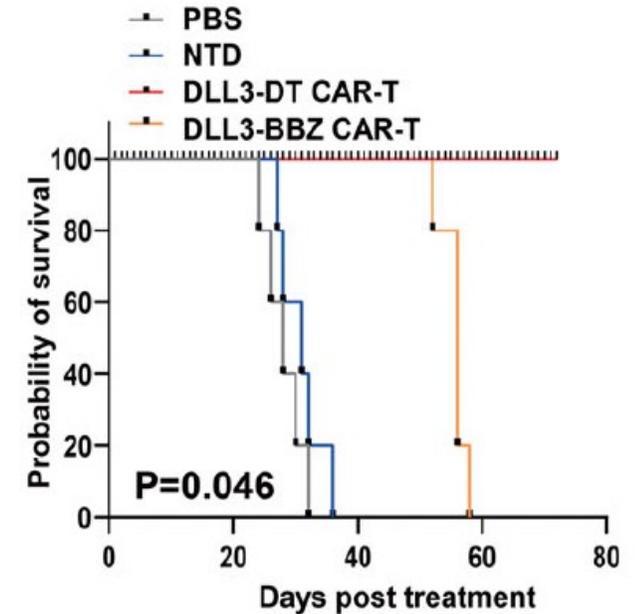
Novel non-linear CAR-T construct with increased pre-clinical efficacy in pdx model of SCLC



(a)

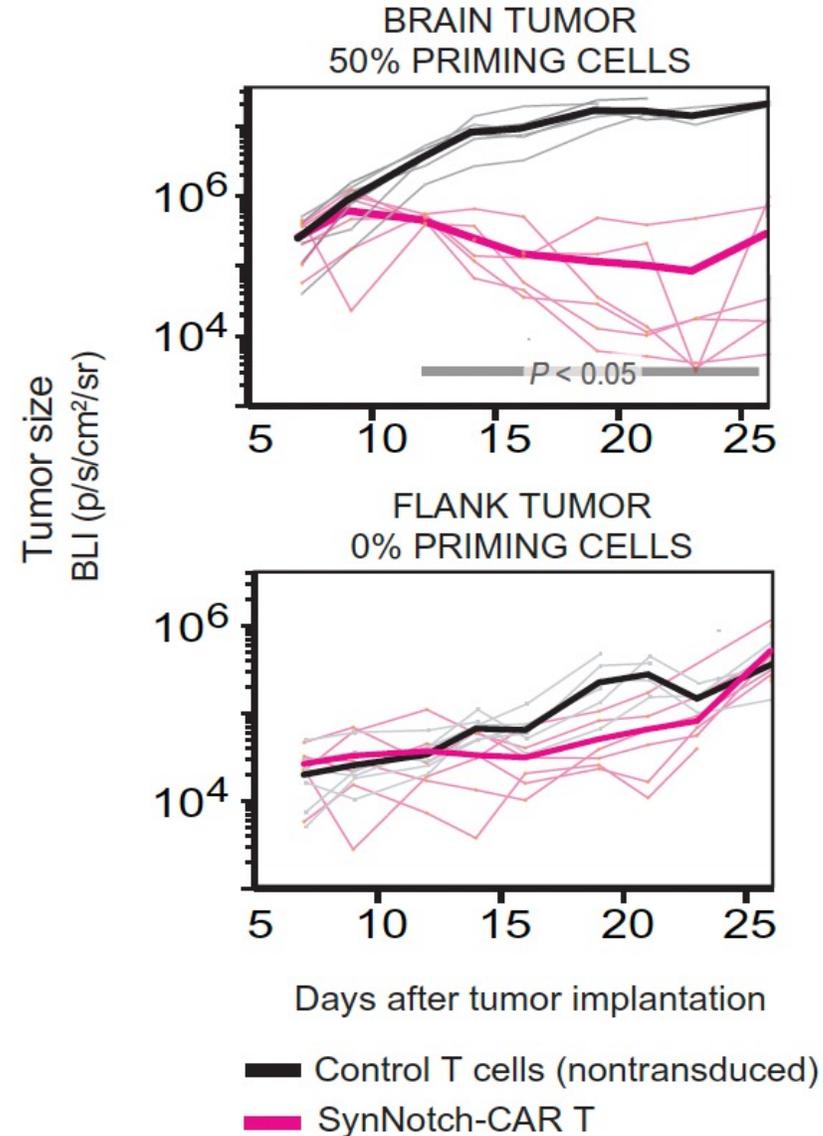
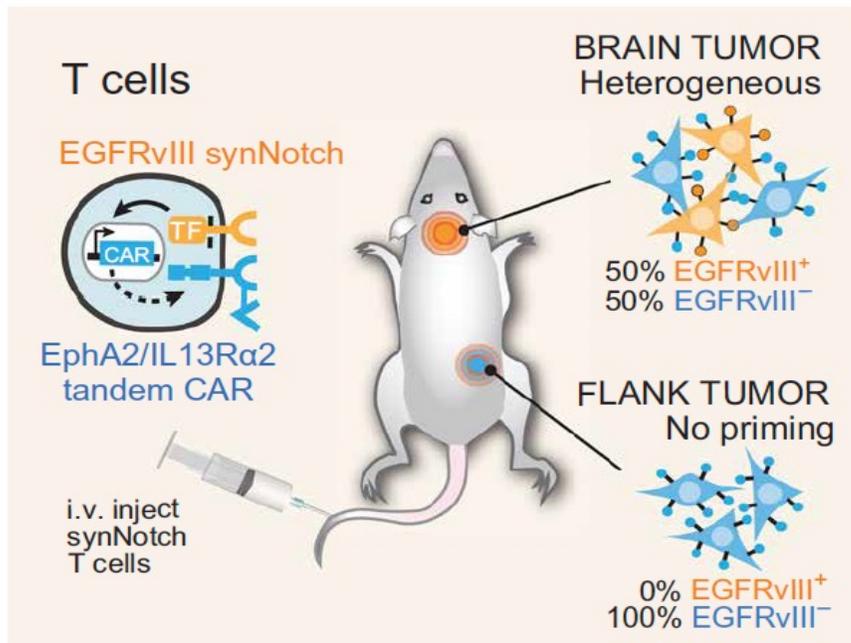
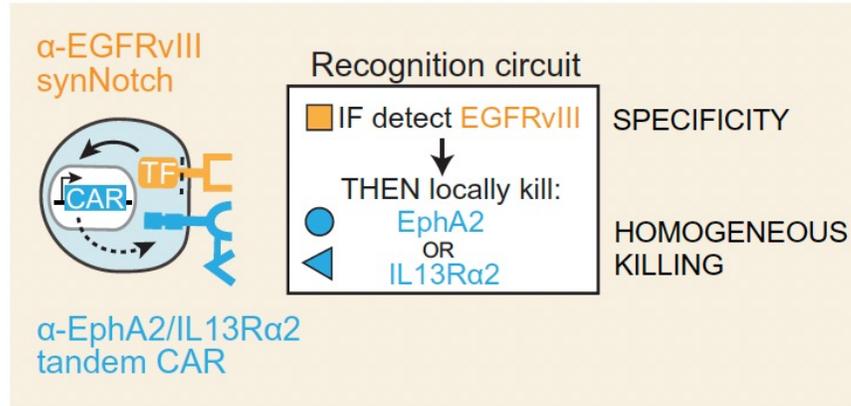


(e)



Nie (2024) TREM1/DAP12 based novel multiple chain CAR-T cells targeting DLL3 show robust anti-tumour efficacy for small cell lung cancer. *Immunology*. 72:362–374.

SynNotch-CAR T cells have tissue-specific inducible specificity useful to treat Glioblastoma



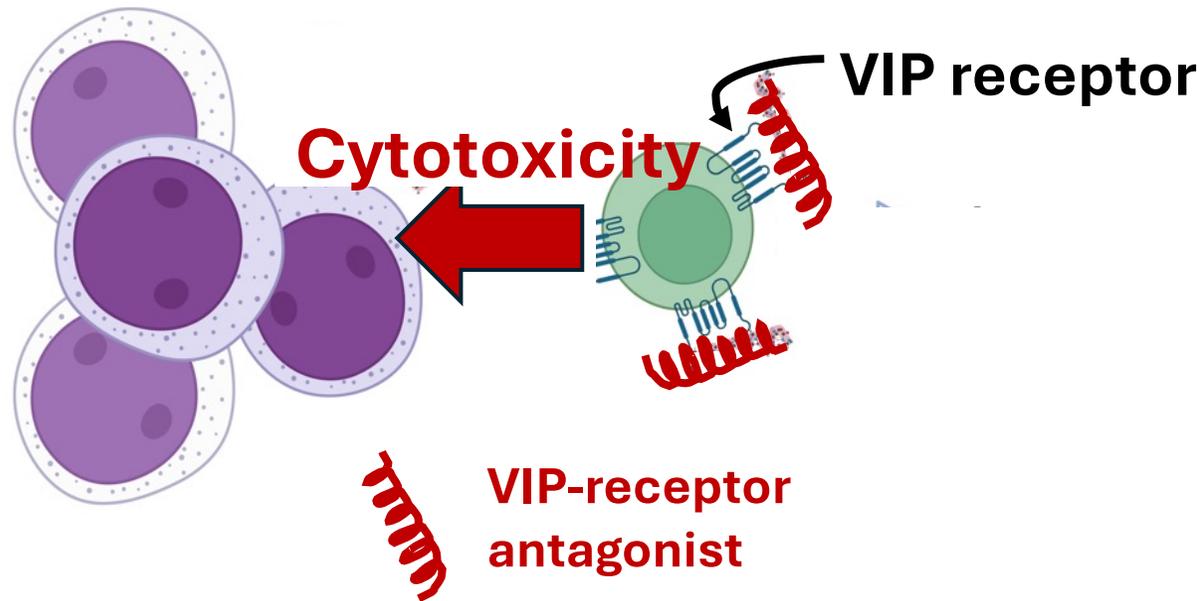
4. Targeting the VIP pathway to enhance anti-cancer immunity

- Vasoactive Intestinal Peptide (VIP) has parasympathetic and immunosuppressive functions
- Synthesized by the enteric neural plexus, activated immune cells, and cancer cells
- Supports the immunosuppressive tumor microenvironment
- Targetable by novel antagonist peptide-based drugs

Why target the VIP immune check-point pathway in CAR T therapy?

Cancer Cells

T cells



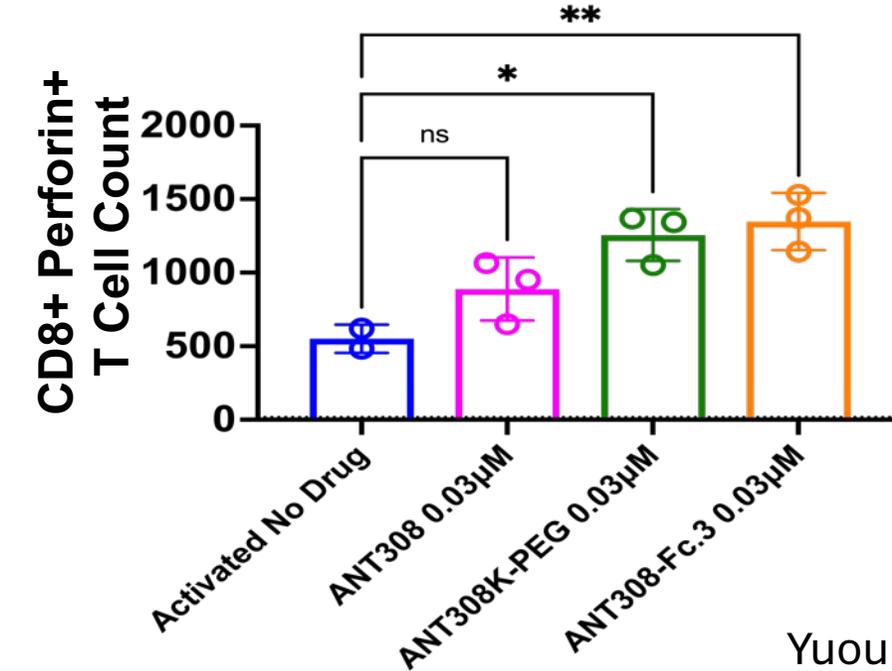
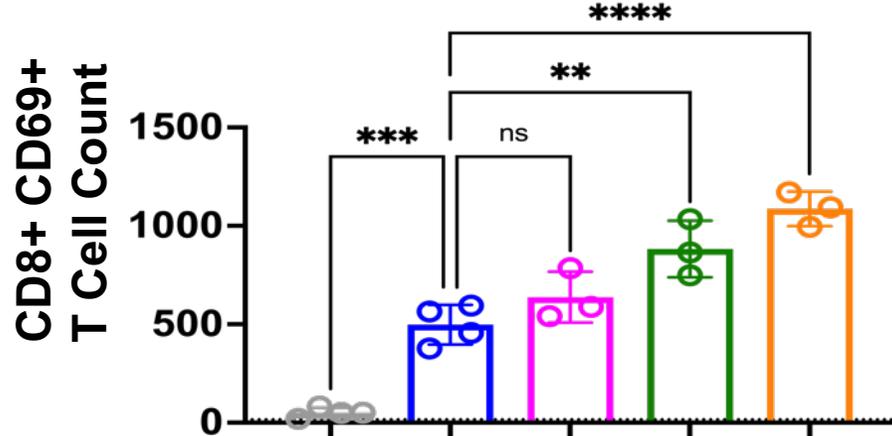
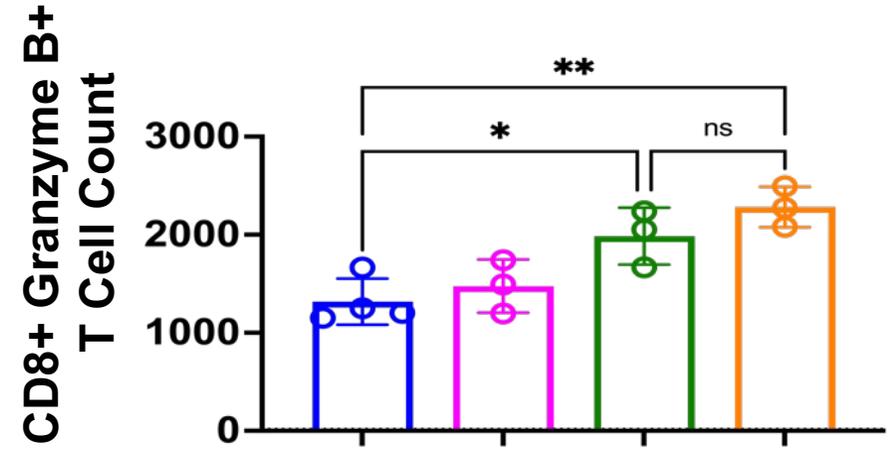
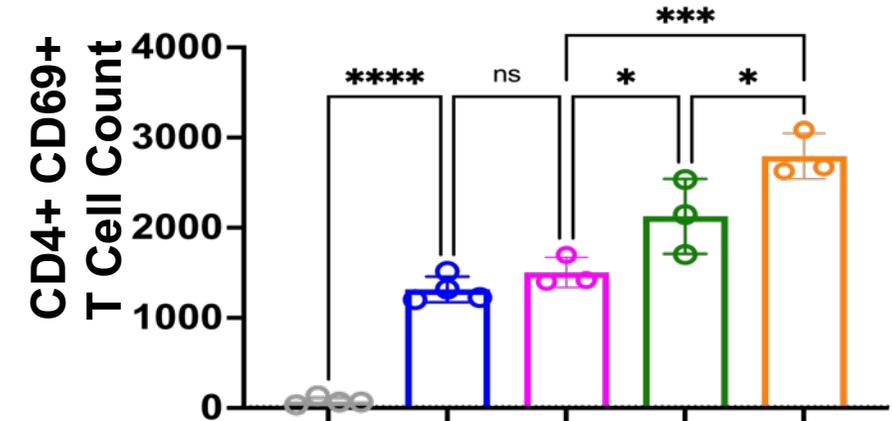
Lin



Rafiq

Lin et al. In prepc

Soluble VIP-receptor antagonist drugs potently expand activated CD4+ and CD8+ human T cells

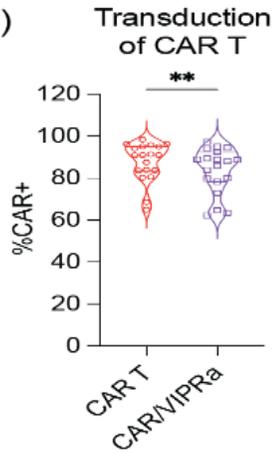


Anti-Muc1 CART that secrete VIP-receptor antagonists have equivalent cytotoxicity to conventional CART

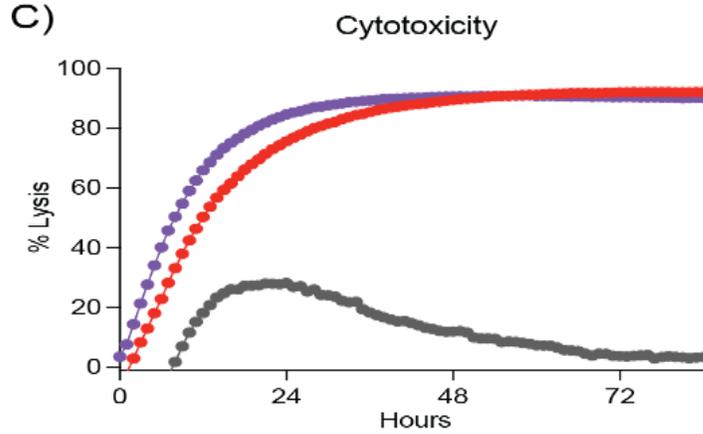
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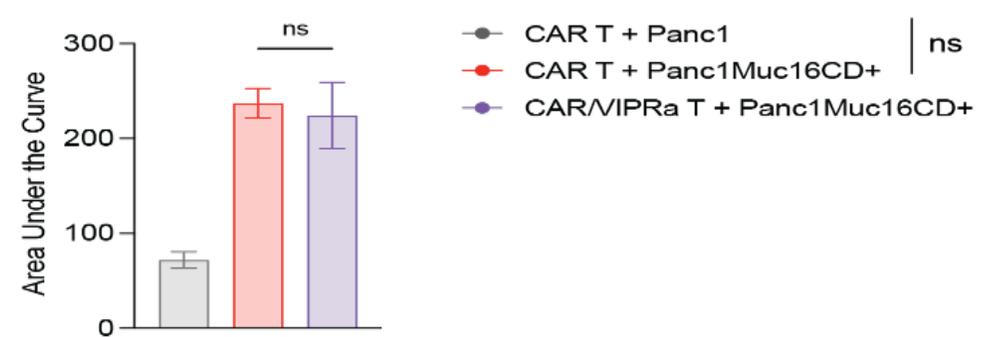
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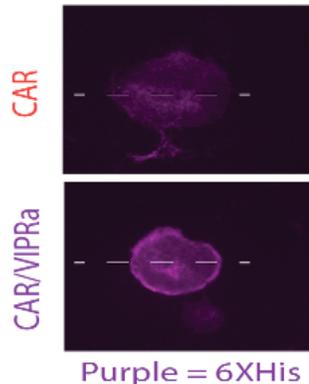
C)



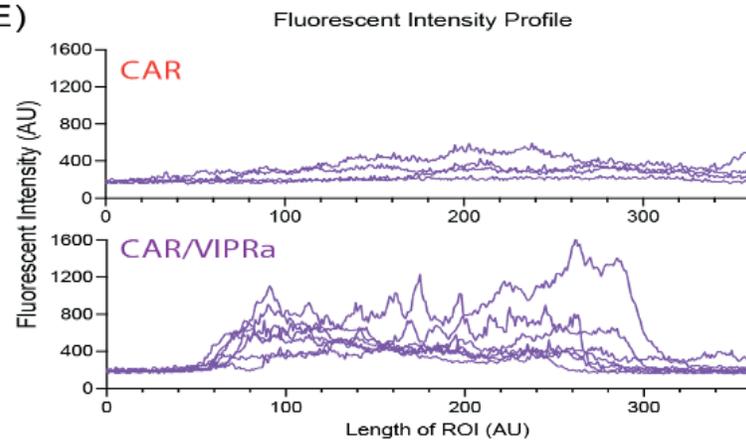
AUC



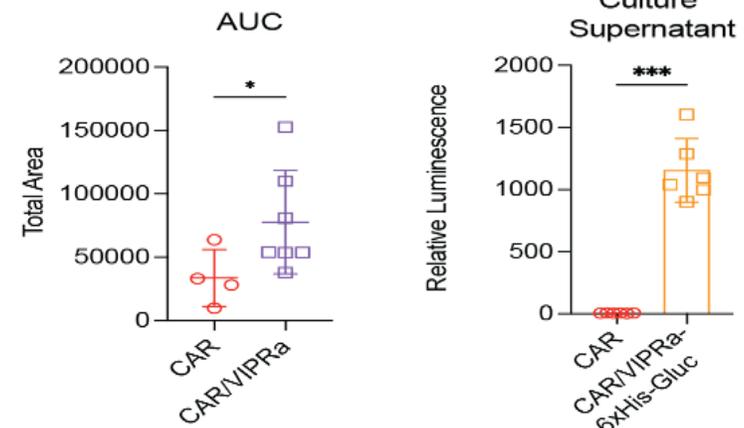
D)



E)

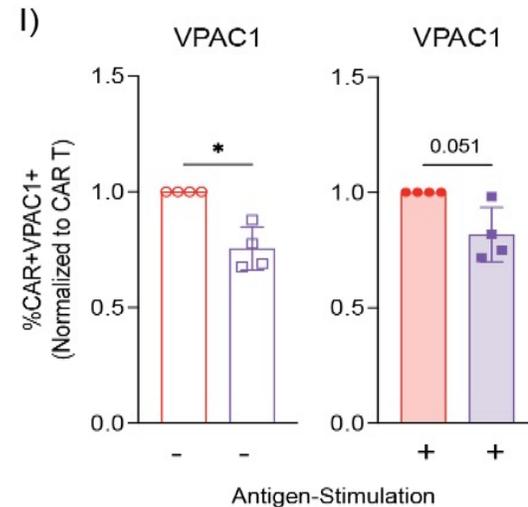
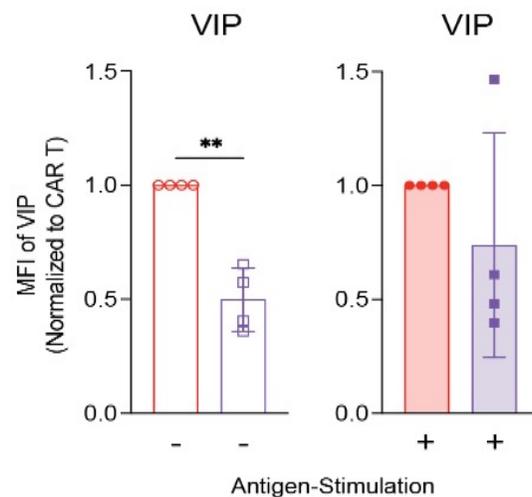
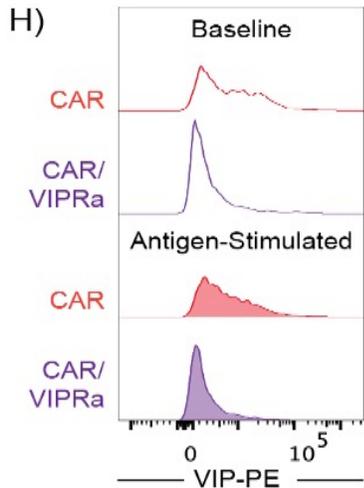
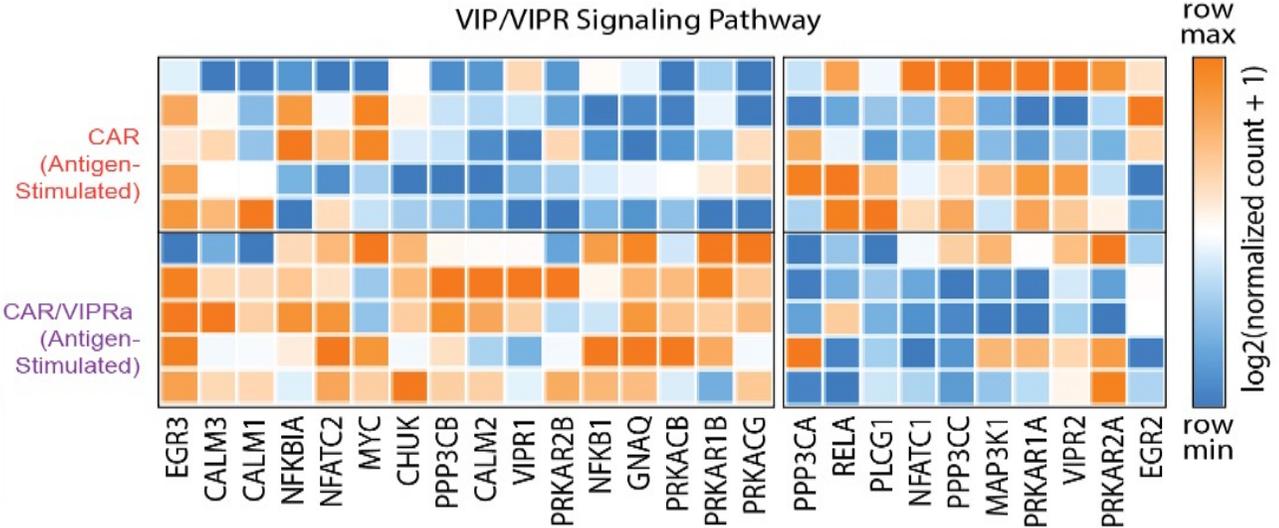
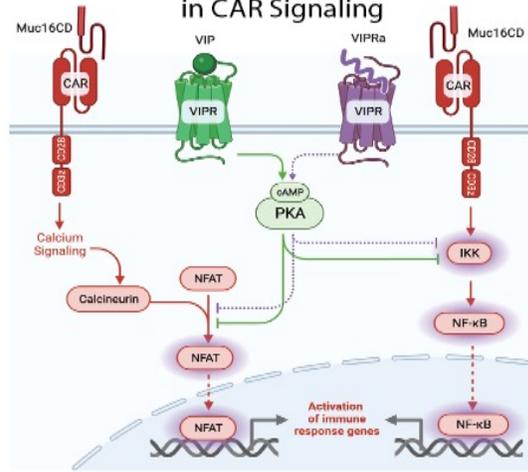


F)

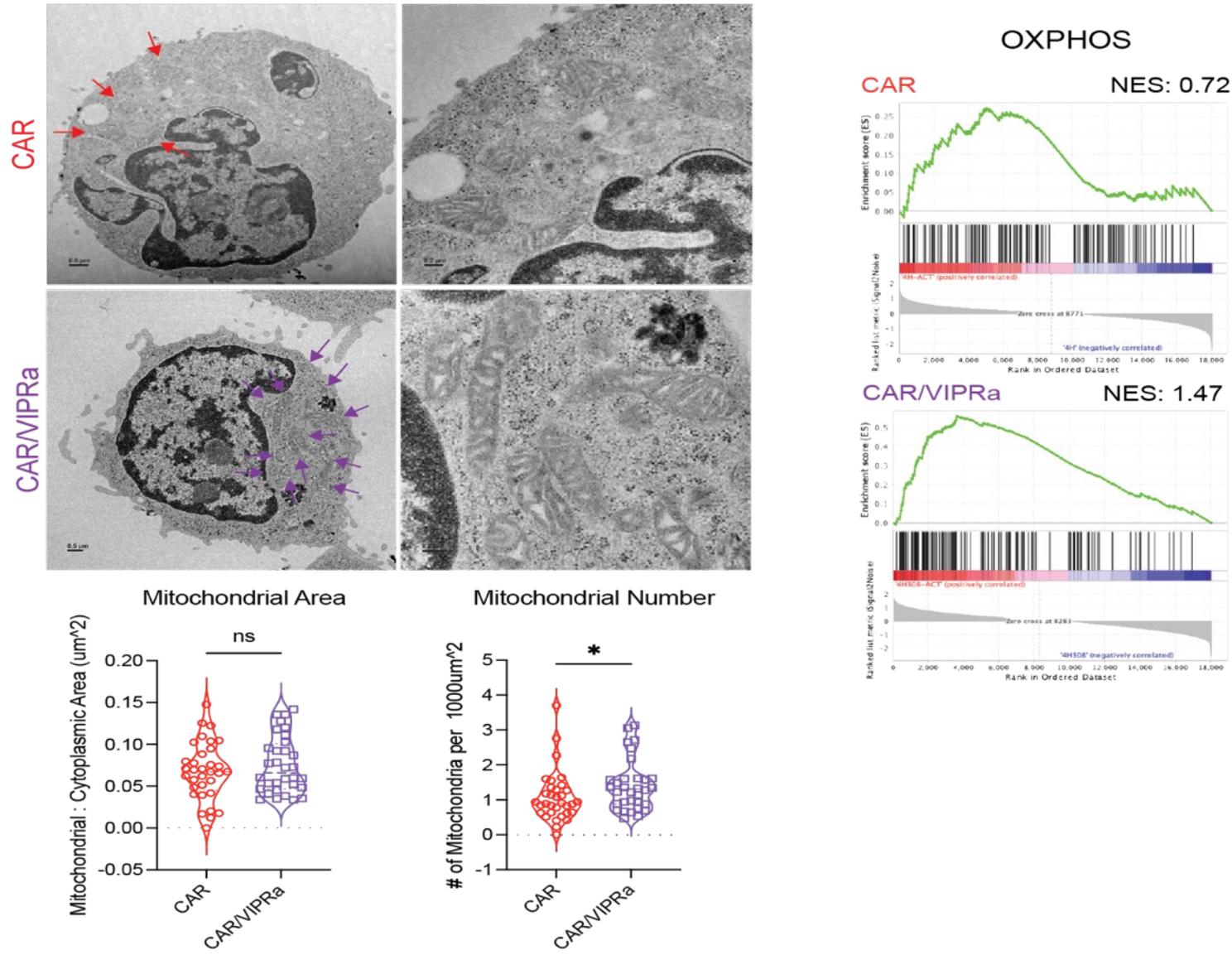


Anti-Muc1 CART that secrete VIP-receptor antagonists have increased activation, decreased VIP signaling

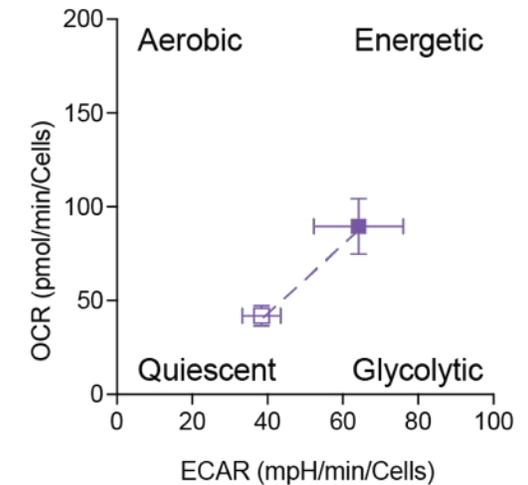
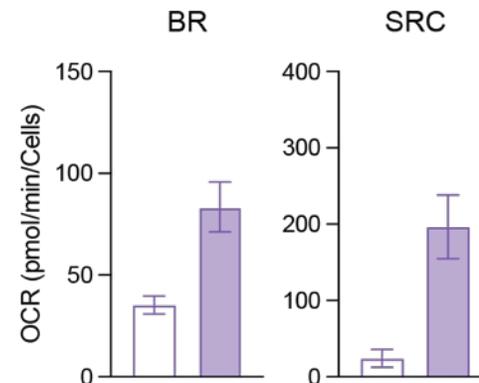
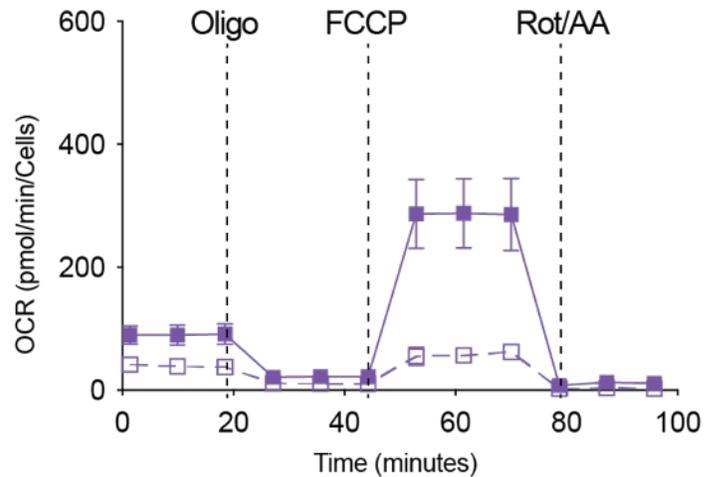
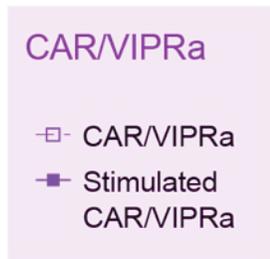
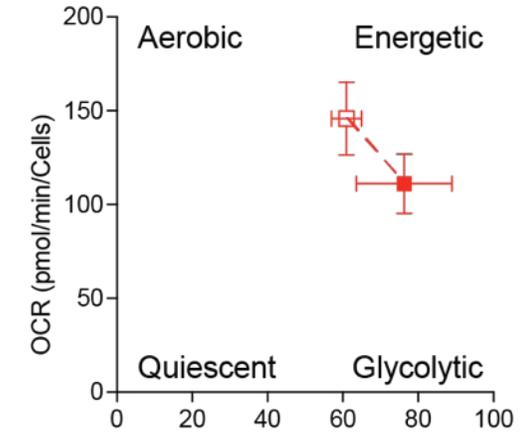
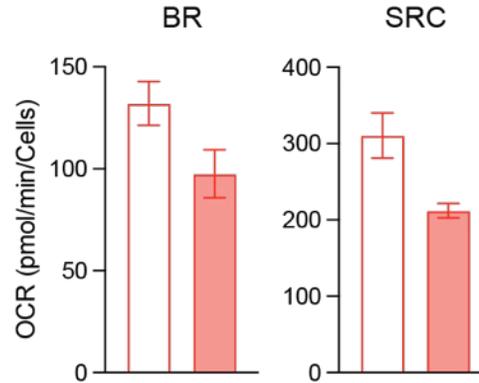
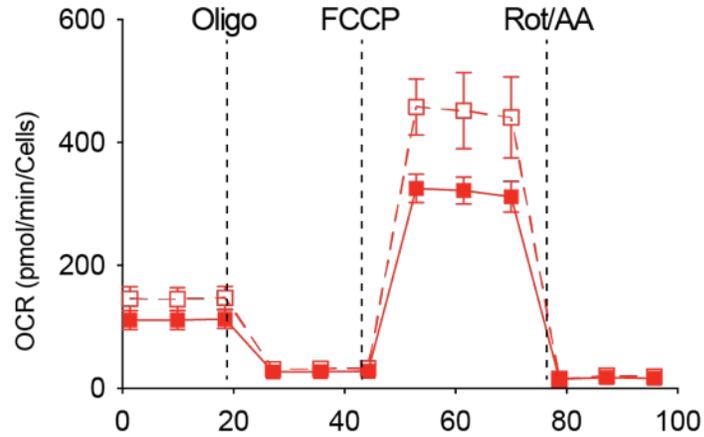
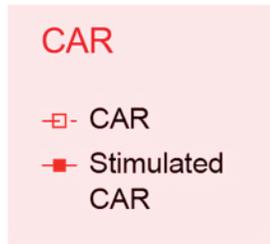
G) Predicted Effects of VIPR Antagonism in CAR Signaling



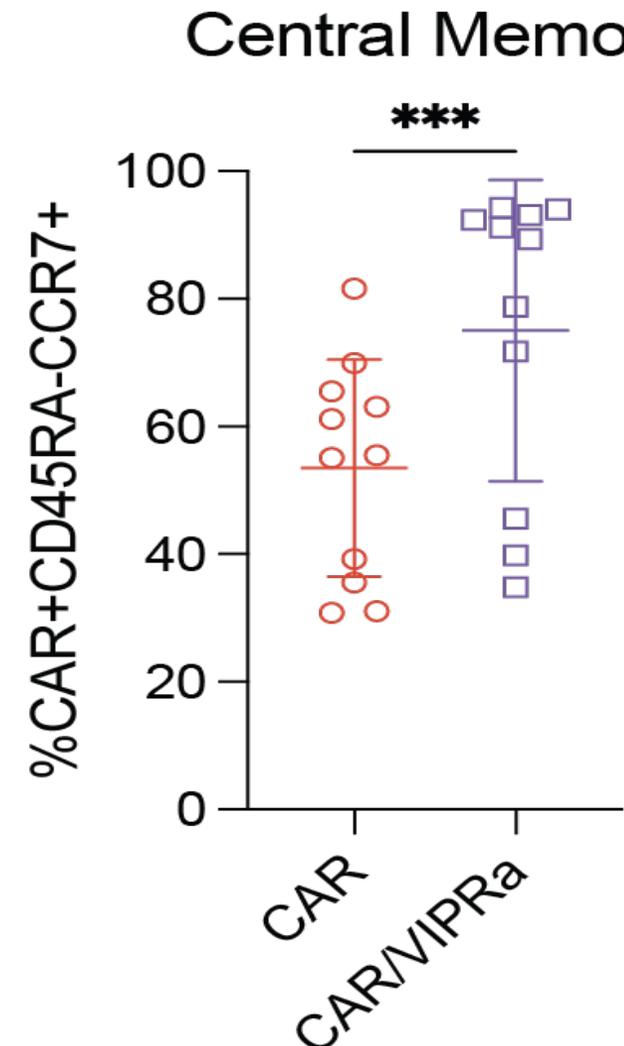
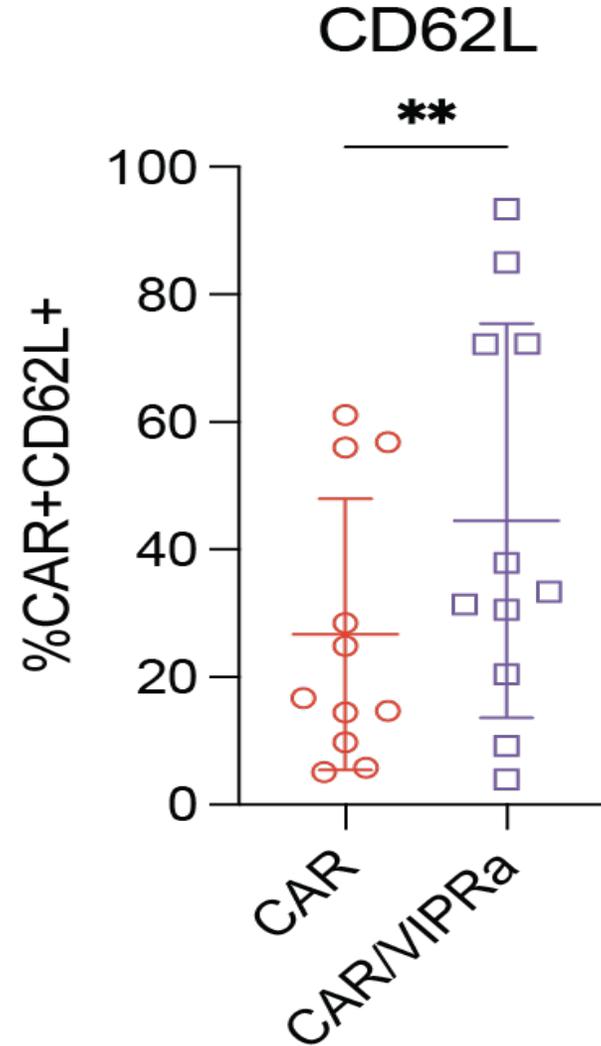
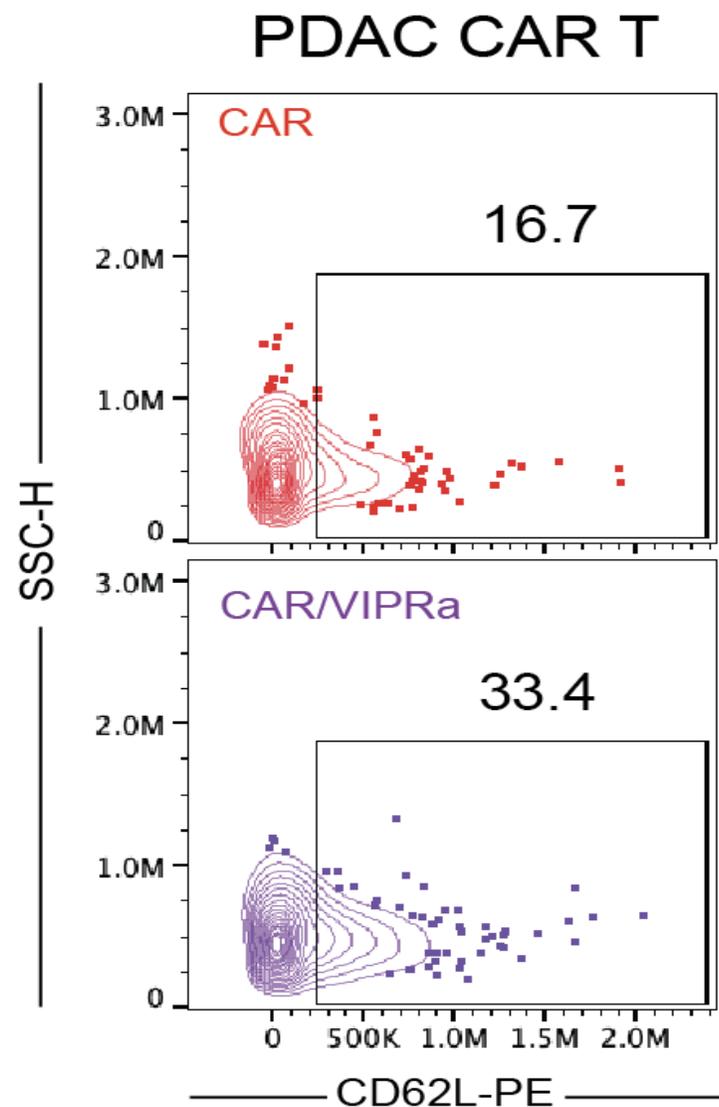
CAR/VIPRa T cells have more mitochondria and utilize oxidative phosphorylation than conventional CART



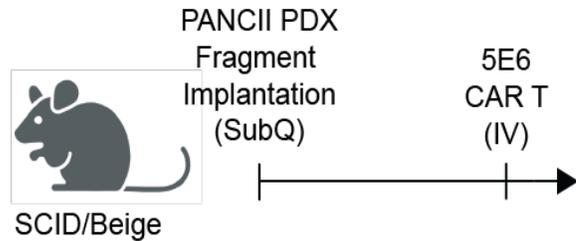
CAR/VIPRa T cells have enhanced metabolic responsiveness



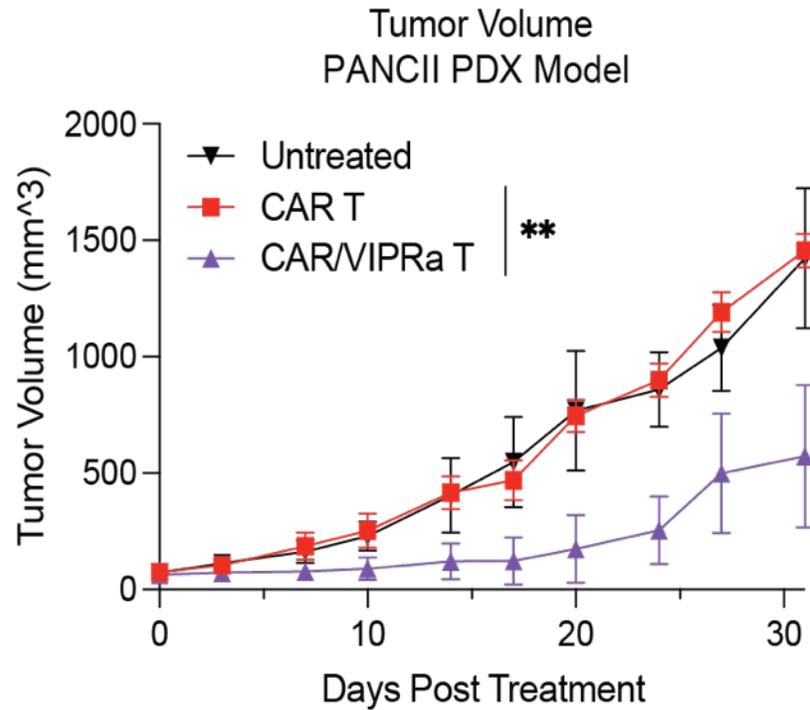
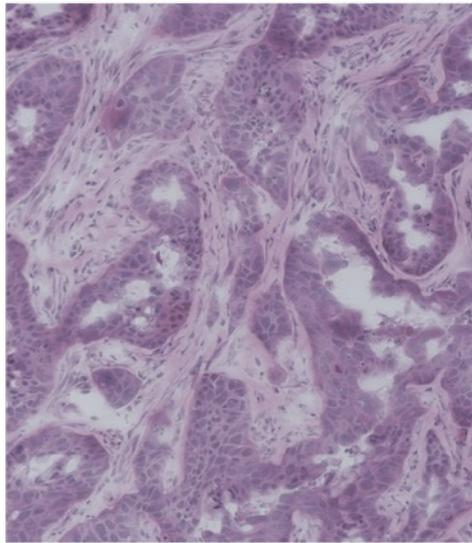
VIPR antagonism increases CAR T cell Tcm phenotype



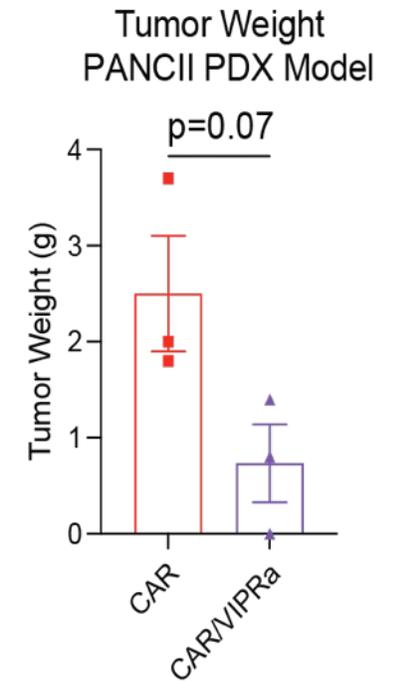
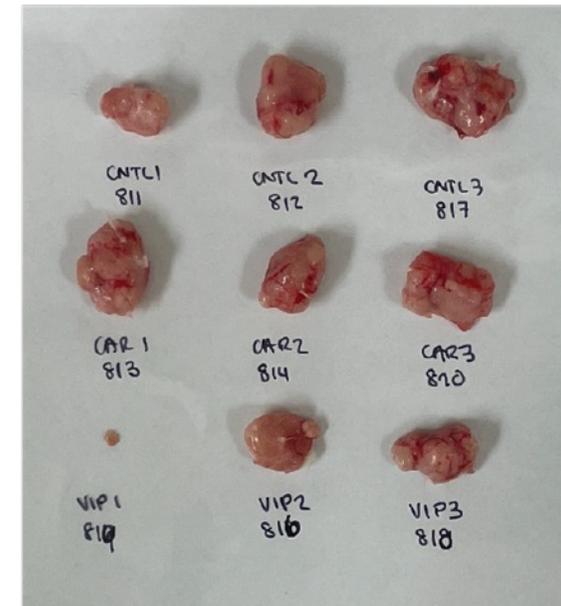
VIPR antagonism enhances anti-tumor efficacy against patient-derived pancreatic cancer xenografts



PANCII PDX

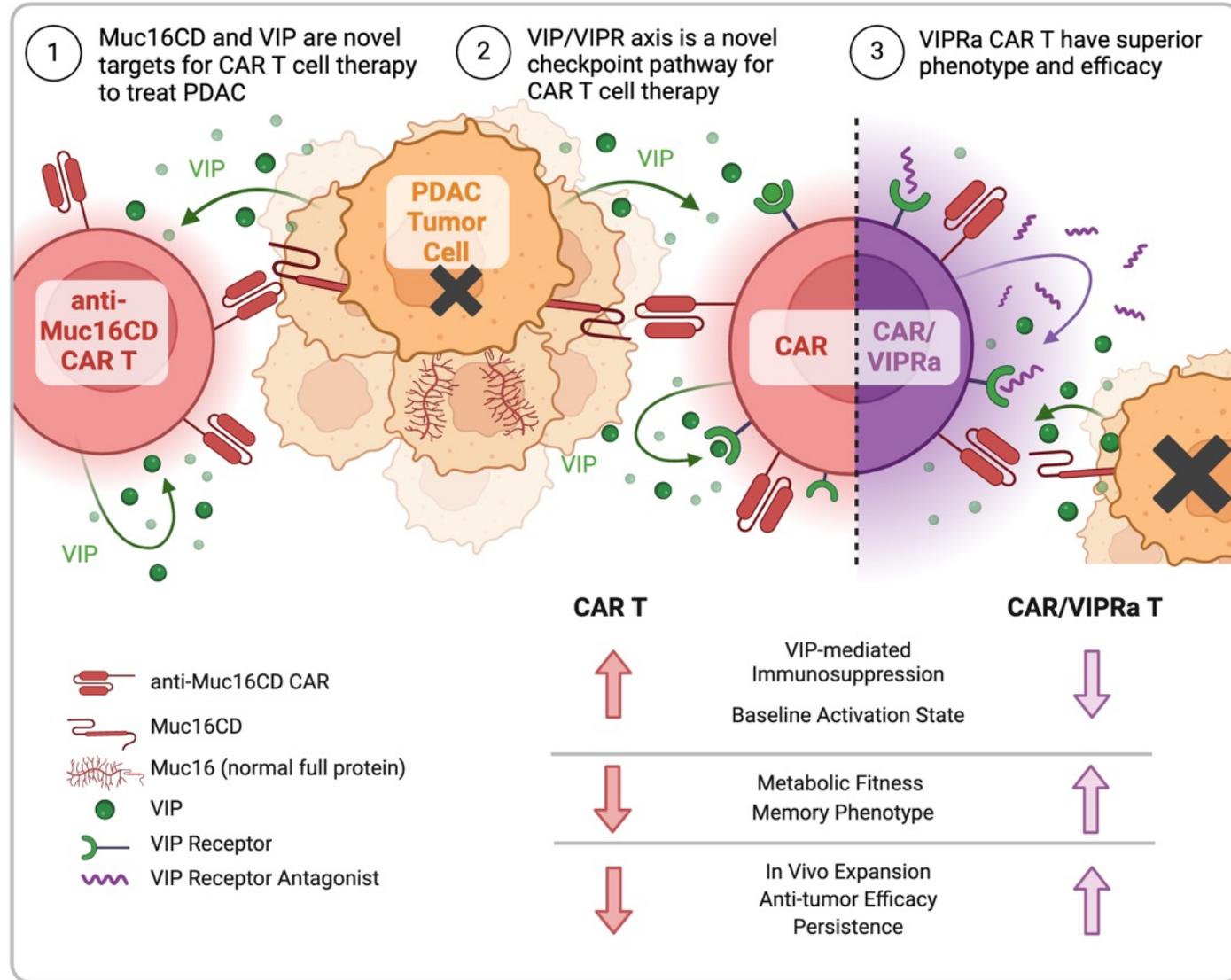


Tumor Weight - Day 36



Dr. Lily Yang and Tongrui Liu)

Model for the therapeutic advantage of ANT308-producing CART

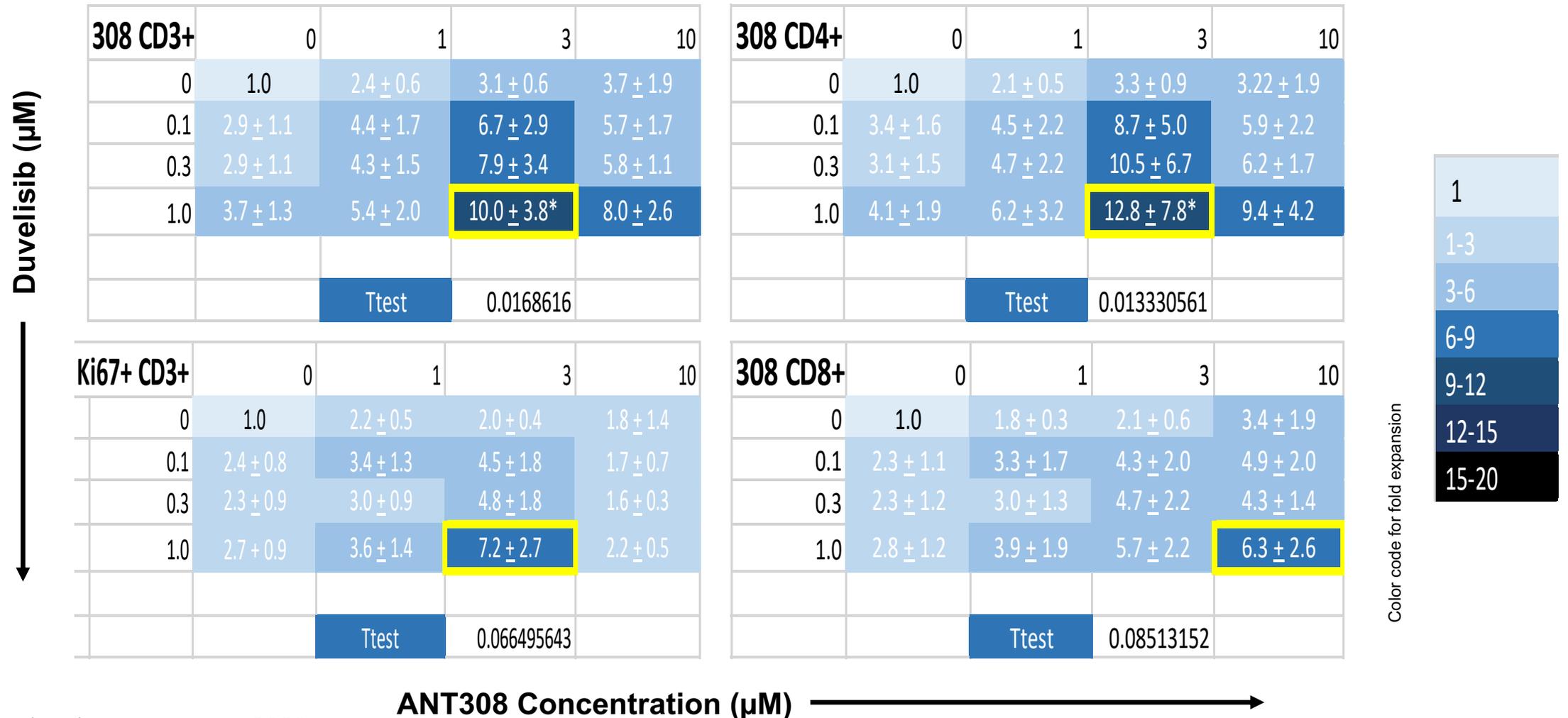


Lin

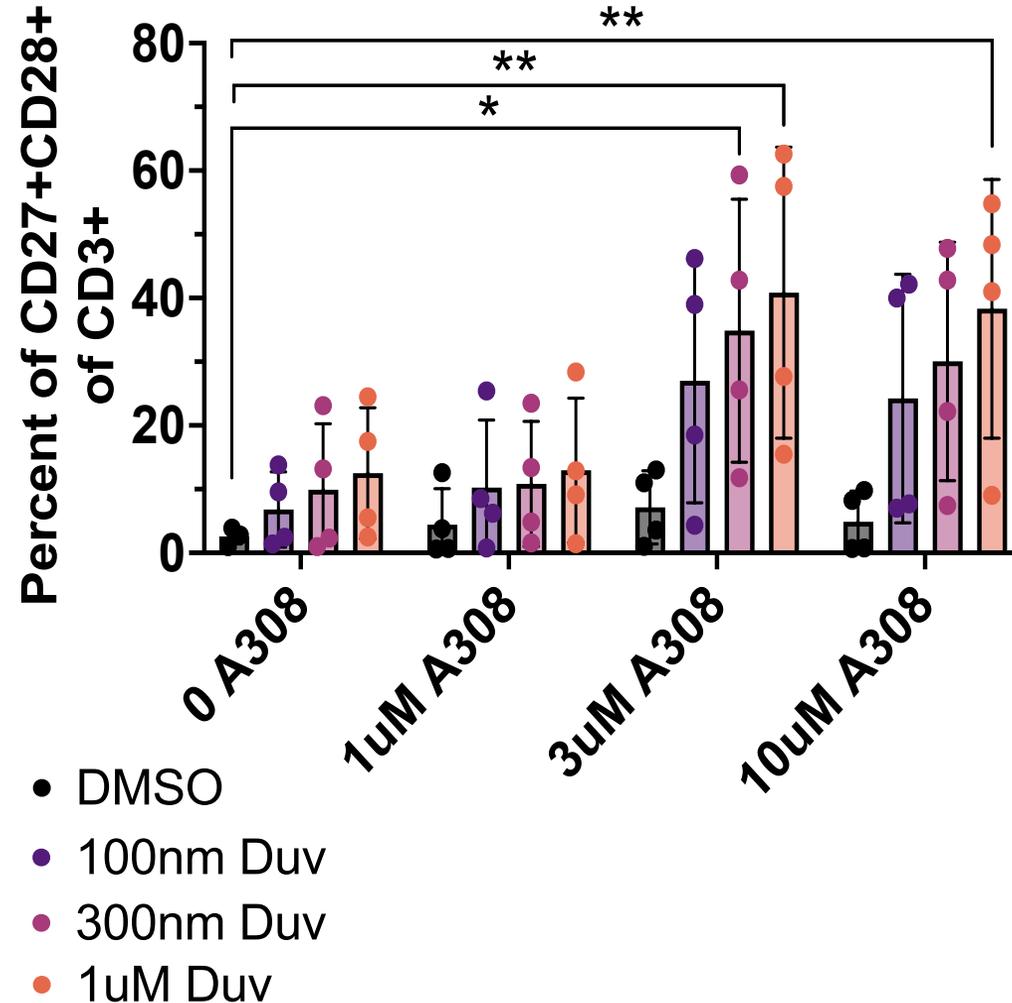
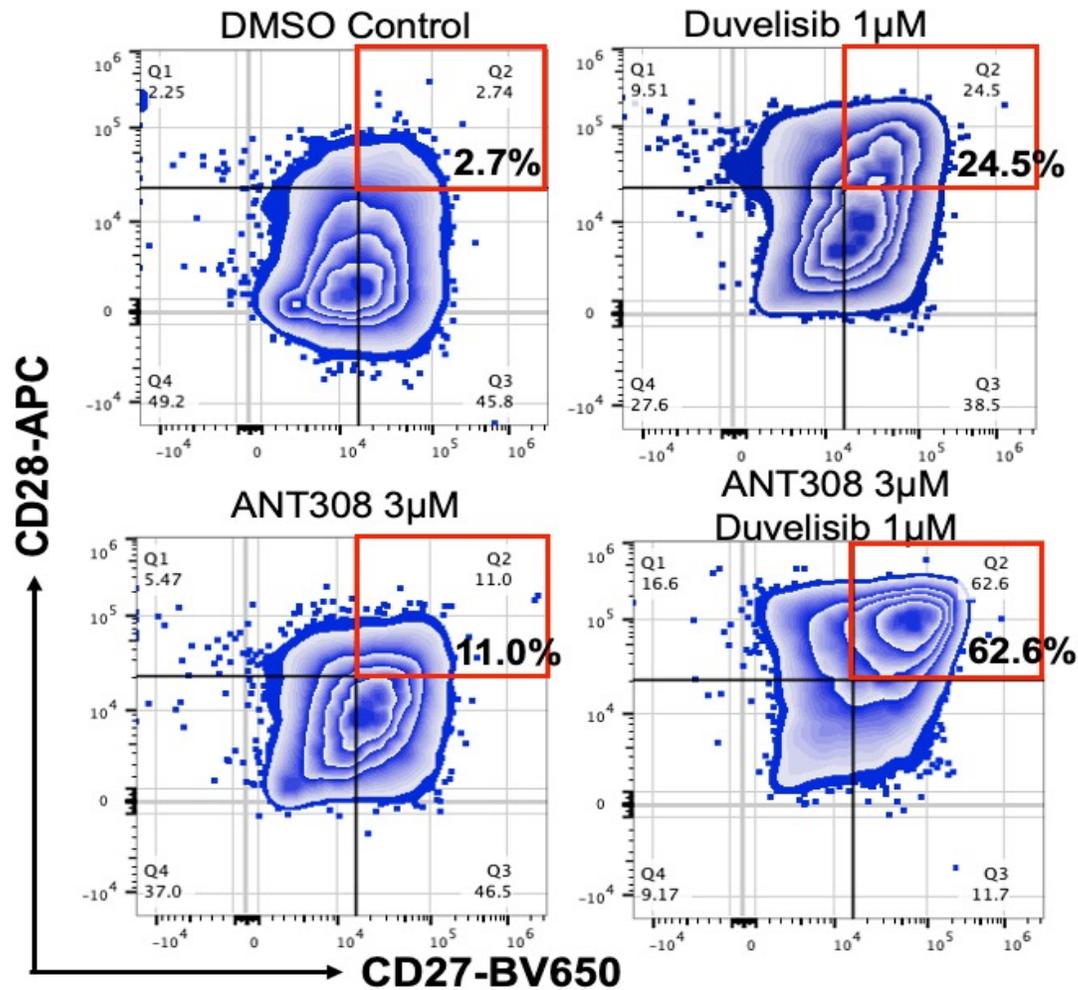


Rafiq

5. Combining VIP receptor antagonists and Pi3K inhibitors for expansion of T Cells



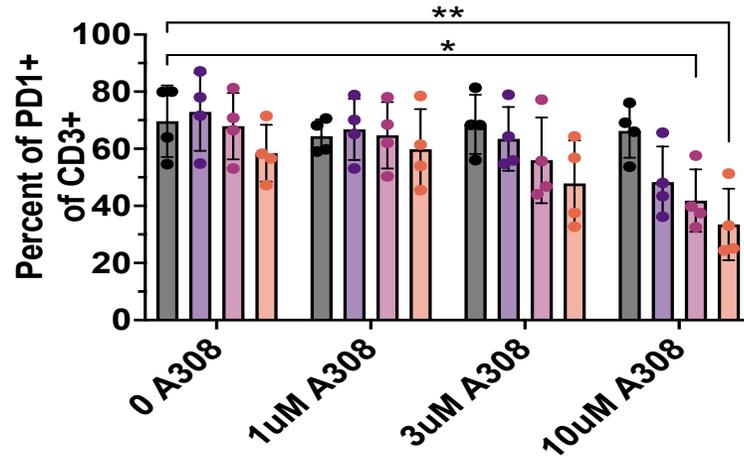
The combination of VIP-R antagonist and Pi3Ki expand Tcm CD27+ CD28+ human T cells



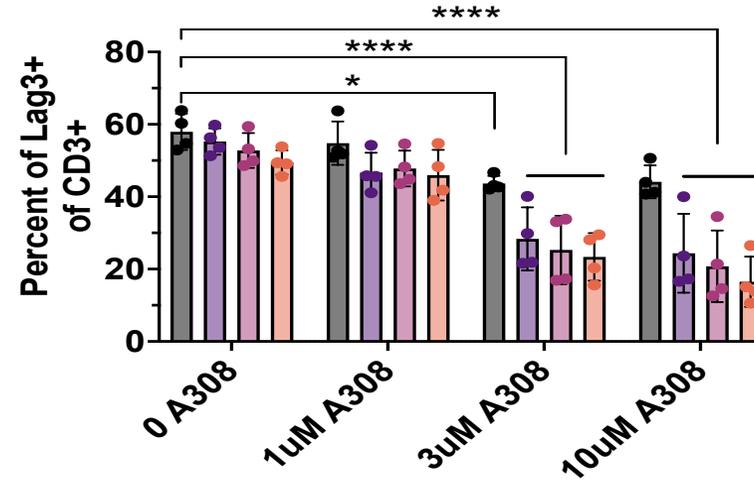
- DMSO
- 100nm Duv
- 300nm Duv
- 1uM Duv

Combining VIP-R antagonist and Pi3Ki down-regulate expression of check-points on human T cells

PD1+



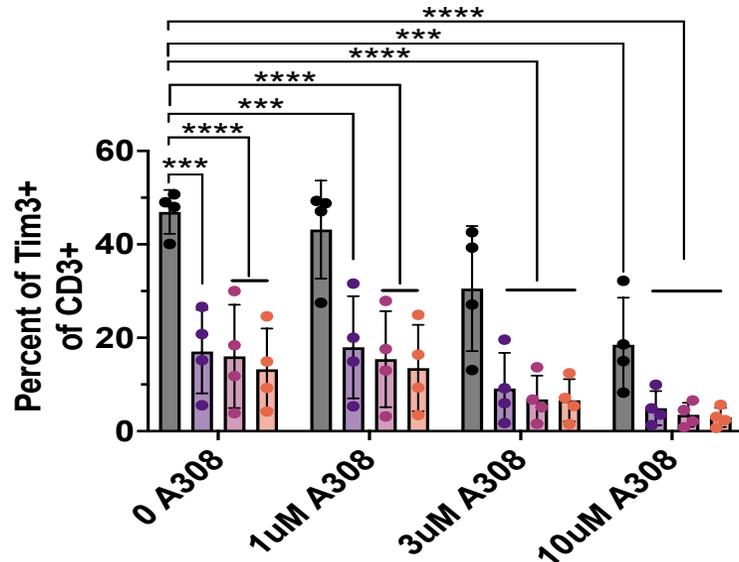
Percent of Lag3+
of CD3+



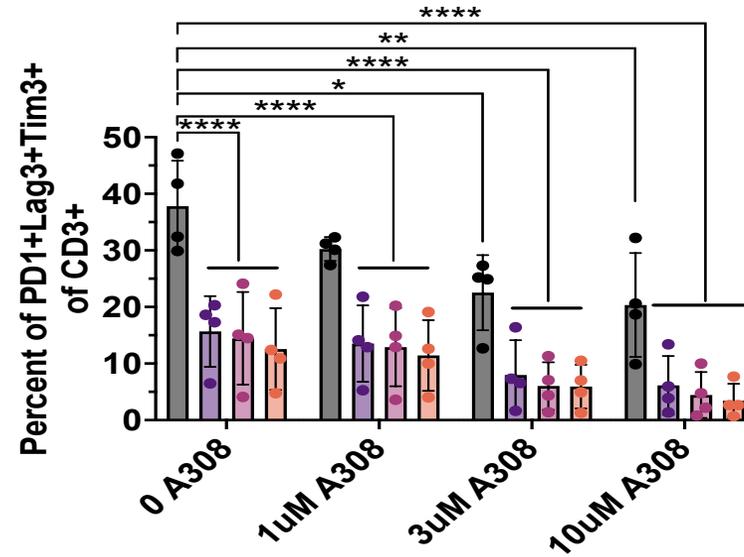
LAG3+

- DMSO
- 100nm Duv
- 300nm Duv
- 1uM Duv

TIM3+

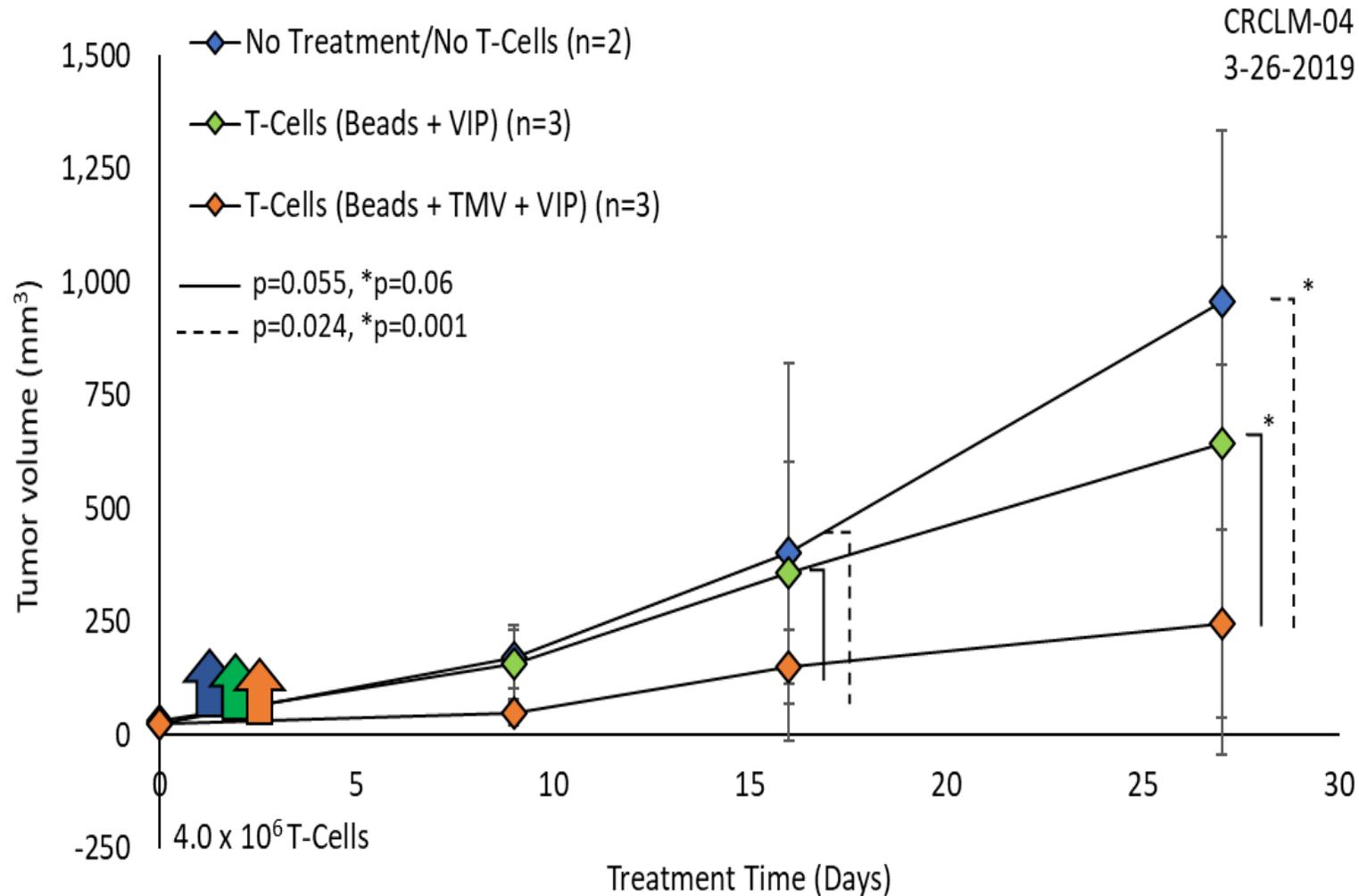


Percent of PD1+Lag3+Tim3+
of CD3+



PD1+
LAG3+
TIM3+

Human T cells expanded with tumor antigen VIP-R antagonists and PI3Ki control colon cancer in Pdx model



6. CD26^{hi} PI3-kinase inhibited CD4⁺ CART for pancreatic cancer

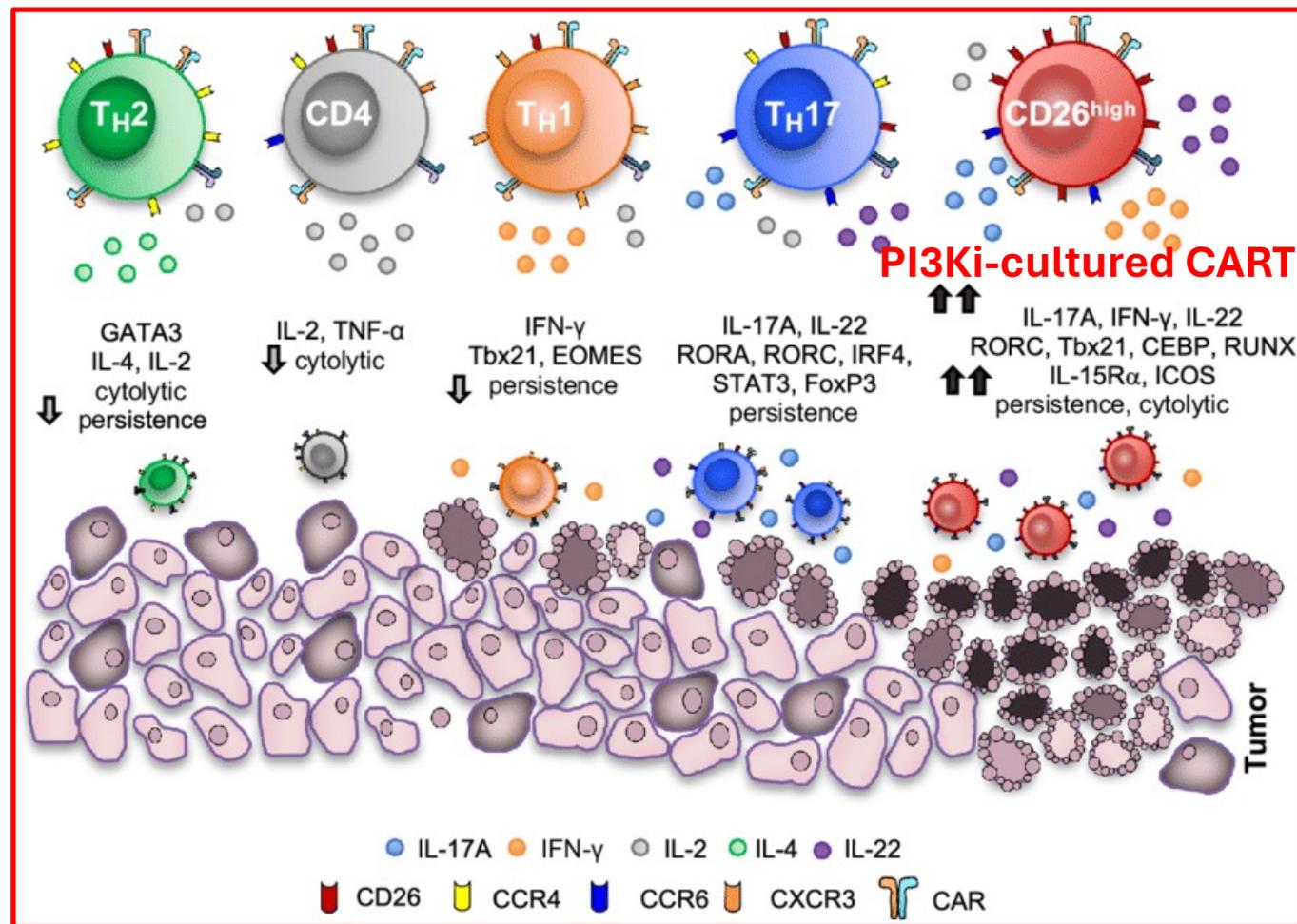
Chrystal Paulos



Olatunji Alese



Greg Lesinski



Ned Waller



Yuan Liu

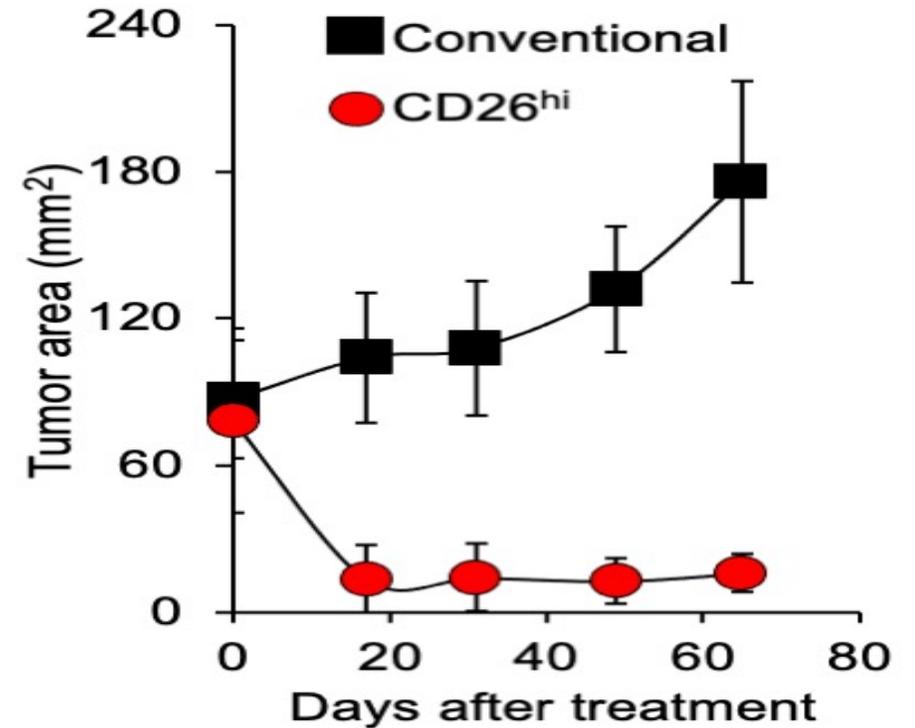
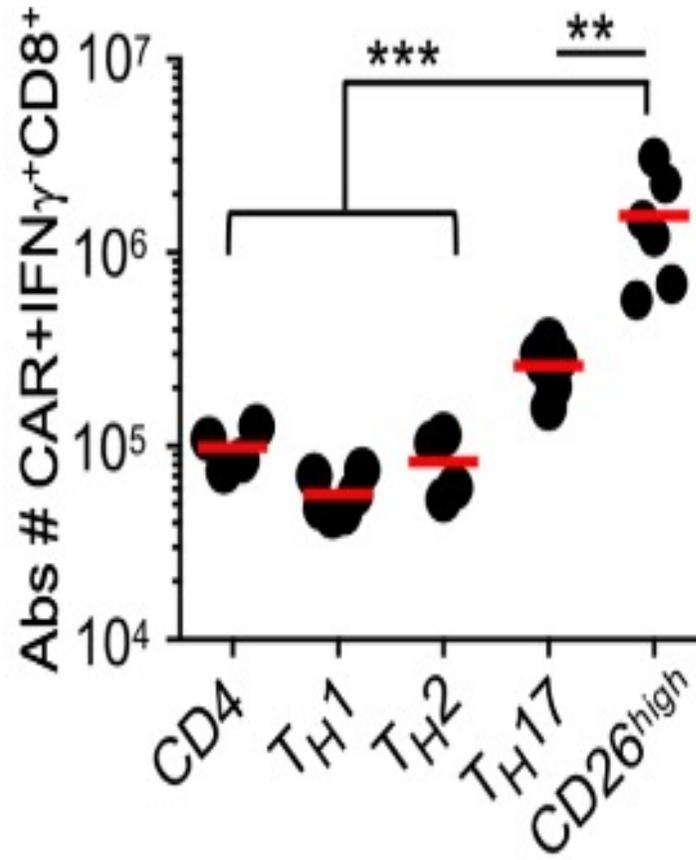
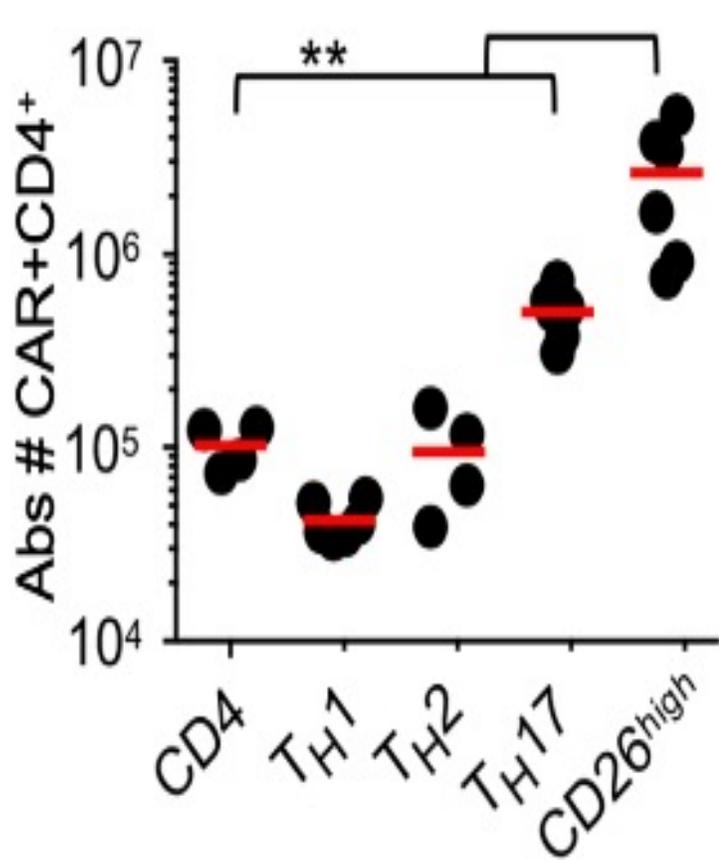


Carl June

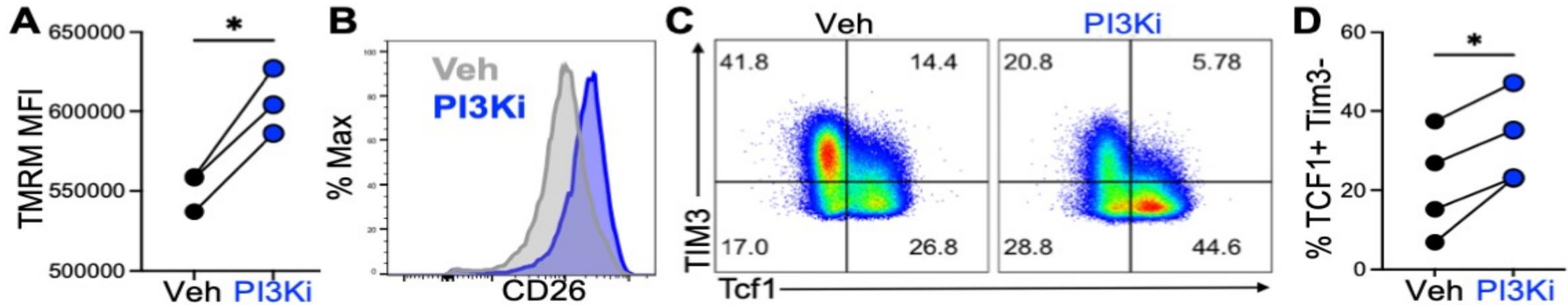


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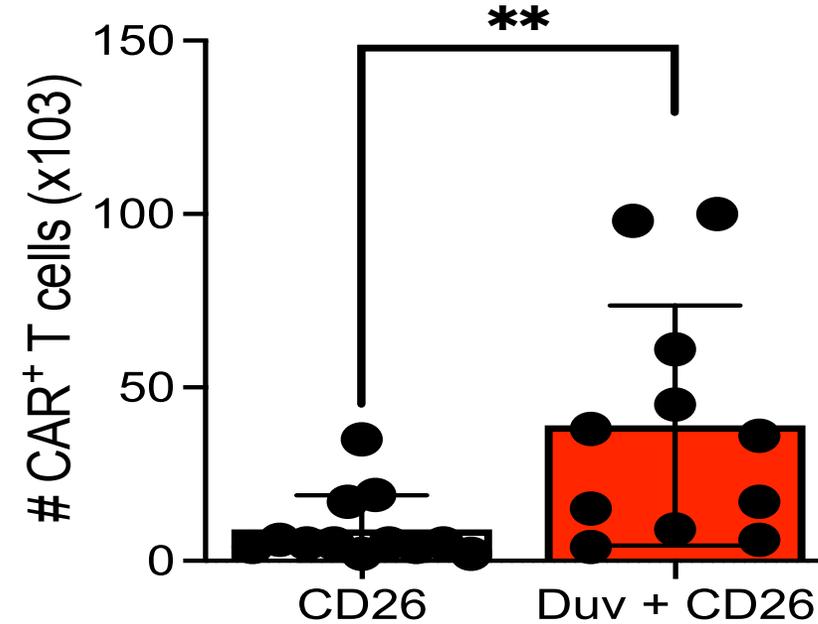
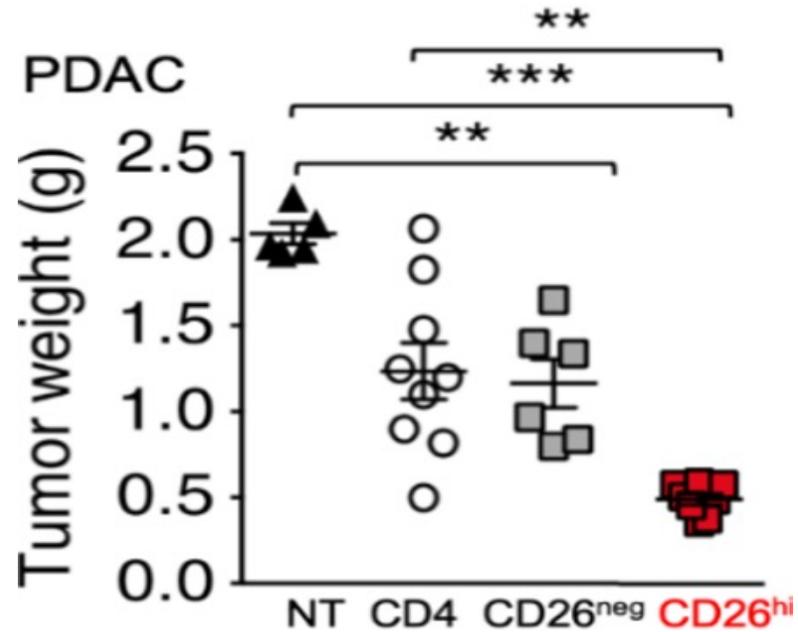
Greater expansion and anti-tumor activity when CART are manufactured from CD26^{hi} Meso-41BB-CD4⁺ CAR T cells



Duvelisib augments bioenergetics, CD26 expression, and stem-like phenotype of CD26+CD4+ Meso-CAR-BBz CART



Murine meso-CAR CD26+ T cells limit KPC orthotopic PDAC growth in vivo and increase T cell infiltration into the tumor.



Paulos, unpublished

R01 Aim 3: Phase 1 trial of meso-CAR CD26+ T cells in Pancreatic Cancer Patients

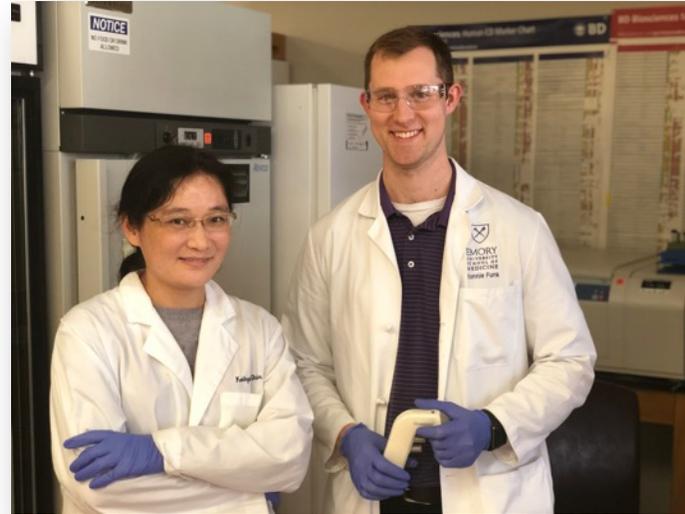
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**Heather
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**Sarwish
Rafiq**





ewaller@emory.edu

Toxicity of CART

