MD Anderson Cancer Center

Allogeneic CAR T cell expansion and rejection

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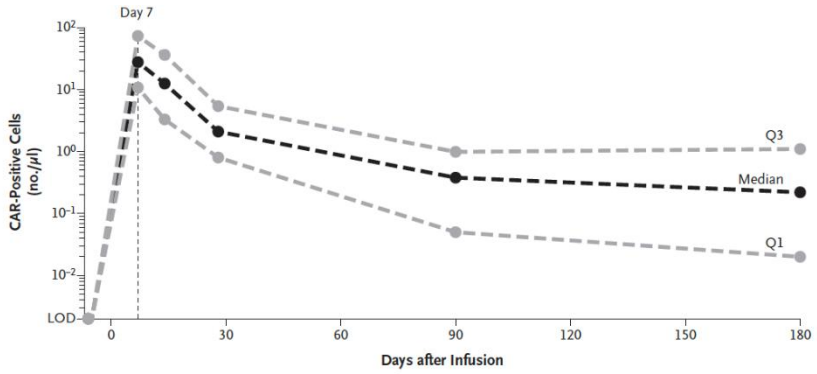
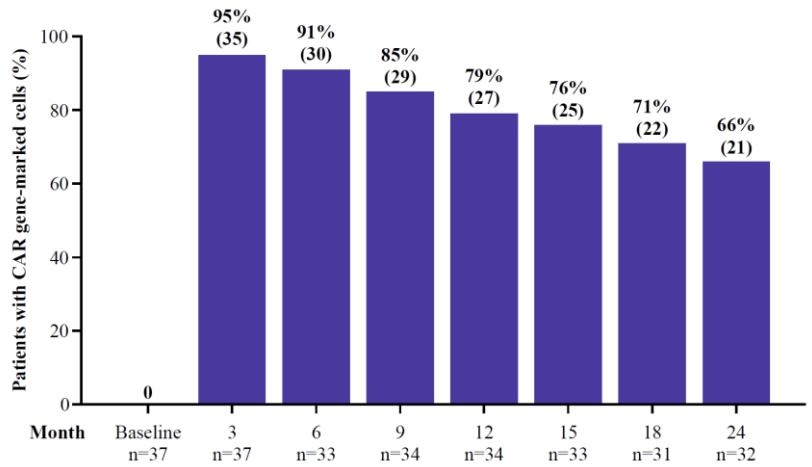
Disclosures

Disclosure	Company name
Research Support	Kite/Gilead, BMS, Allogene, Precision Biosciences, Adicet Bio, Sana Biotechnology, Cargo Therapeutics
Advisory Board / Consultant	Kite/Gilead, Sellas Life Sciences, Athenex, Allogene, Incyte, Adicet Bio, BMS, Bluebird Bio, Fosun Kite, Sana Biotechnology, Caribou, Astellas Pharma, Morphosys, Janssen, Chimagen, ImmunoACT, Orna Therapeutics, Takeda, Synthekine, Carsgen, Appia Bio, GlaxoSmithKline, Galapagos
Honoraria	MJH Life Sciences, PeerView, MD Education
Speaker's Bureau	None
Employment	None
Royalties	None
Stocks / Stock Options	Longbow Immunotherapy
Patents	Related to cell therapy

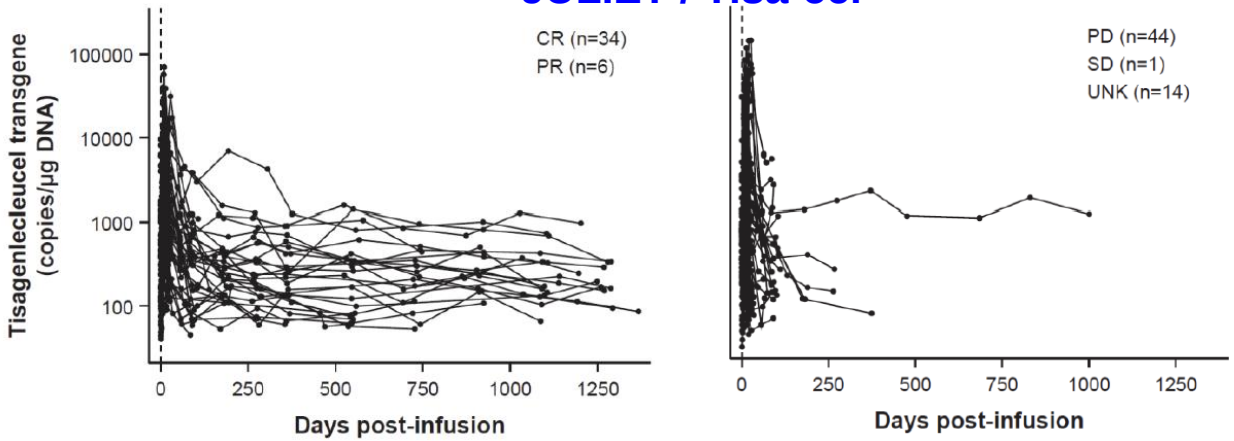
CAR T cell expansion and persistence after autologous CD19 CART

ZUMA-1 / Axi-cel

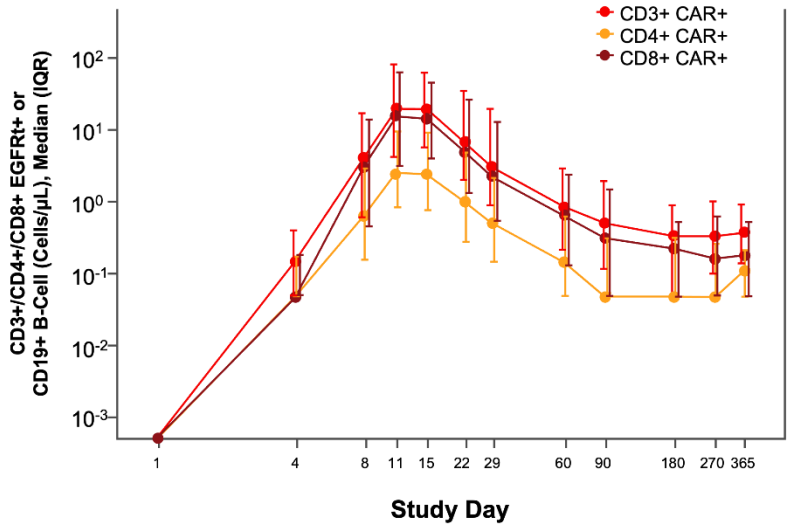




JULIET / Tisa-cel

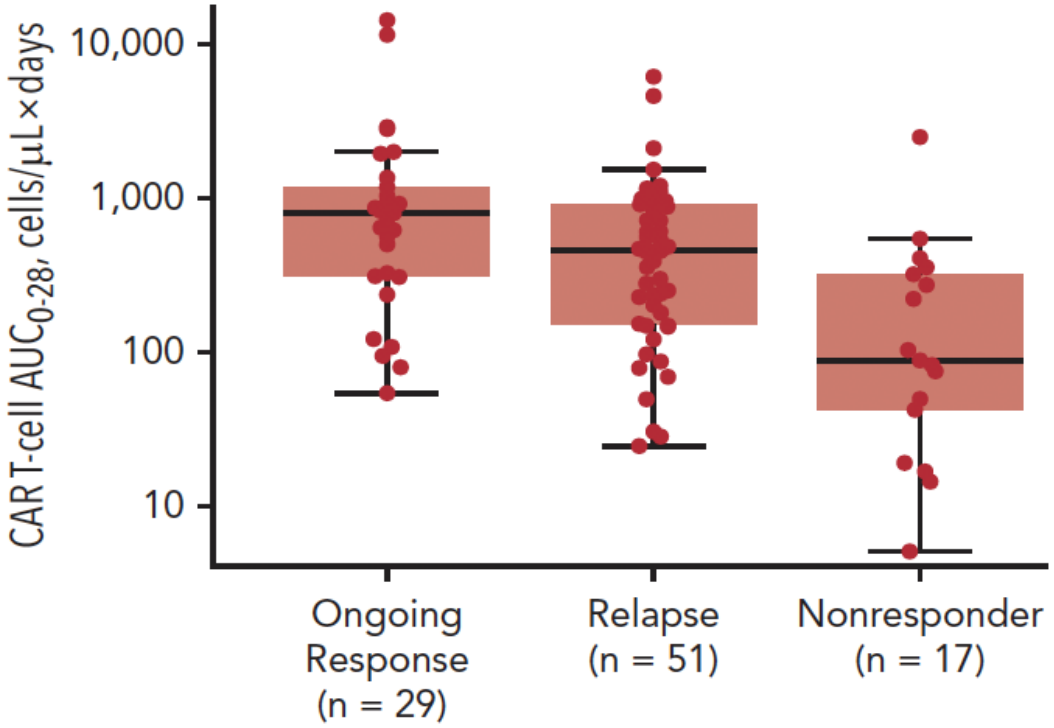


TRANSCEND / Liso-cel



Neelapu et al. *N Eng J Med*, 2017
Locke et al, *Lancet* Oncol, 2019
Schuster et al, Lancet Oncol, 2021
Abramson et al, ASH 2019, Abstract 241

ZUMA-1: CAR $AUC_{0\text{-}28}$ days associates with ongoing response at 5 years



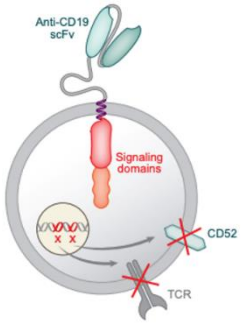
	Ongoing Response (n = 29)	Relapse (n = 51)	Nonresponder (n = 17)
Median $AUC_{0\text{-}28}$, cells/µL×days	799.69	455.32	88.47

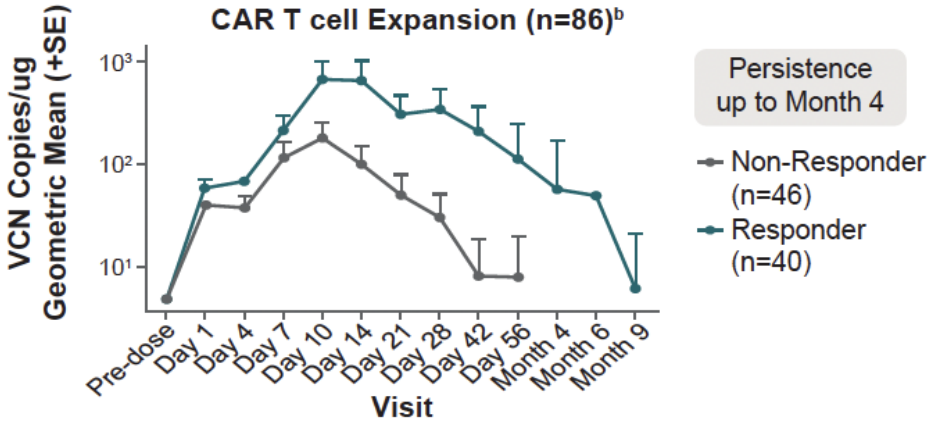
Neelapu et al, *Blood* 2023 May 11;141(19):2307-2315

CAR T cell expansion and persistence after allogeneic CART

(With intensified lymphodepletion)

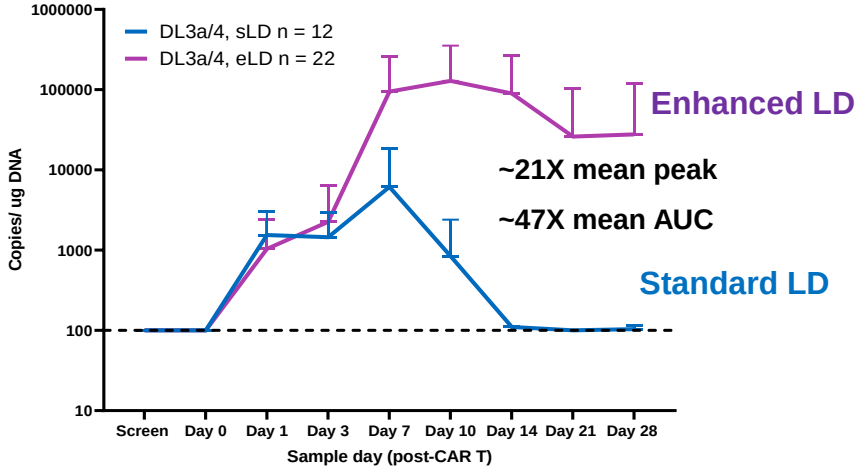
ALPHA / Cema-cel (ALLO-501)



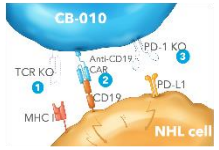


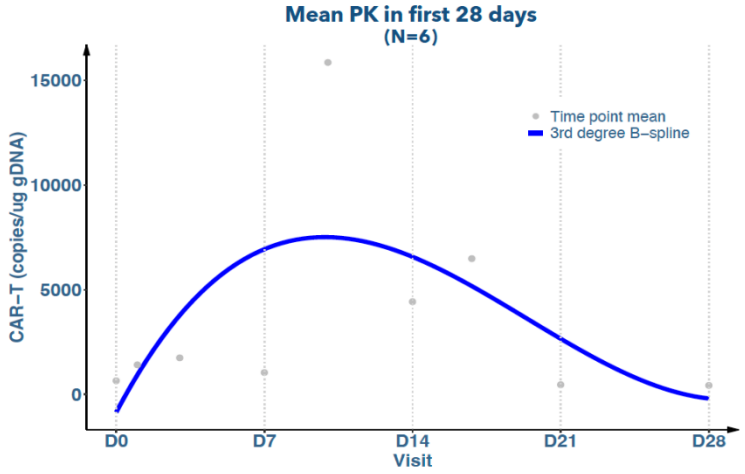
	Pre-dose	Day 1	Day 4	Day 7	Day 10	Day 14	Day 21	Day 28	Day 42	Day 56	Month 4	Month 6	Month 9
Responder	25	44	38	44	44	46	44	46	16	13	9	4	4
Non-Responder	33	35	36	35	38	37	35	27	10	8			

PBCAR0191

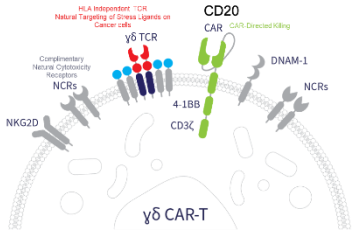


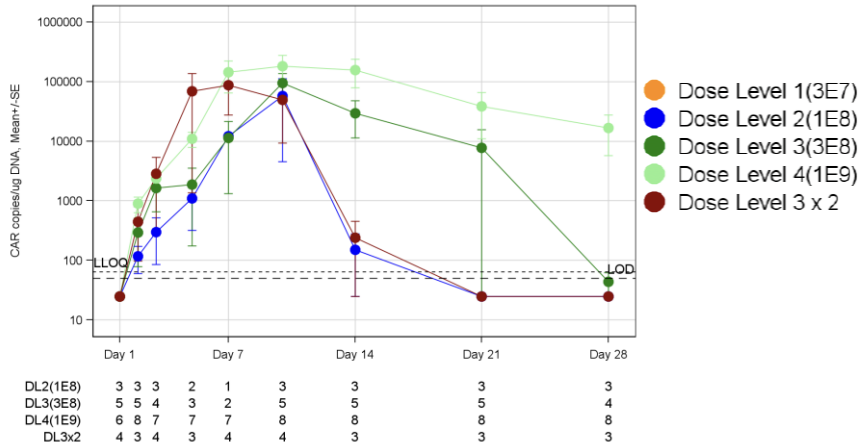
CB-010





ADI-001 / γδ CD20 CART



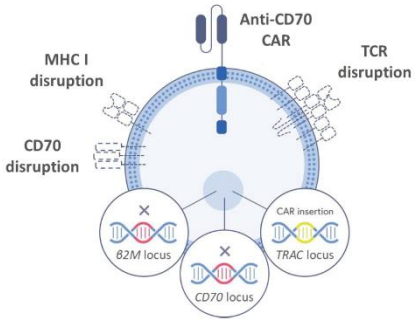


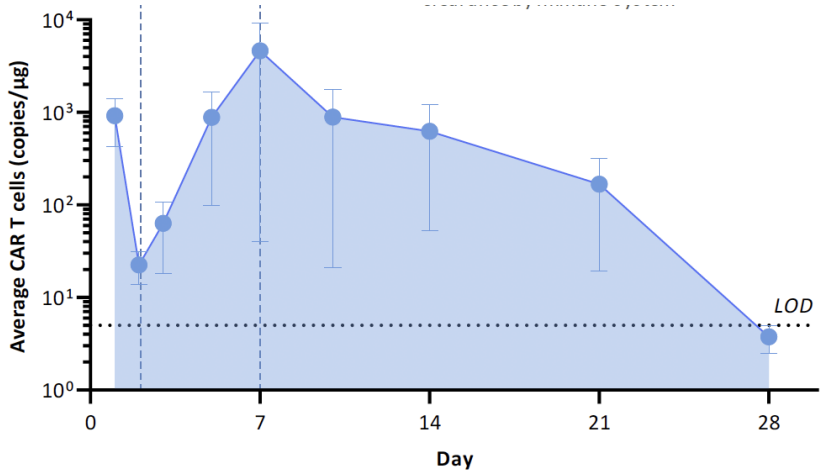
	Day 1			Day 7			Day 14		Day 21		Day 28	
DL2(1E8)	3	3	3	2	1	3	3		3		3	
DL3(3E8)	5	5	4	3	2	5	5		5		4	
DL4(1E9)	6	8	7	7	7	8	8		8		8	
DL3x2	4	3	4	3	4	4	3		3		3	

CAR T cell expansion and persistence after allogeneic CART

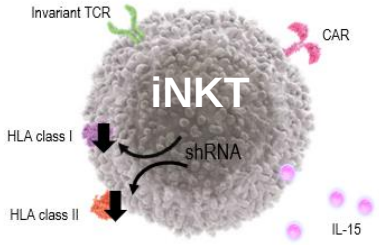
(With built-in immune evasion and standard lymphodepletion)

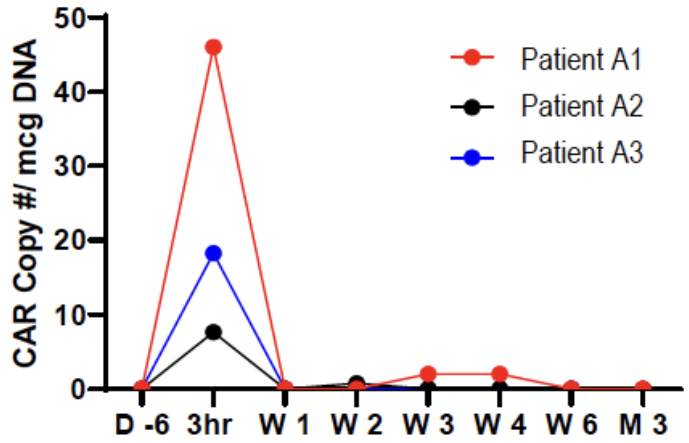
CTX130



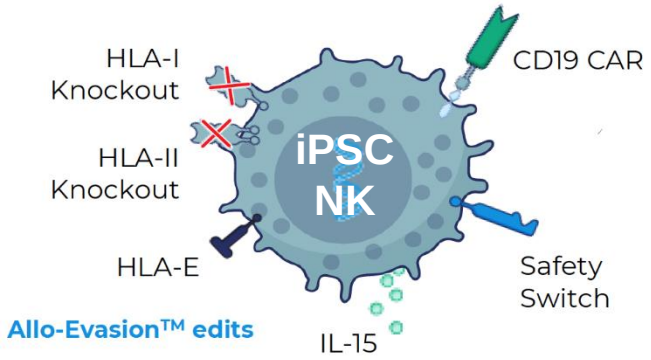


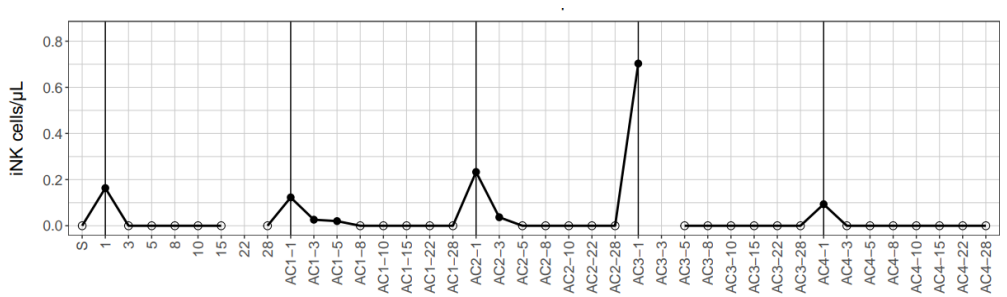
KUR-502





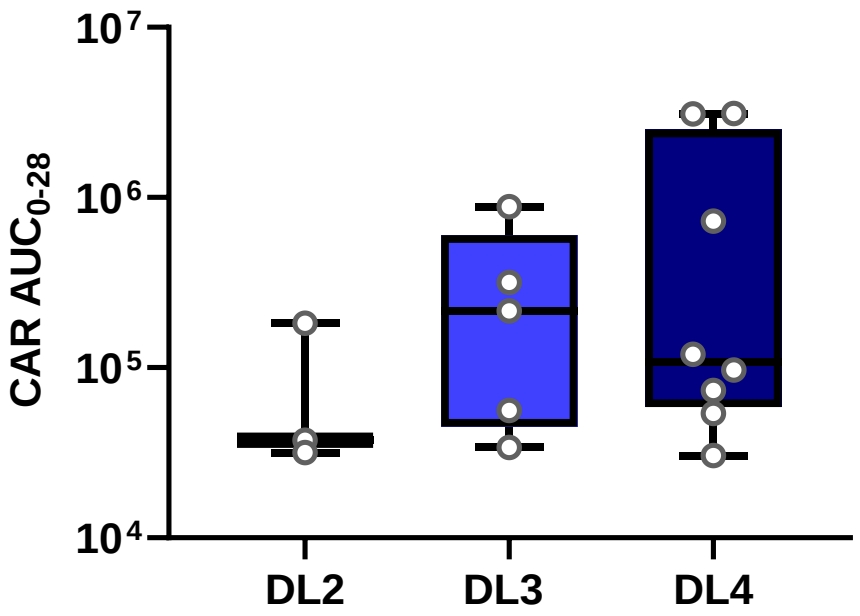
CNTY-101



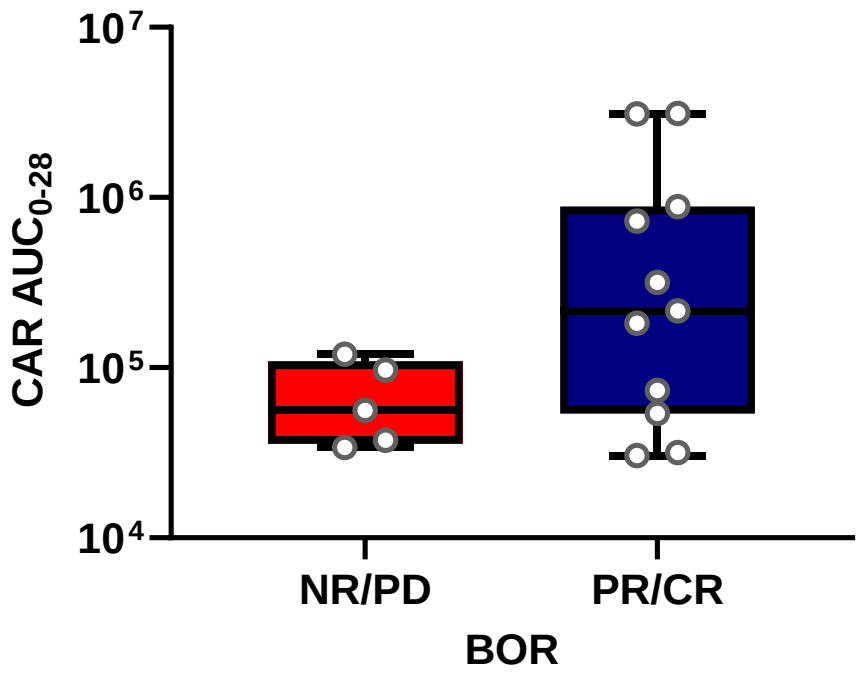


ADI-001: Association of AUC_{0-28} with dose level and response

AUC_{0-28} associates with dose level



Response associates with AUC_{0-28}



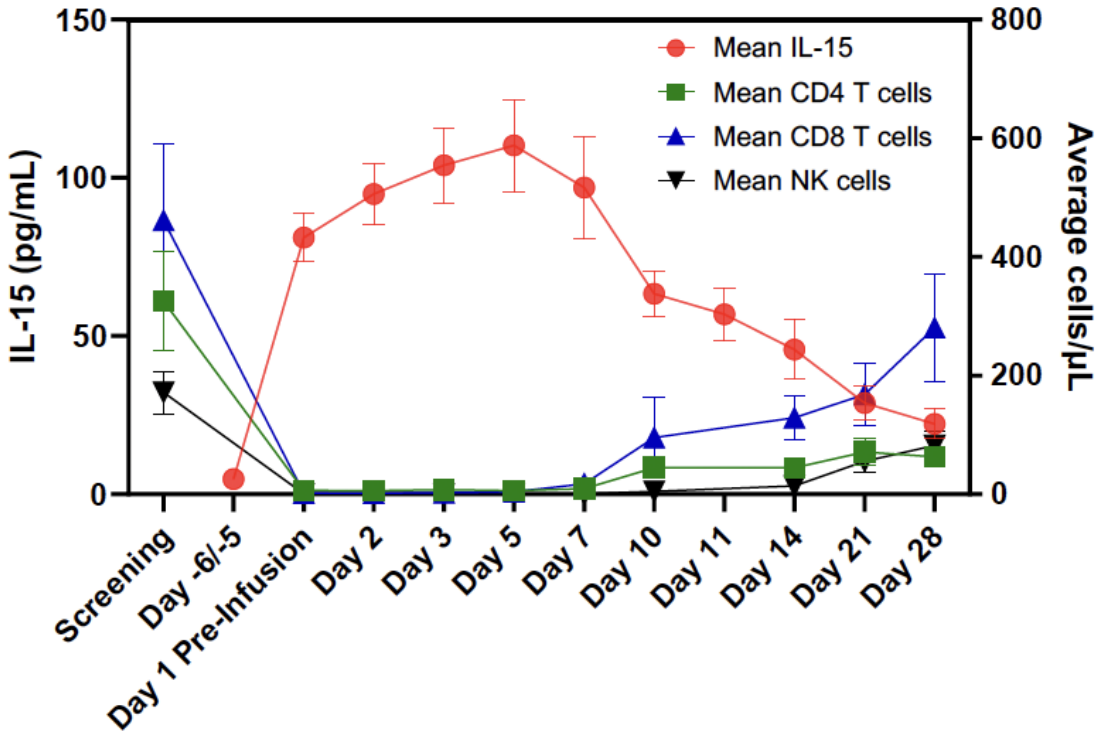
- Similar results observed in other allogeneic CART studies

Neelapu et al, ASH 2022 ASH, Abstract 2018
Moreno et al, ASH 2023, Abstract 3478

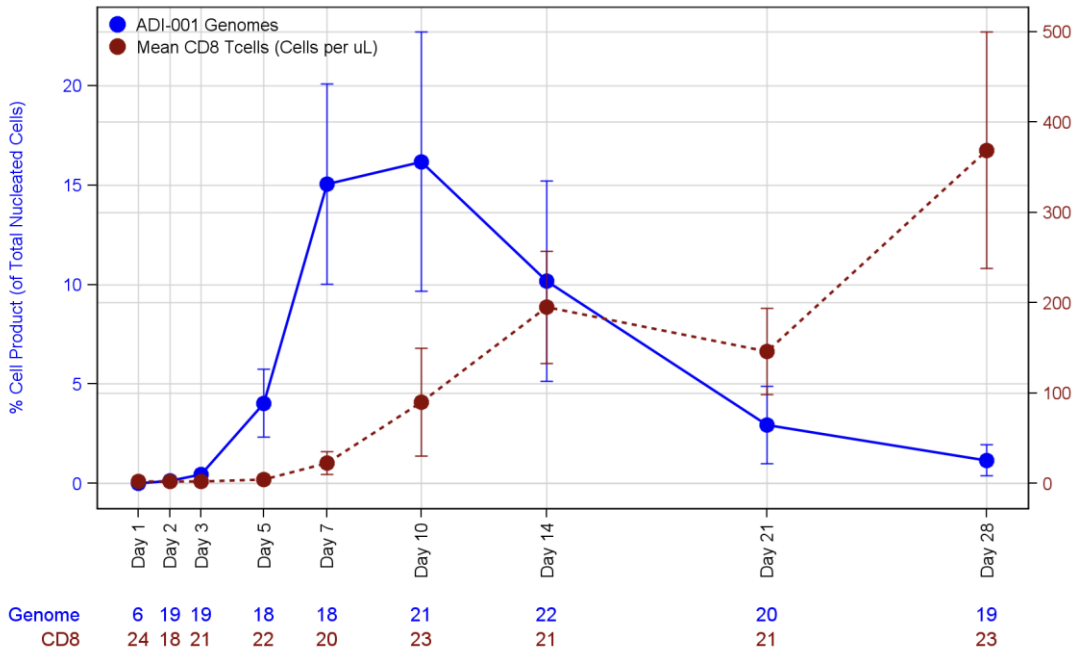
Loss of allogeneic CAR T persistence associates with host lymphocyte recovery

ADI-001 Study
(γδ CD20 CART)

Host T and NK recovery



CAR persistence vs. CD8 T cell recovery



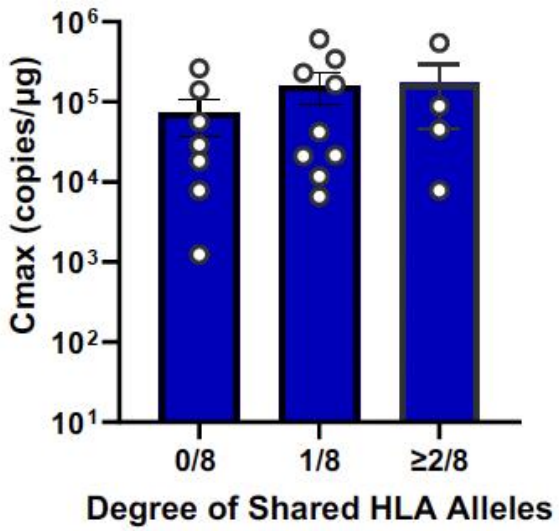
- Similar results observed in other allogeneic CART studies

Moreno et al, ASH 2023, Abstract 3478

Cellular kinetics and response are not associated with degree of shared HLA alleles

ADI-001 Study
(γδ CD20 CART)

A



B

Shared HLA Alleles	CR/PR Rate n/N (%)
0/8	7/8 (87.5)
1/8	7/11 (63.6)
≥2/8	3/5 (60.0)

- Similar results observed in other allogeneic CART studies

Moreno et al, ASH 2023, Abstract 3478

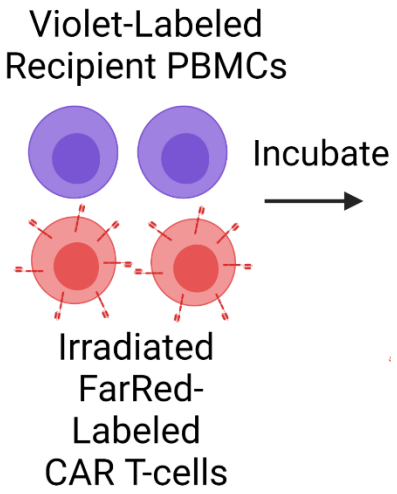
Allogeneic CAR-T cellular kinetics

- Expansion and persistence remain challenges in clinical implementation of allogeneic CAR T cell therapy
- Despite the use of products derived from the same donor, CAR T cell expansion and clinical responses are heterogeneous

- Can we identify alloreactive T cell clones against the donor CAR-T product in patients apriori at baseline?
- Does the degree of host alloreactivity at baseline correlate with donor CAR-T expansion and clinical efficacy *in vivo*?
- What are the kinetics of expansion of alloreactive T cell clones following donor CAR T cell infusion?

Identifying alloreactive T cell clones against donor CAR T cells

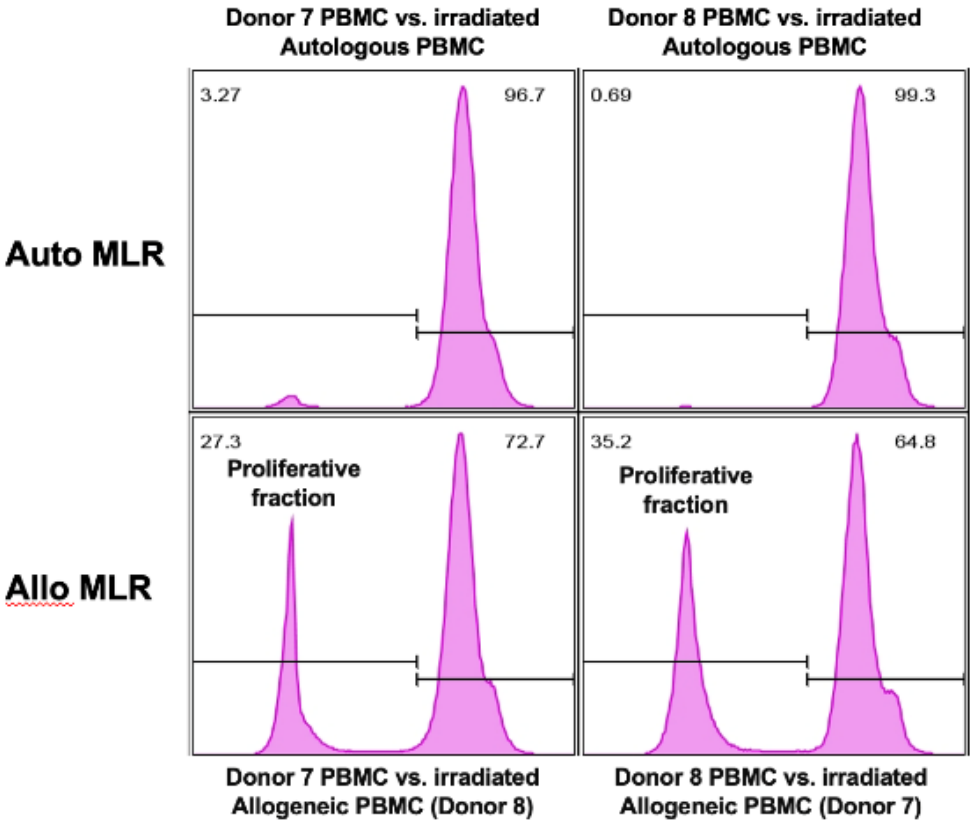
Mixed Lymphocyte Reaction (MLR) Assay (9 days)



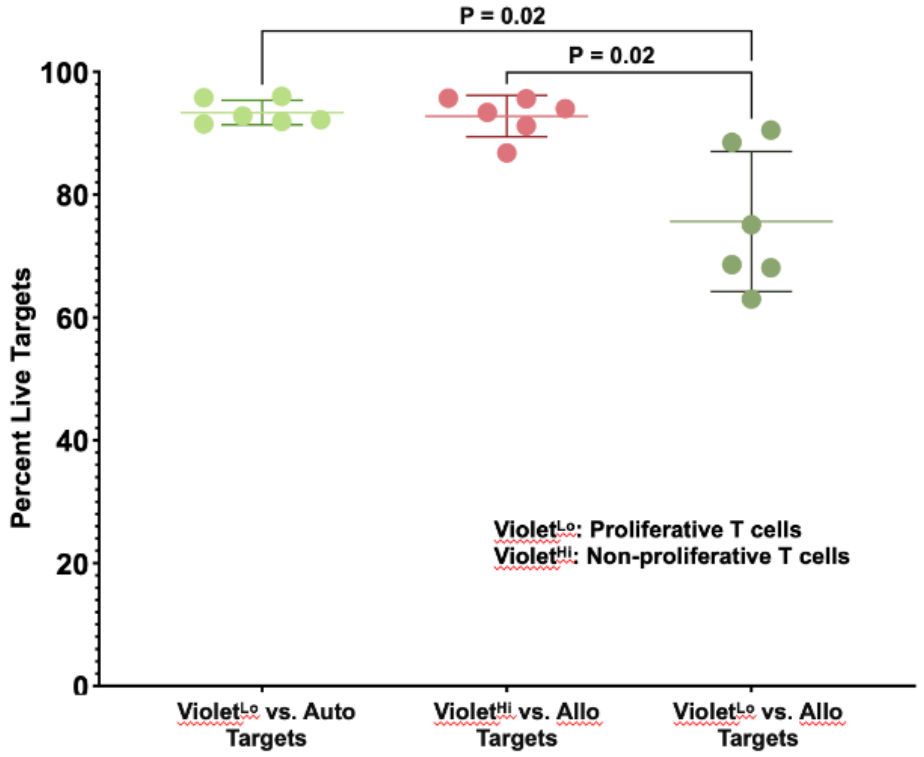
Jallouk et al, ASH 2023, Abstract 4832

Alloreactive T cell identified by MLR mediate cytotoxicity against donor targets

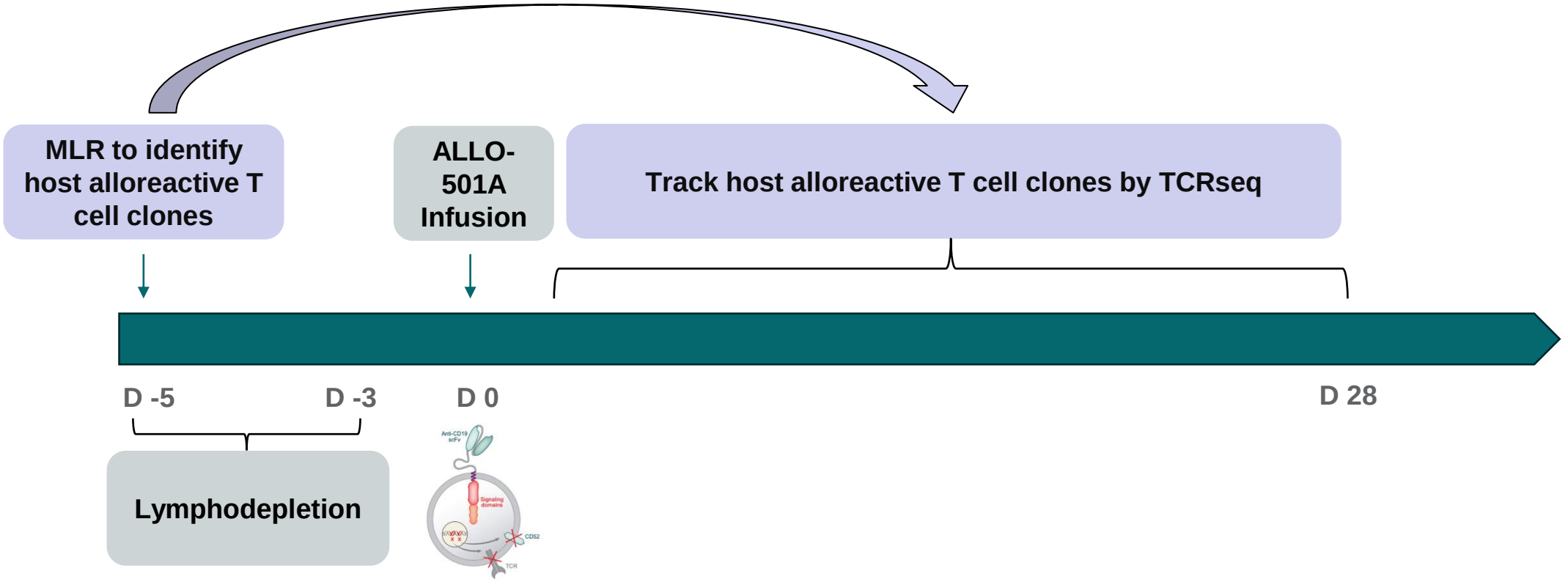
Assay to identify alloreactive T/NK cells



Cytotoxicity by alloreactive T cells (24 h)



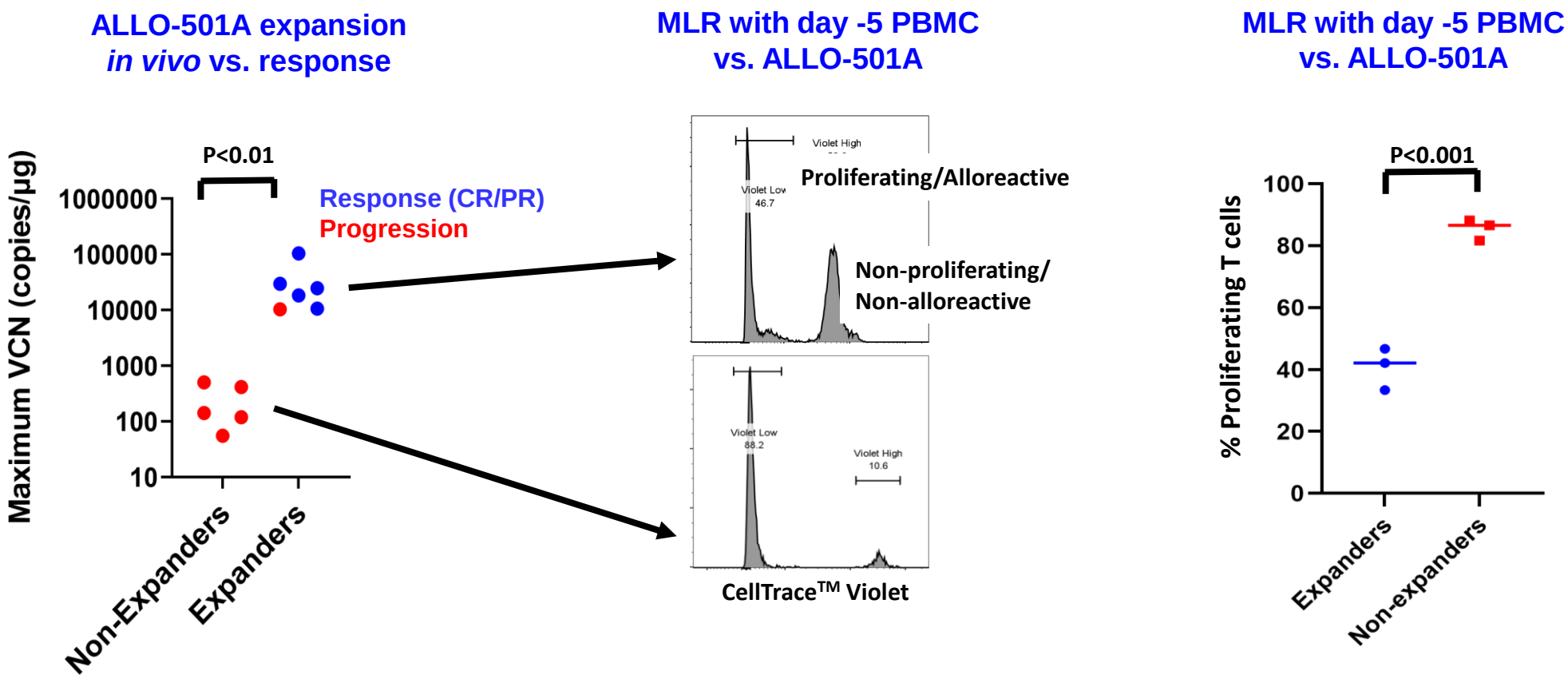
Identifying and tracking alloreactive T cell clones



Fludarabine 30 mg/m^2/day; day -5 to day -3
Cyclophosphamide 300-500 mg/m^2/day; day -5 to day -3
ALLO-647 from 30 mg/day from day -5 to day -3

Jallouk et al, ASH 2023, Abstract 4832

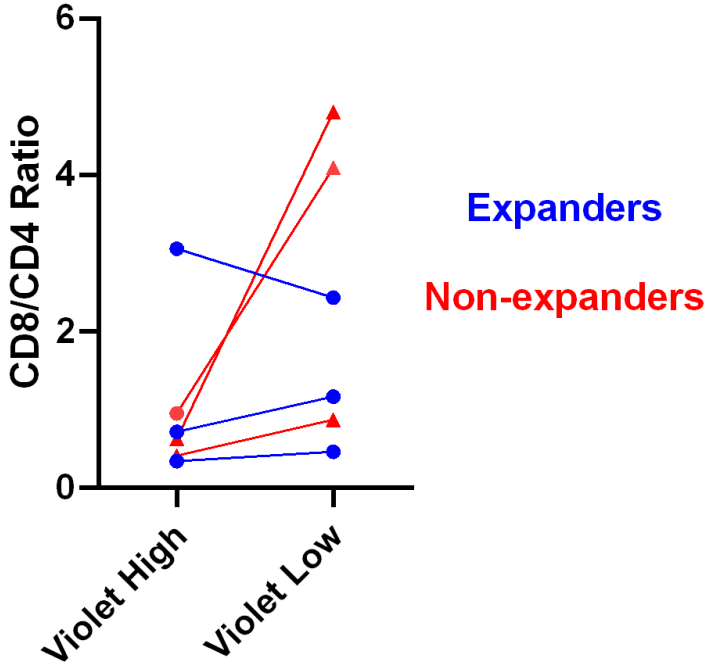
Low CAR T expansion *in vivo* is associated with progressive disease and increased alloreactivity in MLR at baseline



- All patients were treated with the same donor CAR-T lot.

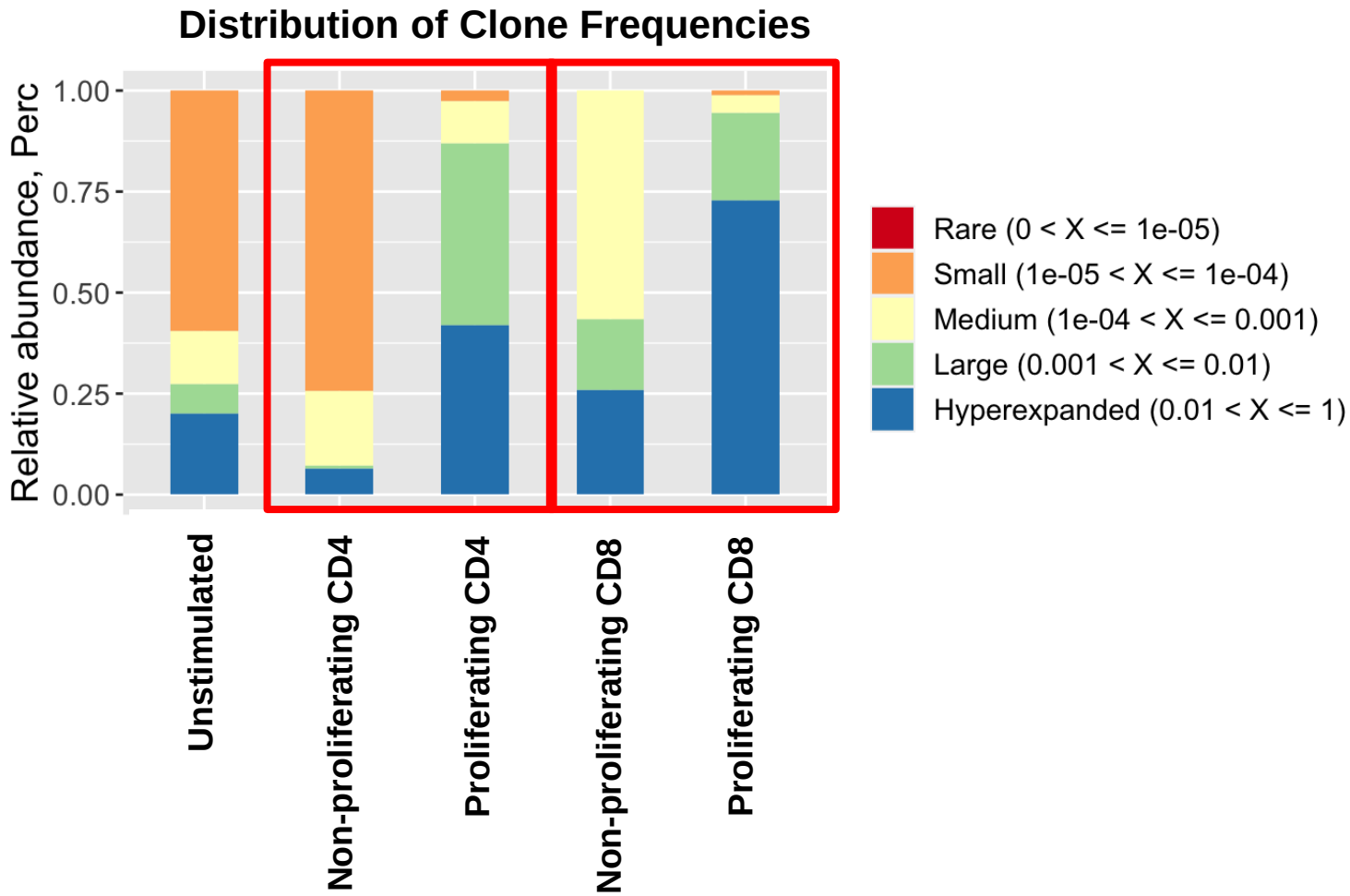
Jallouk et al, ASH 2023, Abstract 4832

Proliferating/Alloreactive T cells are disproportionately CD8+ and exhibit increased clonality



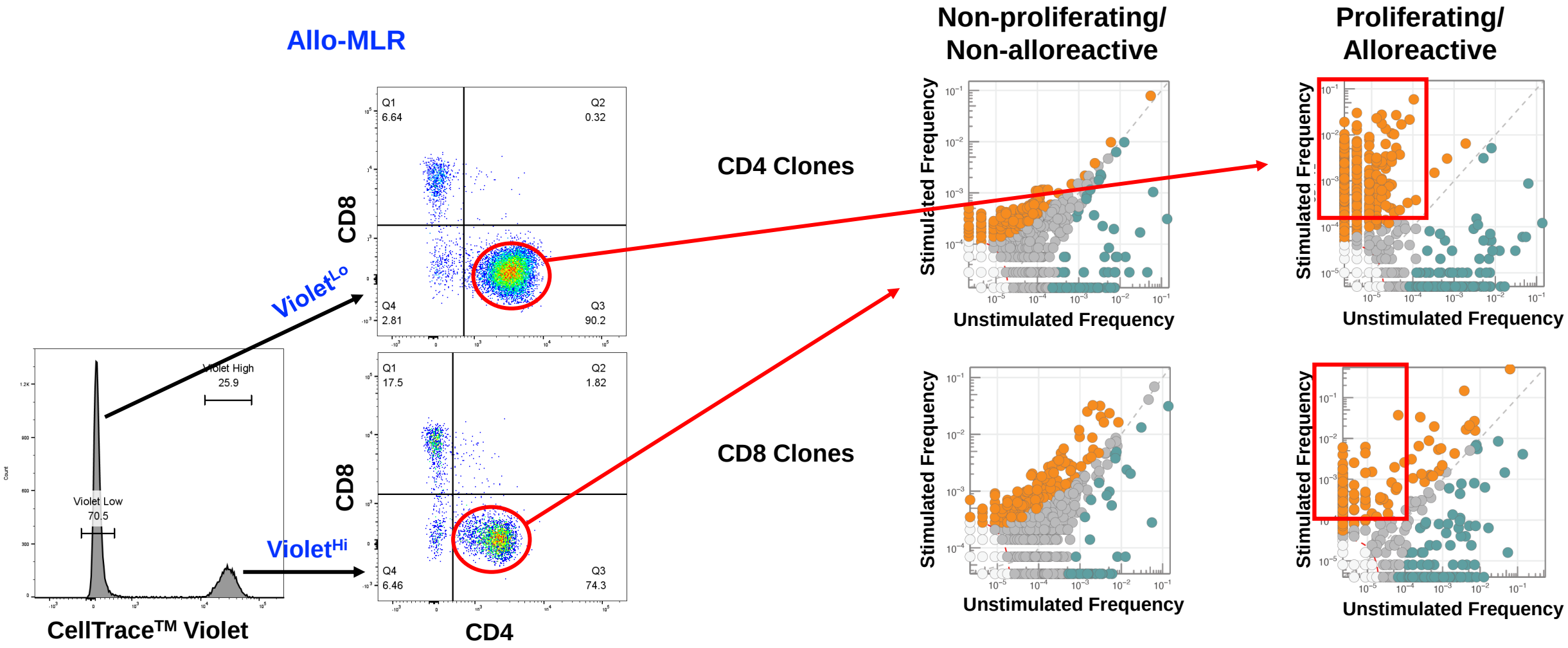
Expanders

Non-expanders



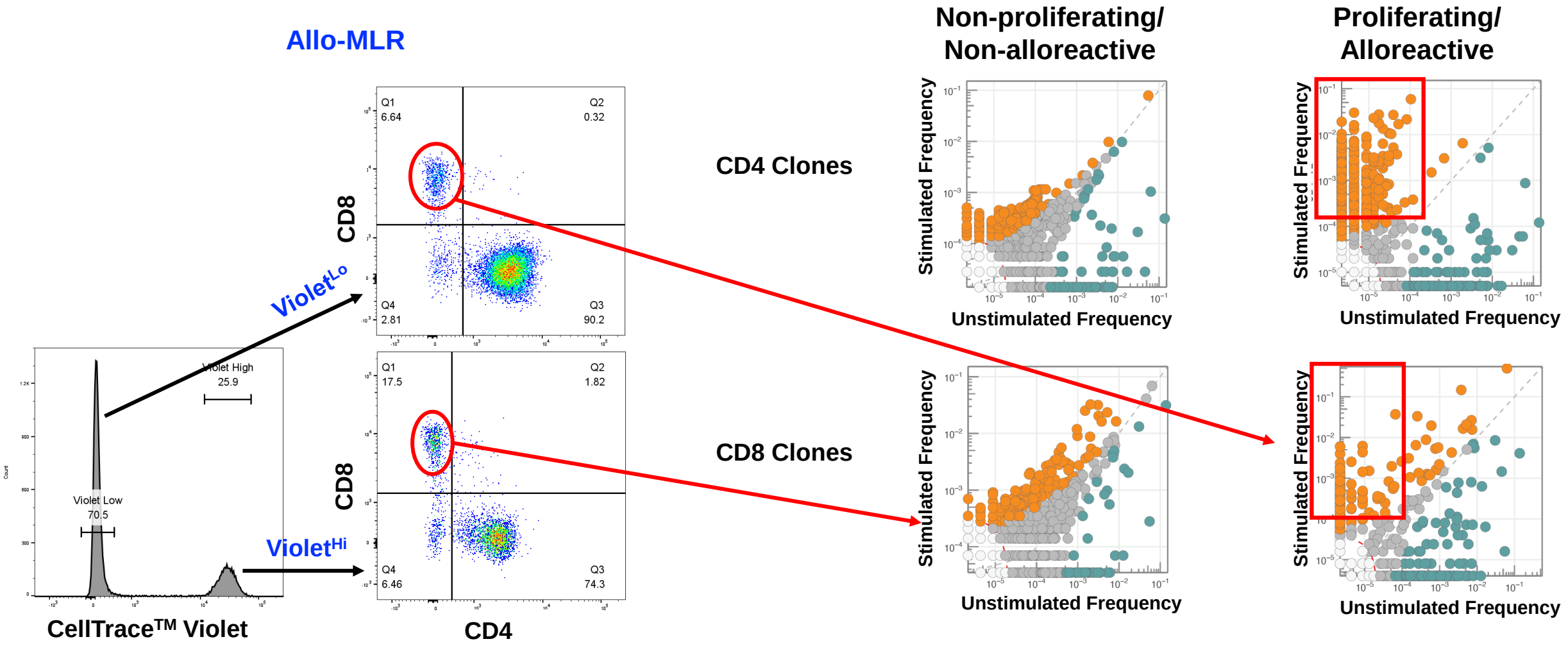
Jallouk et al, ASH 2023, Abstract 4832

Proliferating/Alloreactive populations from MLR have distinct pattern of clonotype enrichment



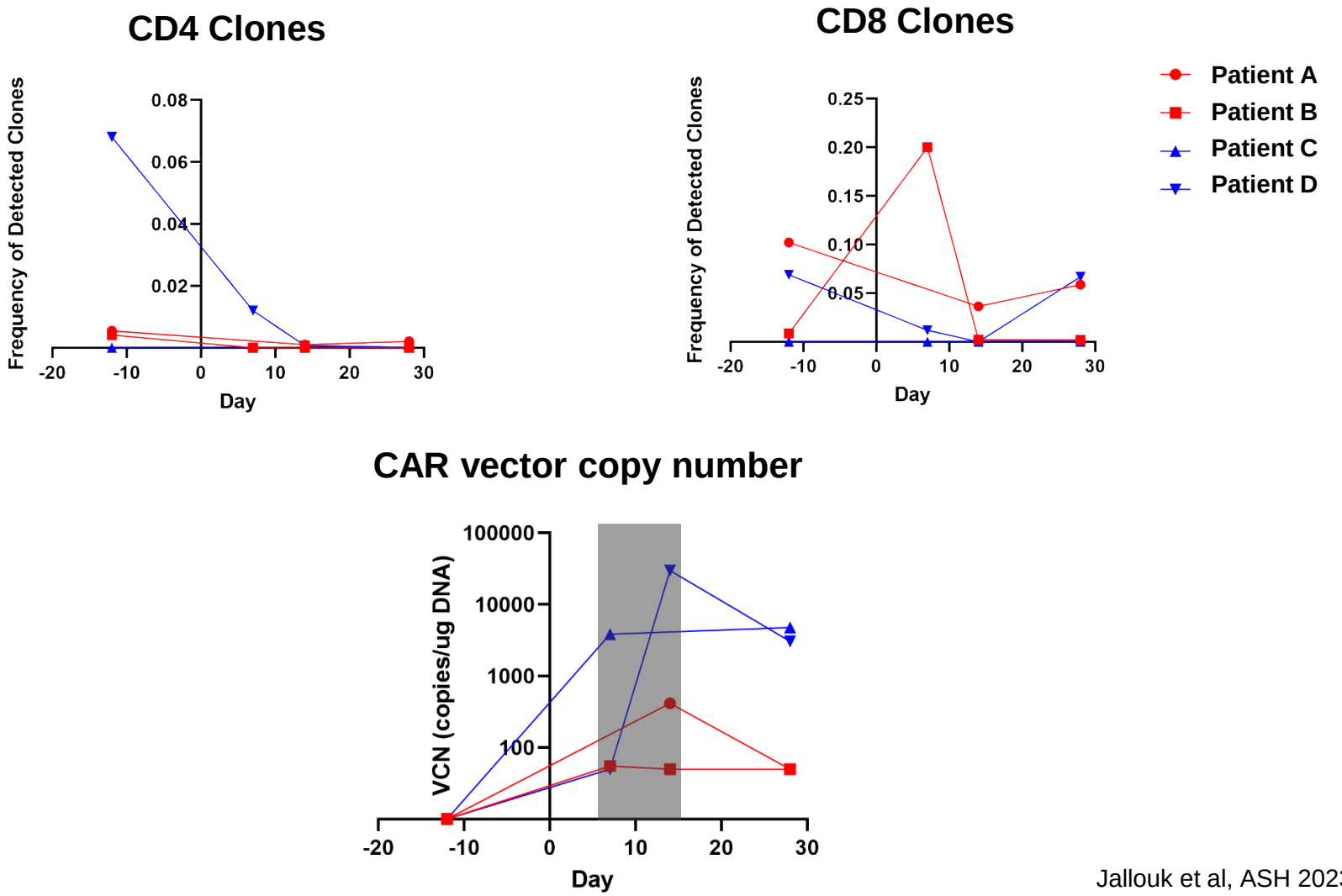
Jallouk et al, ASH 2023, Abstract 4832

Proliferating/Alloreactive populations from MLR have distinct pattern of clonotype enrichment



Jallouk et al, ASH 2023, Abstract 4832

Alloreactive CD8+ clones are enriched in non-expanders



Jallouk et al, ASH 2023, Abstract 4832

Allogeneic CAR-T expansion and rejection: Summary

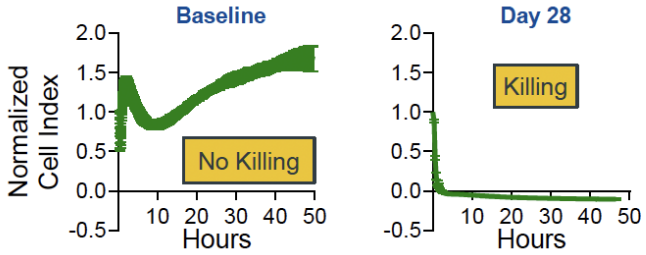
- A 9-day MLR assay can be used to identify alloreactive $CD4^+$ and $CD8^+$ T cell clones at baseline

- Subjects with more robust *in vitro* T cell proliferation upon exposure to allogeneic CAR-T product have poor CAR-T expansion *in vivo*
  - Suggests that MLR assay may recapitulate some aspects of expander vs. non-expander phenomenon

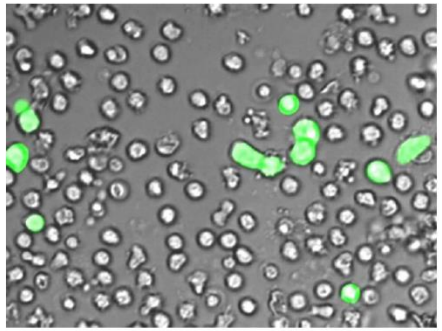
- Higher frequencies of alloreactive $CD8^+$ clones following treatment associates with poor CAR-T expansion *in vivo*
  - Similar pattern not apparent for $CD4^+$ clones
  - Suggests that alloreactive $CD8^+$ clones may be involved in early rejection of allogeneic CAR T cells

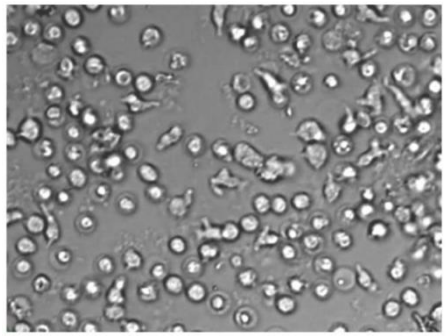
SC291: Immune evasion by host T and NK cells

Patients T cells kill WT CART

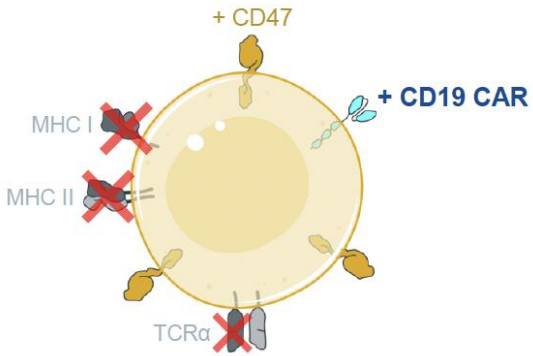


Patients NK cells kill MHC I/II^{KO} CART





HIP CART

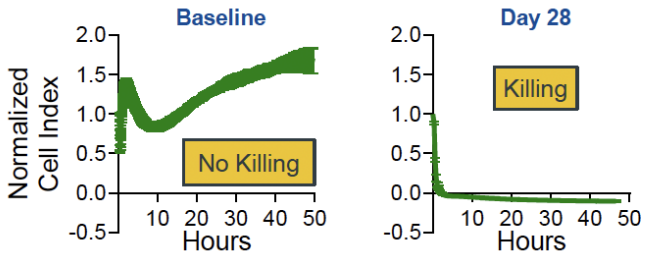


HIP – Hypoimmune platform

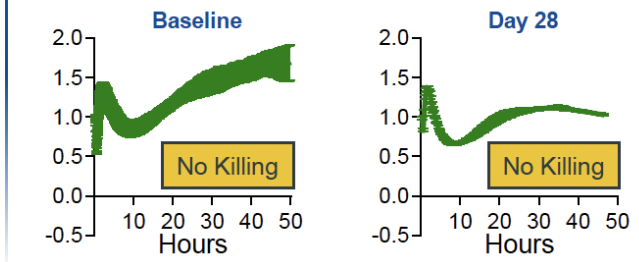
Neelapu et al, ASH 2023
Sana Biotechnology Corporate presentation, Jan 2024

SC291: Immune evasion by host T and NK cells

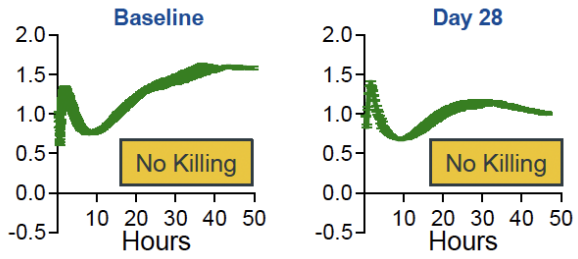
Patients T cells kill WT CART



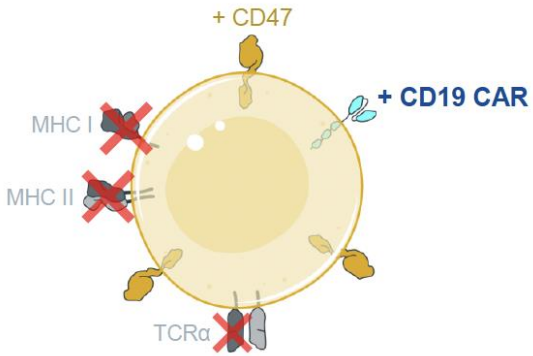
Patients T cells do not kill MHC I/II^{KO} CART



Patients T cells do not kill HIP CART



HIP CART



HIP – Hypoimmune platform

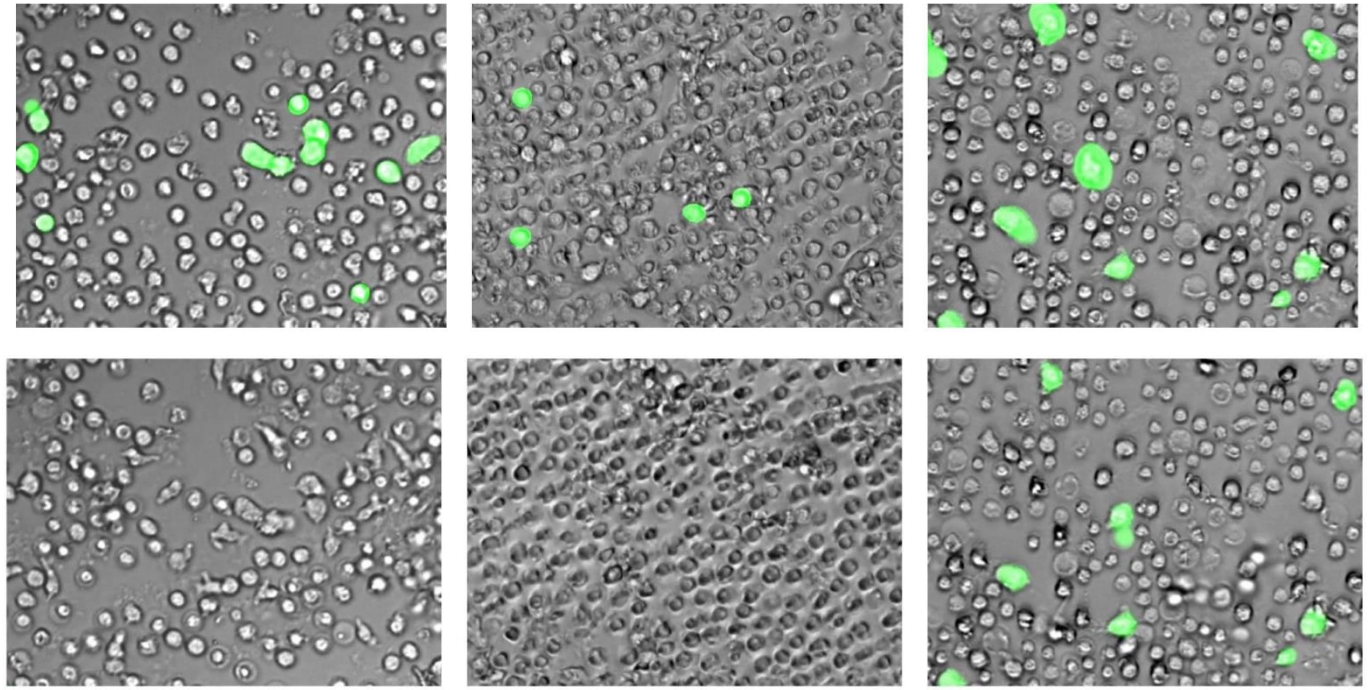
Patients NK cells kill MHC I/II^{KO} CART

Patients NK cells kill MHC I/II^{KO} + HLA-E CART

Patients NK cells do not kill MHC I/II^{KO} + CD47 CART

Baseline

Day 13

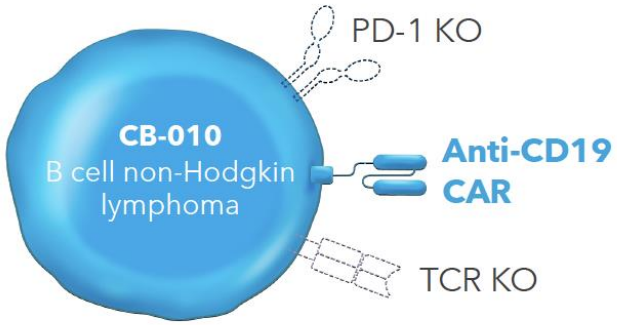


4-hour assay

Neelapu et al, ASH 2023
Sana Biotechnology Corporate presentation, Jan 2024

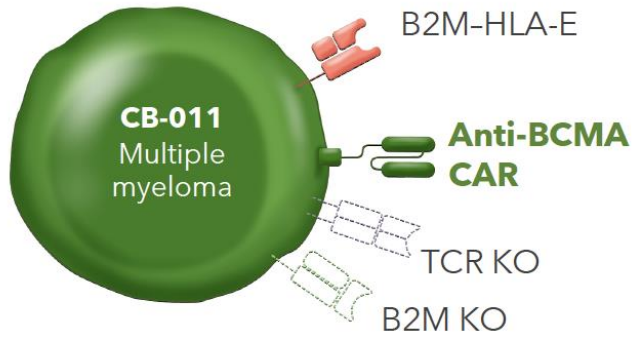
Next generation allogeneic CAR T

3 Edits



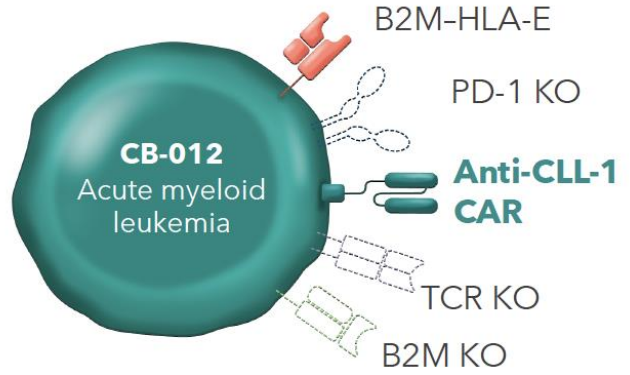
1st allogeneic anti-CD19 CAR-T cell therapy in the clinic with **checkpoint disruption** via PD-1 knockout (KO)[1] to reduce CAR-T cell exhaustion

4 Edits



1st allogeneic anti-BCMA CAR-T cell therapy with **immune cloaking** via *B2M* KO and insertion of B2M-HLA-E fusion protein[1]

5 Edits

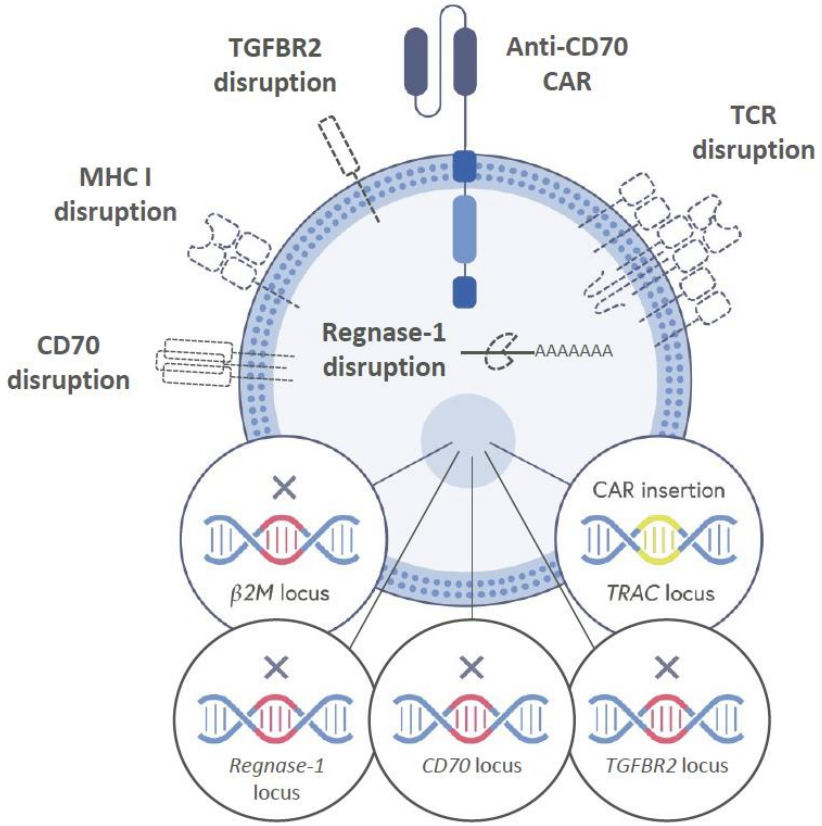


1st allogeneic CAR-T cell therapy with both **checkpoint disruption** and **immune cloaking**[1]

Next generation CD70 allogeneic CAR T

CTX131 (6 edits)

- **Regnase-1:** Removes intrinsic "brake" on T cell function
- **Increases functional persistence, cytokine secretion and sensitivity, effector function on tumors**



- **TGFBR2 KO:** Removes key extrinsic "brake" on T cell anti-tumor activity
- **Reduces TME inhibition of multiple CAR-T cell functions**

Adapted from Terrett et al. *AACR*, 2023

Thank you for your attention!

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