Società Italiana di Ematologia

3rd MEETING ON T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

Carlos Ramos

CAR-T for T-Cell Lymphomas

Baylor College of Medicine, Houston, TX, USA

BOLOGNA, ROYAL HOTEL CARLTON

September 13-14, 2024

Disclosures of Carlos Ramos

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						×	
Genentech			×				
CRISPR			×				
Tessa Therapeutics	×						
Athenex, Inc.	×						

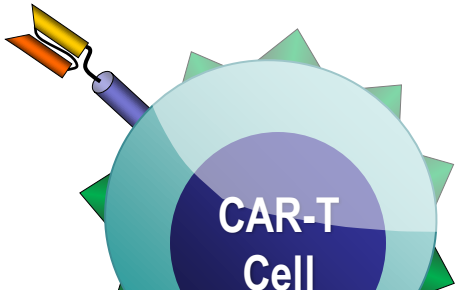
Targeting T-cell malignancies with CAR-T cells

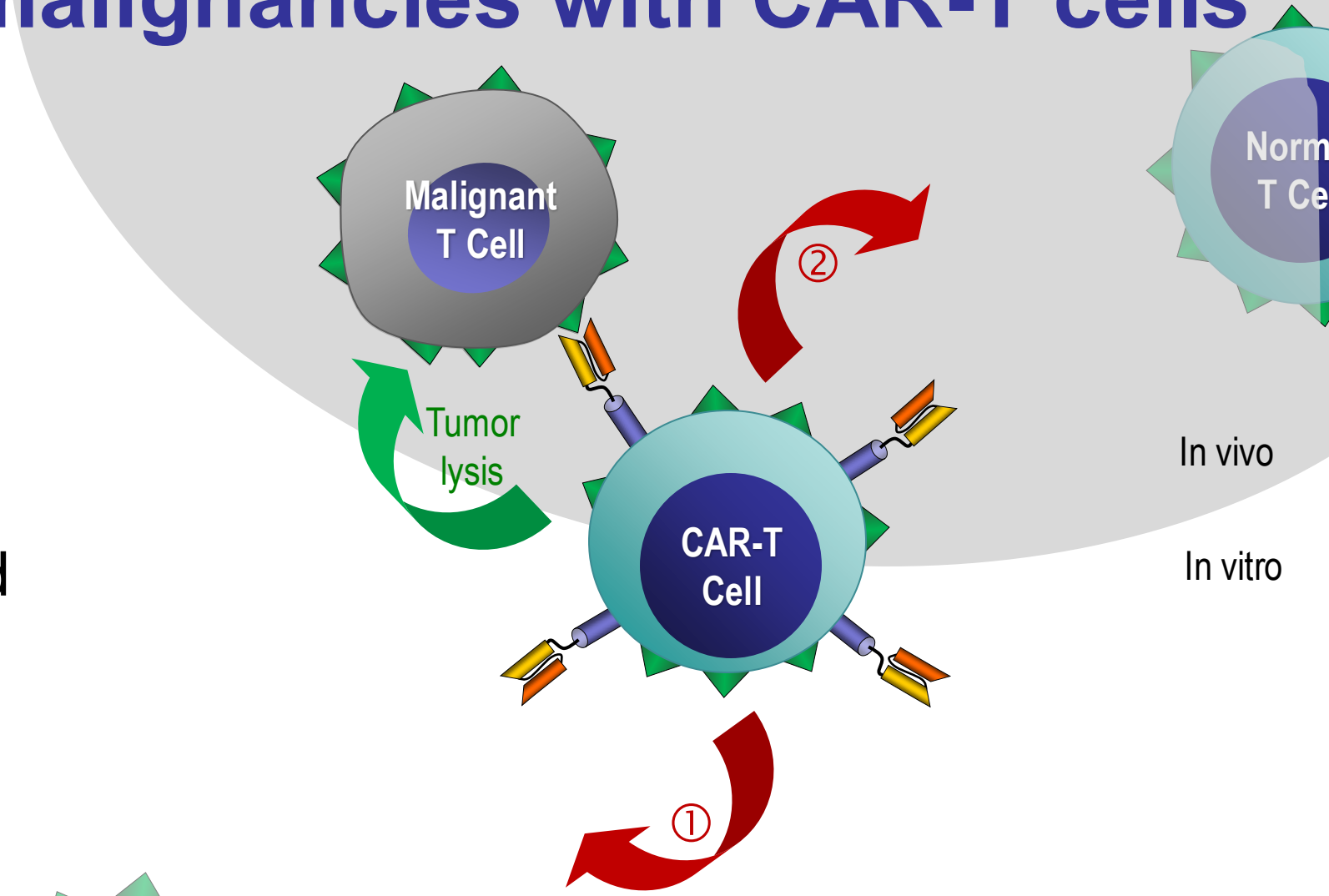
- Major challenges:

  ① Fratricide

  ② Long-term acquired immune deficiency

  ③ Transduction of malignant cells





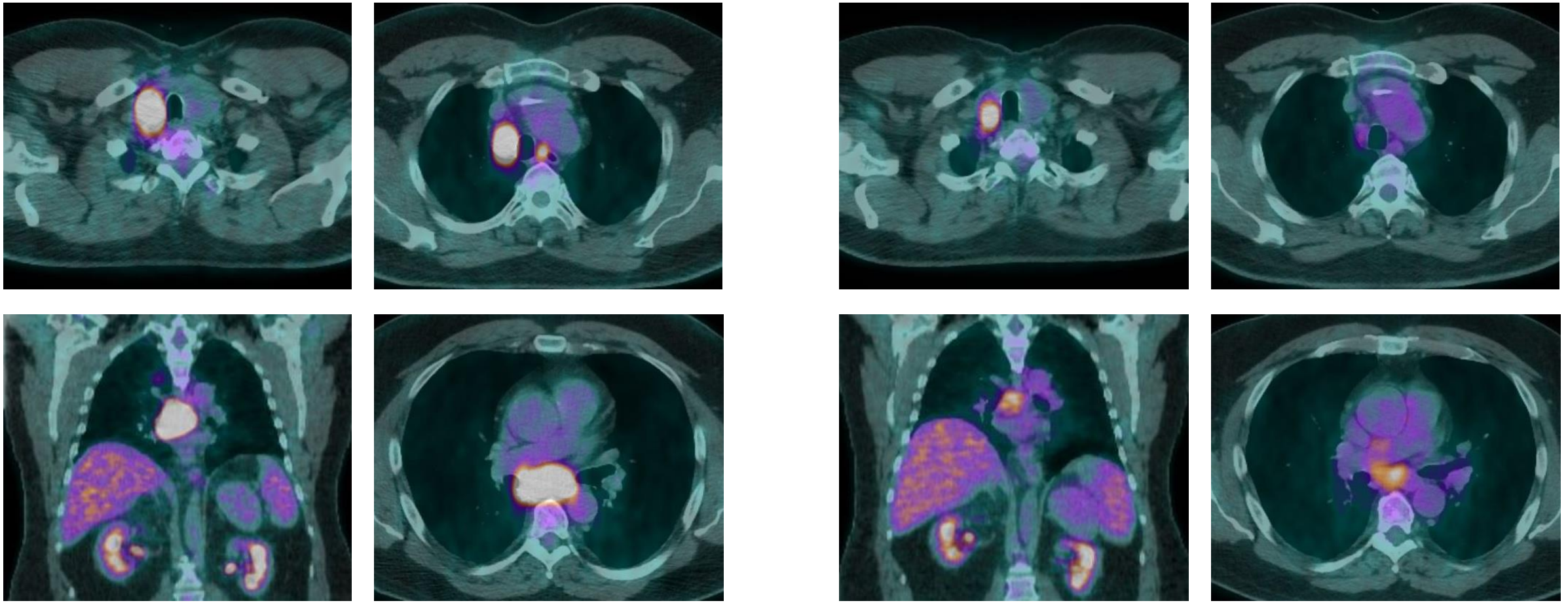
Strategies to mitigate fratricide

- Target a non-universal T-cell tumor marker
- Induce sequestration of target antigen inside CAR-T cells
  - Spontaneously via the CAR (also known as luck…)
  - Through an engineered retainer molecule
- Inactivate target antigen gene with editing techniques
  - CRISPR-Cas9 disruption or base-editing
- Dampen T-cell cytotoxicity after CAR transduction
  - T-cell activation pathways inhibitors

CD30.CART can be active in TCL: Peripheral T Cell Lymphoma (PTCL), NOS

Pre-infusion

6 weeks post-infusion



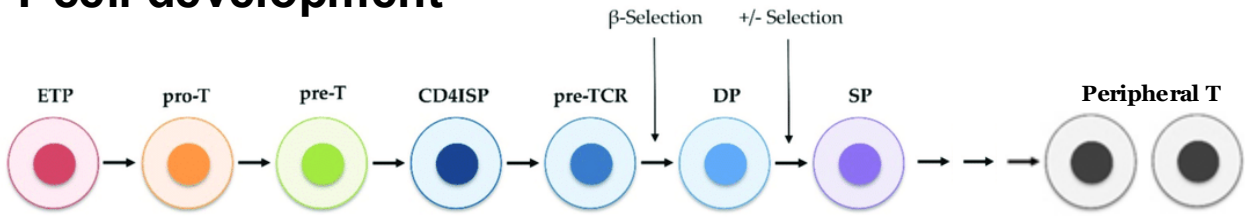
Target antigens for T-cell malignancies

Most common antigens

Antigen	Frequency in T-cell malignancies	
	T-ALL/Ly	TCL
PAN-T CELL ANTIGENS		
CD5	90%	85% (PTCL-NOS) 96% (AITL) 26–32% (ALCL) 36% (NK-T) 85% (ATLL) 91% (CTCL)
CD7	>90%	50% (PTCL-NOS) 57% (AITL) 32–54% (ALCL) 79% (NK-T) 25% (ATLL) 18% (CTCL)

(Bayon-Calderon *et al.*, Int J Mol Sci 2020;
Scherer *et al.*, Front Oncol 2019)

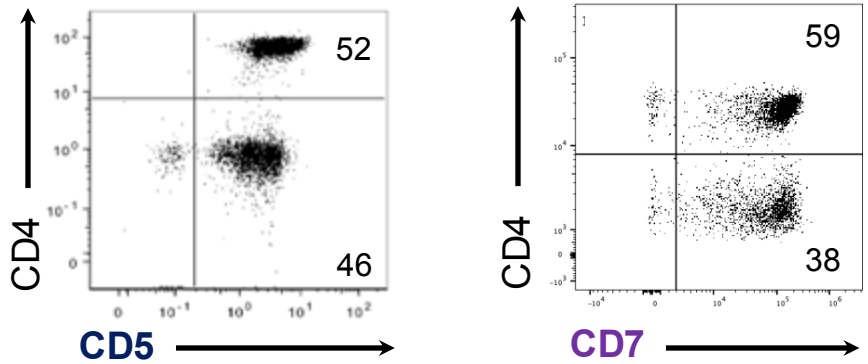
T-cell development



Lymphoblastic leukemia/lymphoma
T-ALL / LBL

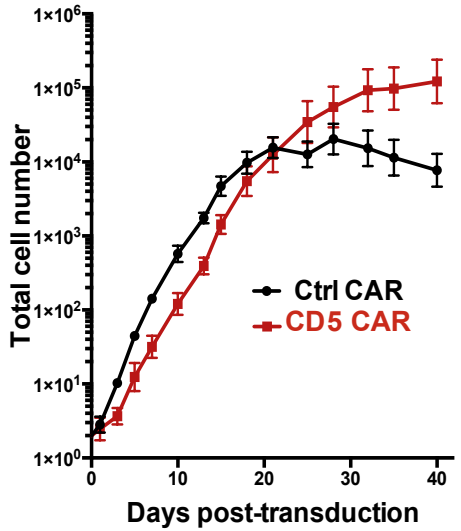
Mature T-cell lymphoma
TCL

Peripheral T-cells

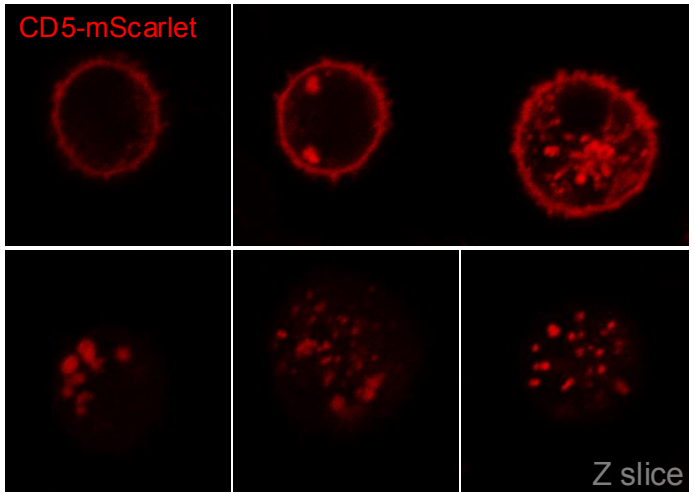


CD5.CART degrade CD5 and evade fratricide

Normal expansion of CD5 CART cells

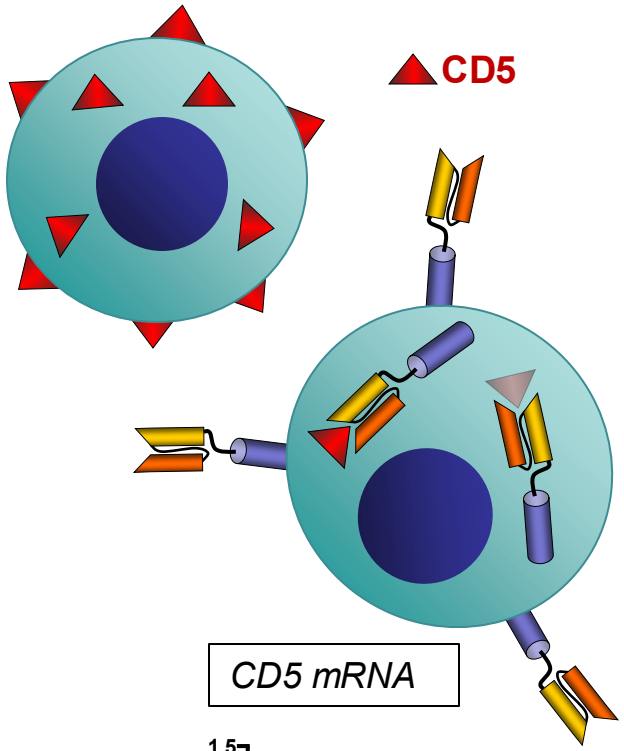


Internalization of CD5 protein in CARTs

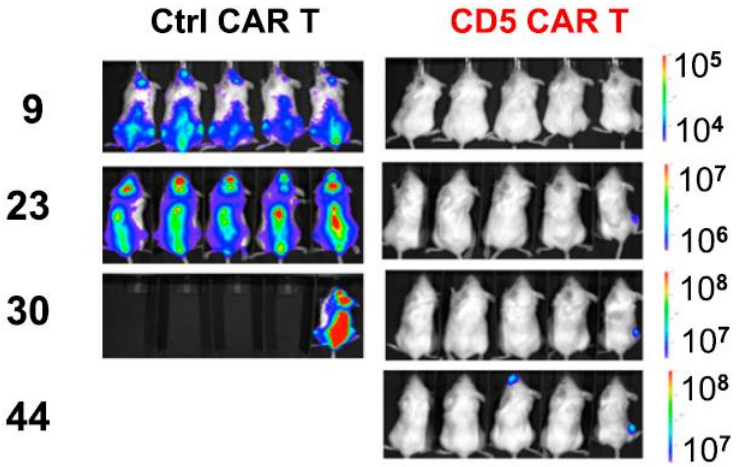


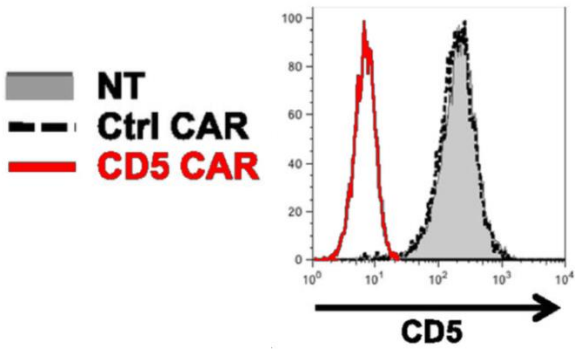
Ctrl T

CAR T

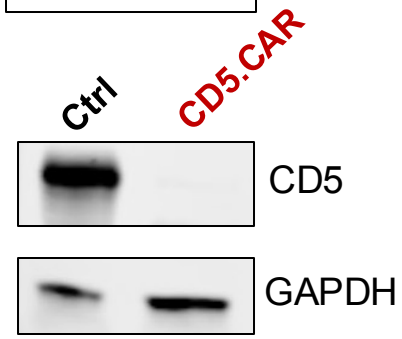


CD5.CART kill T cell tumors

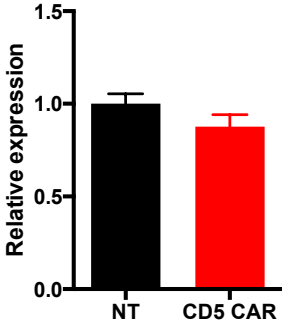




CD5 protein

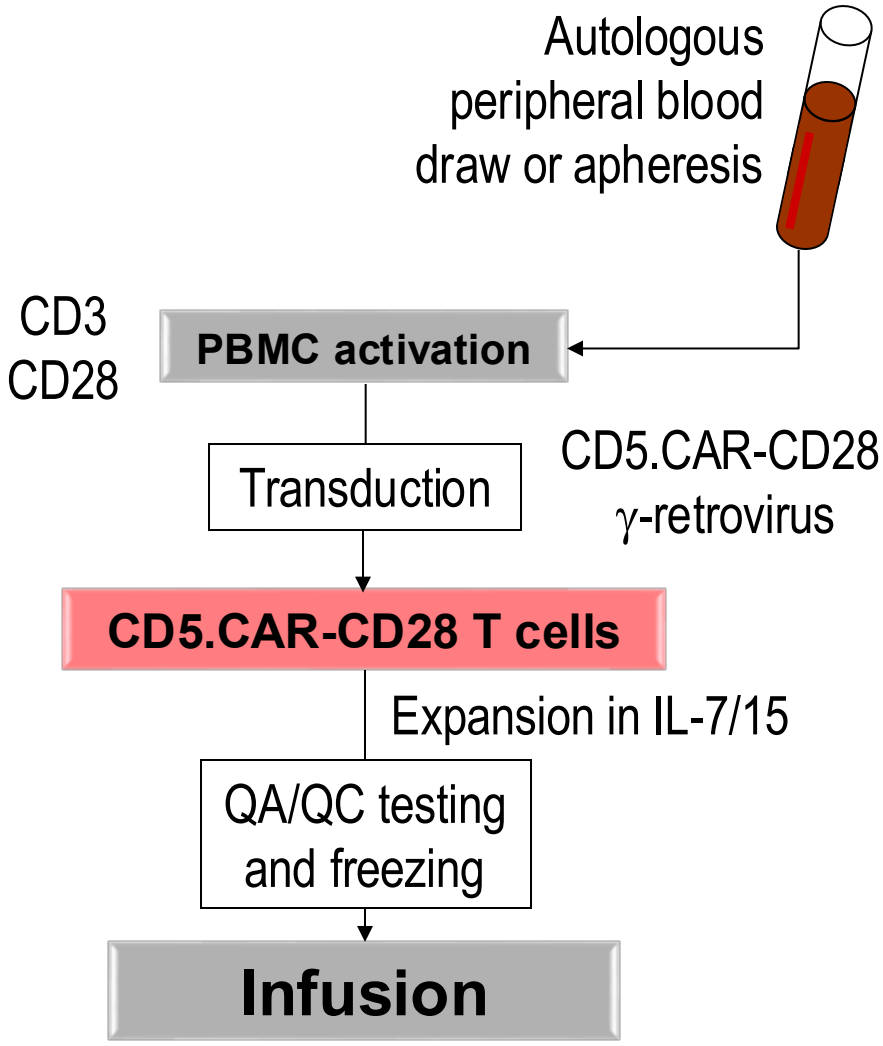


CD5 mRNA



(Mamonkin *et al.*, Blood 2015; Ma et *al., in revision*)

CD5.CART – MAGENTA trial (NCT03081910)

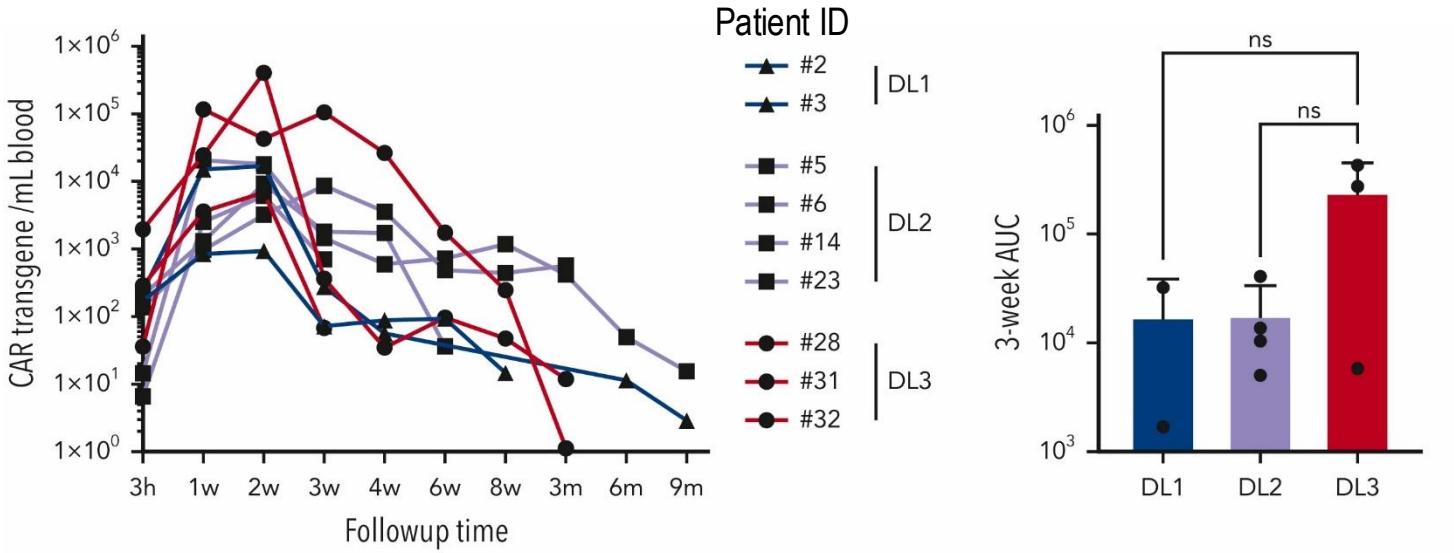


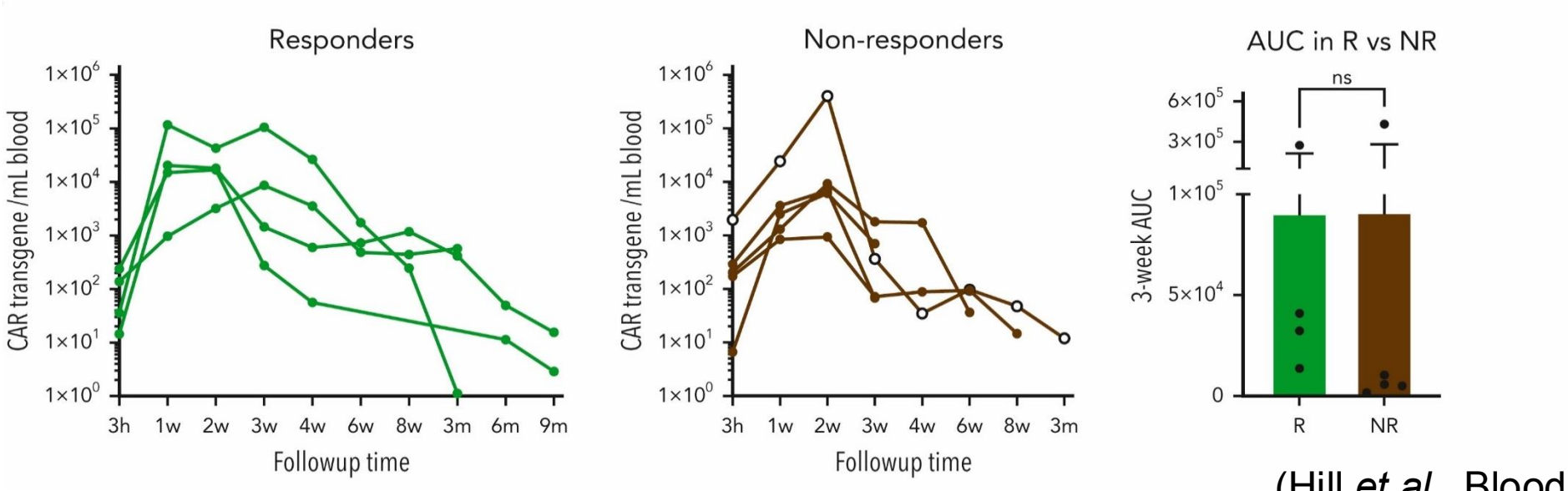
- Phase 1 trial
- $CD5^+$ malignancies (>50% expression)
  - Failure of standard treatment
  - Allogeneic stem cell donor identified
- Dose escalation (modified continual reassessment method)
  - 1, 5, 10 $\times 10^7$ CAR^+ cells/m^2
- Lymphodepleting chemotherapy
  - Cyclophosphamide + fludarabine
- Primary objective: safety
- Secondary: response per Lugano/NCCN
  - Initial assessment at week 4-6

CD5.CART patient characteristics – NHL

Dose Level	ID	Age	Sex	Disease	# of prior therapies	Prior HSCT	% CD5 expression
1	2	63	F	Cutaneous T cell lymphoma/Sézary Sx	18	Allo	51
	3	70	M	Angioimmunoblastic T cell lymphoma	2	Auto	100
2	5	63	F	Angioimmunoblastic T cell lymphoma	7	Auto	75
	6	67	M	Peripheral T cell lymphoma NOS	4	No	51
	14	71	M	Peripheral T cell lymphoma NOS	4	Auto	100
	23	48	M	Peripheral T cell lymphoma NOS	10	No	55
3	28	29	F	Cutaneous T cell lymphoma	7	No	80
	31	63	M	Peripheral T cell lymphoma NOS	5	Allo	98
	32	49	F	Adult T cell leukemia/lymphoma	5	No	56

CD5.CAR-T cell expansion

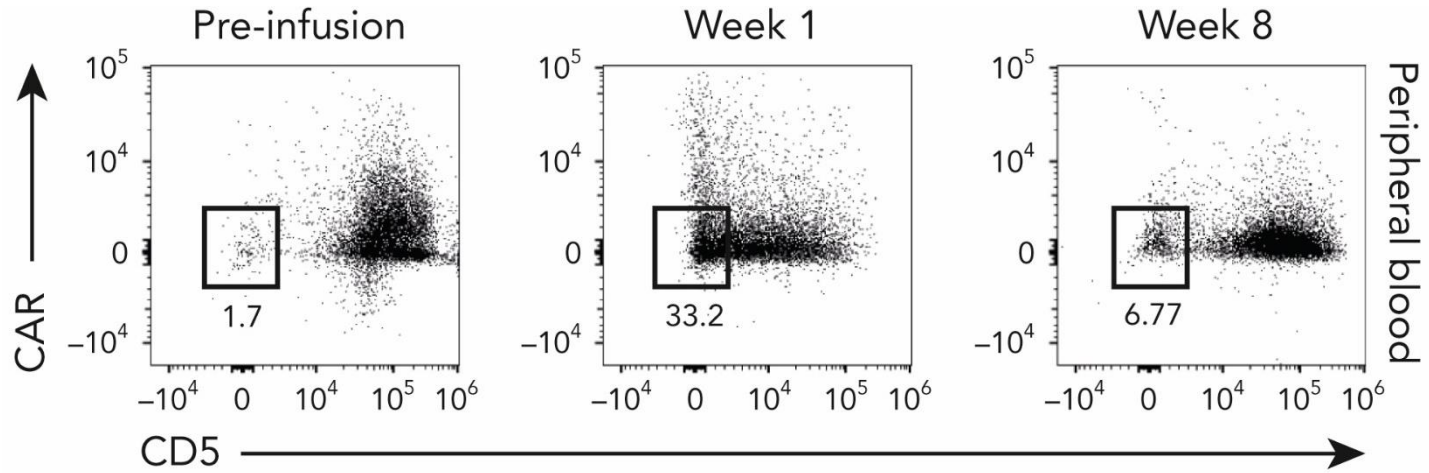


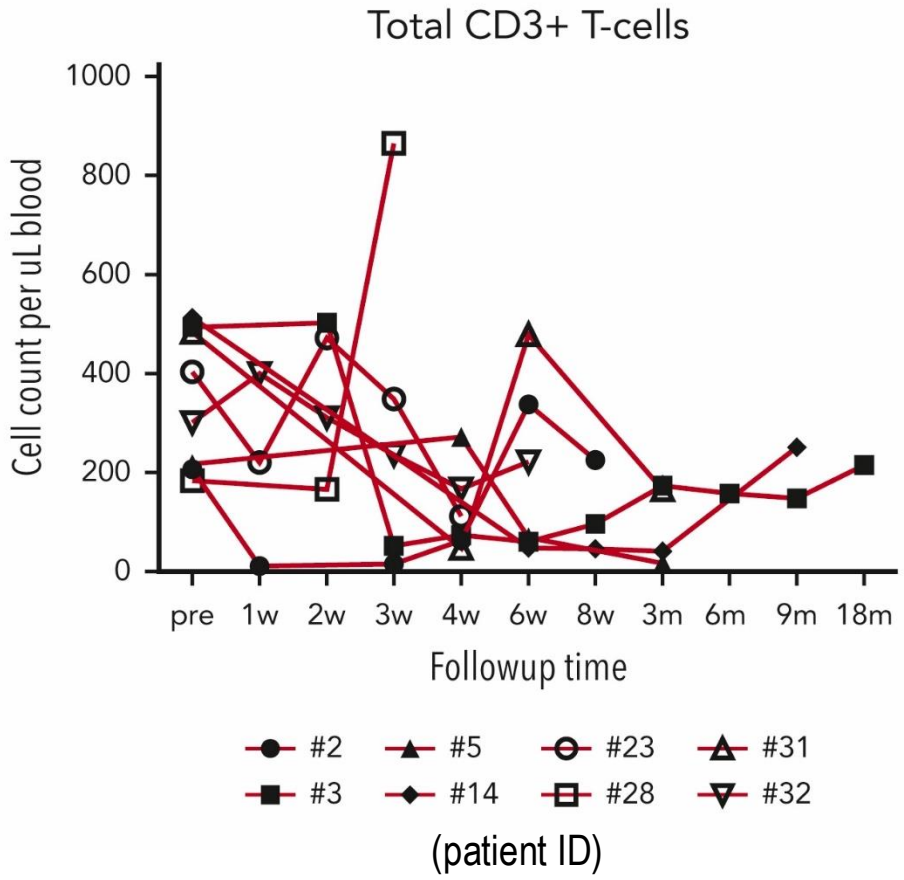


(Hill *et al.*, Blood 2024)

CD5.CART main toxicities and safety

- CRS (4/9)
  - All grade 1-2
- ICANS (1/9)
  - Grade 2
- Other significant AEs:
  - Mostly cytopenias due to chemotherapy
    - 3 prolonged cytopenias
  - Infections requiring treatment
    - 2 bacteremias
    - 1 CMV reactivation

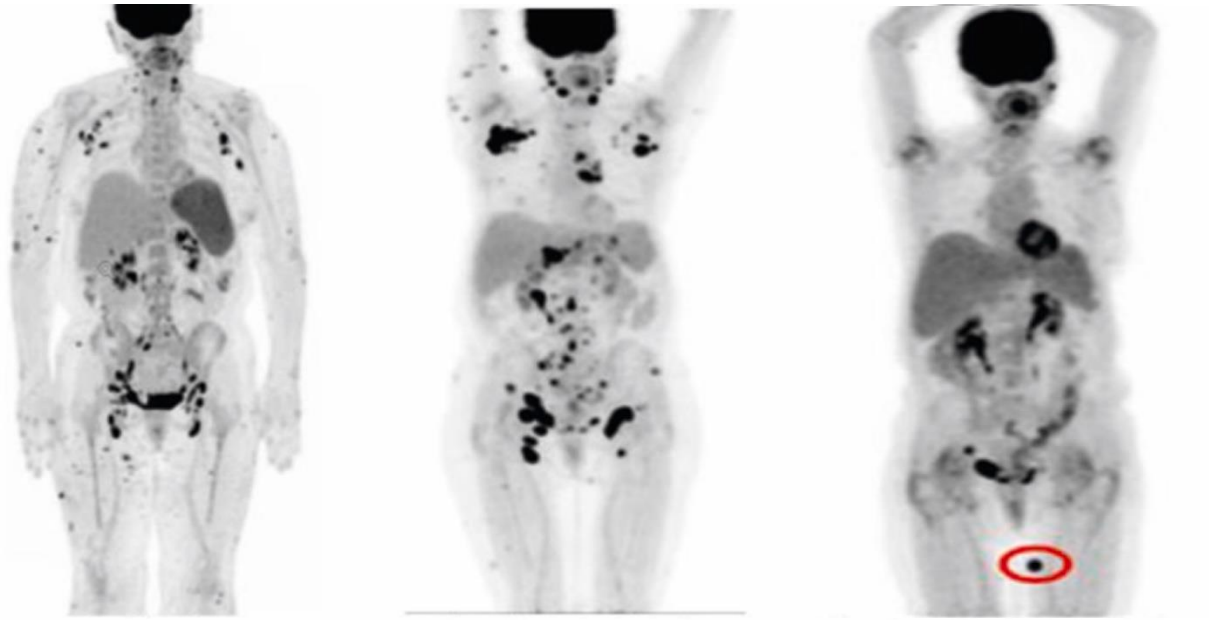




(Hill *et al.*, Blood 2024)

CD5.CART tumor responses

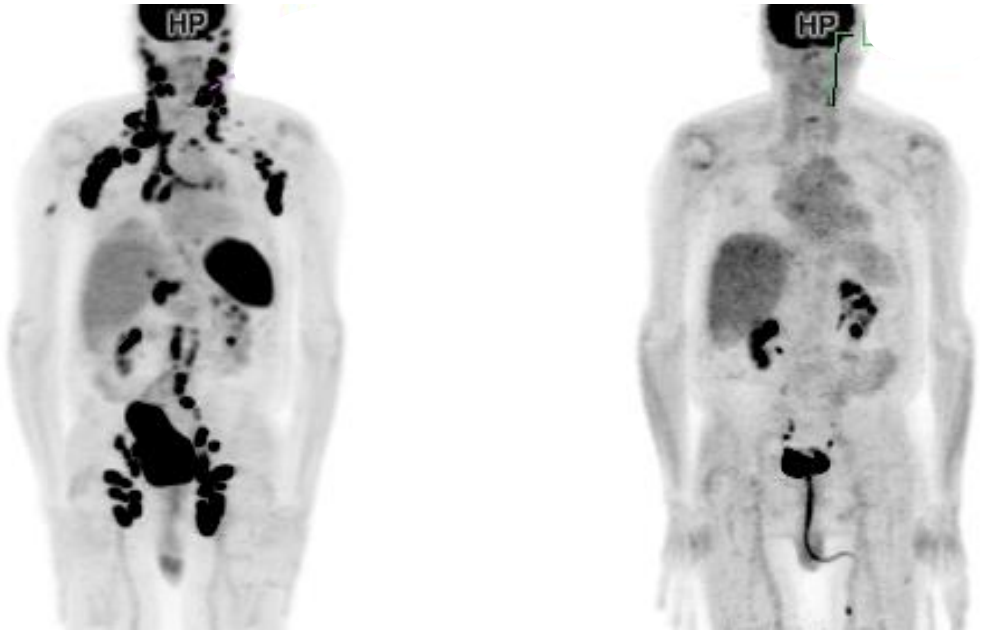
Patient #5, AITL, DL2



Pre-infusion | 4 wk post | 8 wk post

Axillary and inguinal LN biopsy:
necrosis and infiltration by CD5.CAR-T

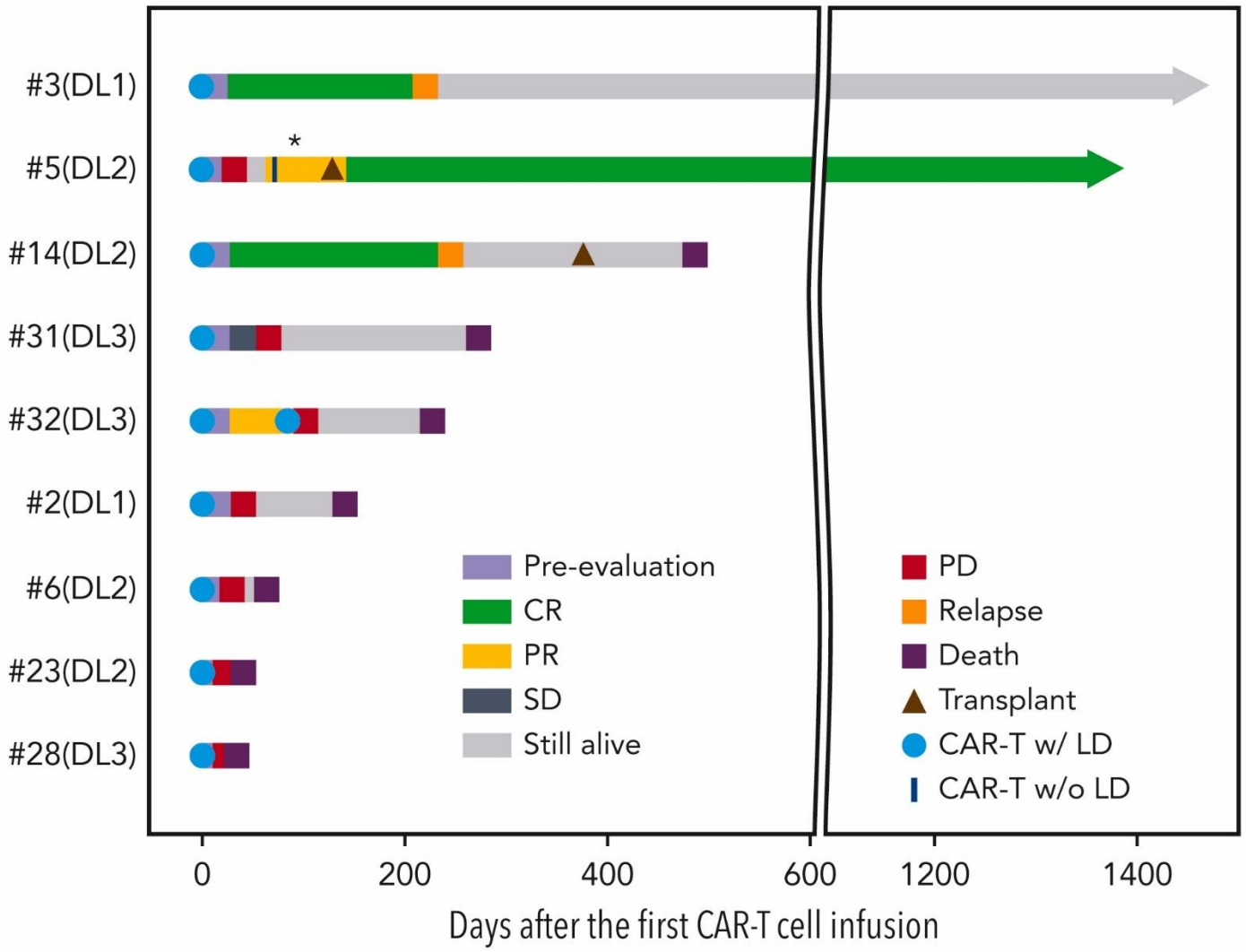
Patient #14, PTCL NOS, DL2



Pre-infusion | 4 wk post-infusion

Summary of CD5.CART responses

DL	Dose	N	CR	PR
1	1×10^7	2	1	–
2	5×10^7	4	1	1
3	10×10^7	3	–	1
All		9	2	2



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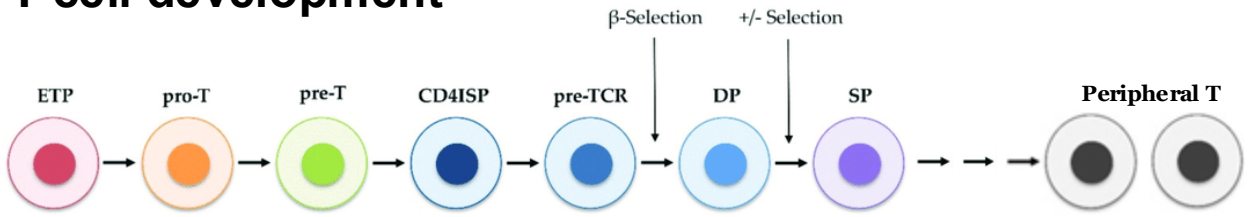
T-cell development



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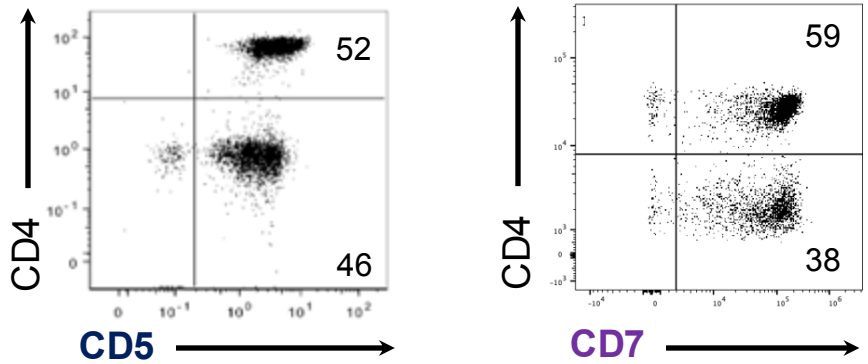
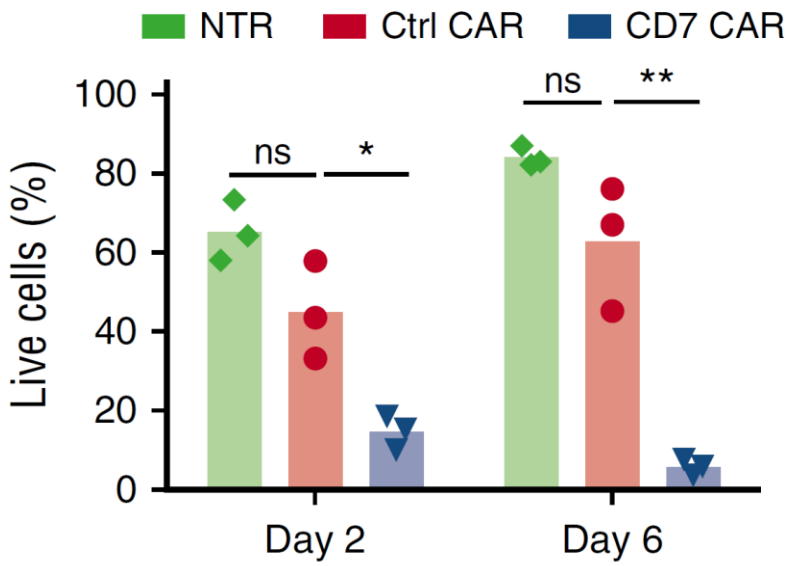
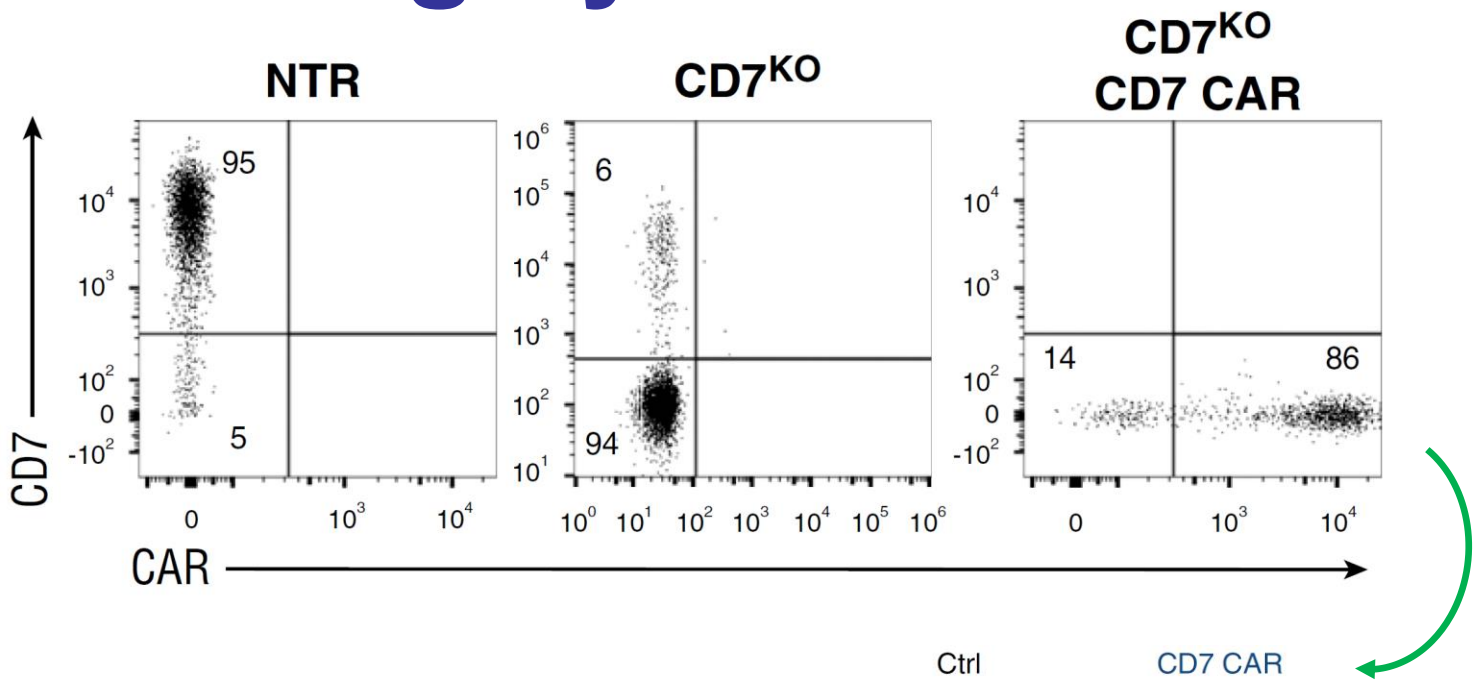


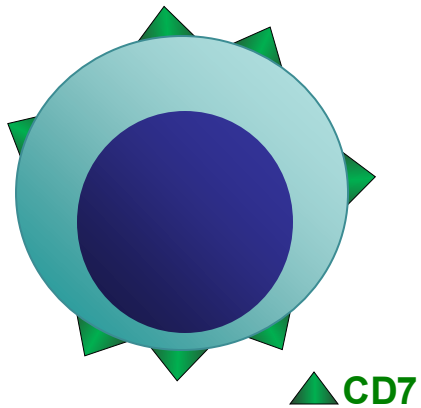
CD7.CART can be highly fratricidal

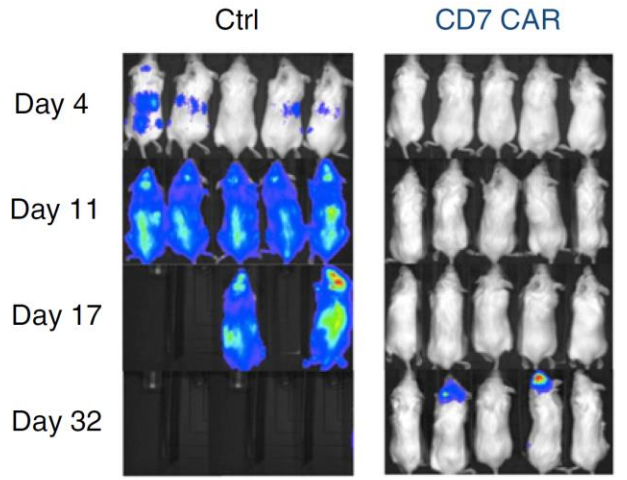
CAR T-cells





- CD7 CRISPR-Cas9 KO allowed expansion of CARTs that are cytotoxic for T cell tumor lines
- But increased complexity of GMP manufacture…

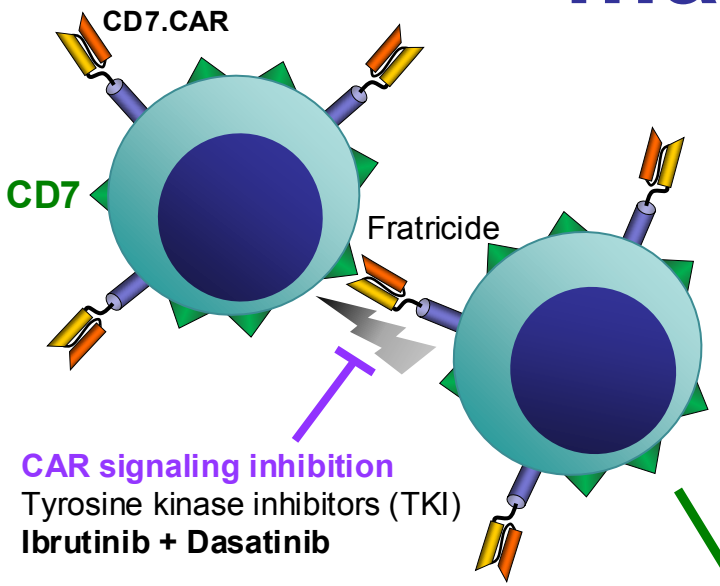




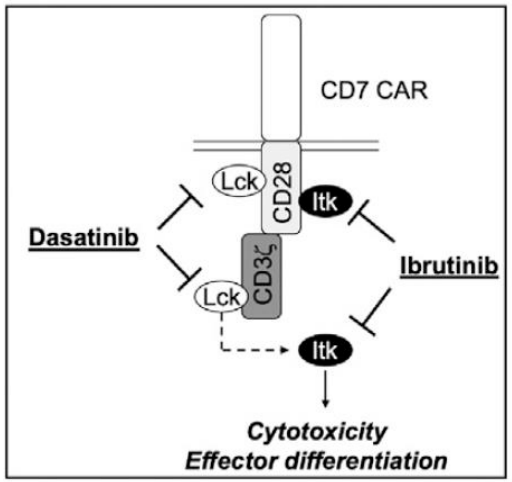
CCRF (CD7+)

(Gomes-Silva *et al.*, Blood 2017)

Functional CD7.CARTs can be made without gene editing



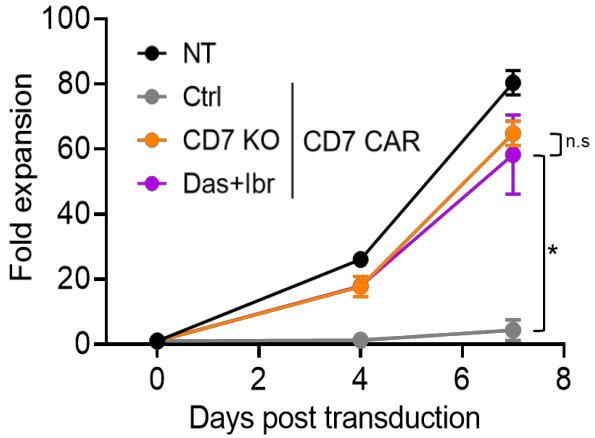
CAR signaling inhibition
Tyrosine kinase inhibitors (TKI)
Ibrutinib + Dasatinib



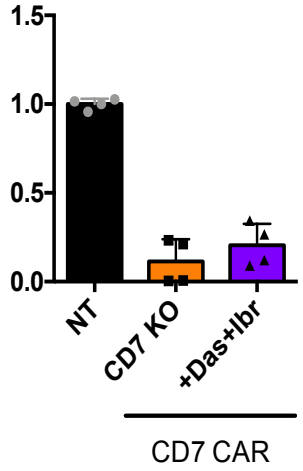
Non-edited (NE) CD7.CARTs

90-95% CD7^{+}
5-10% CD7^{-}

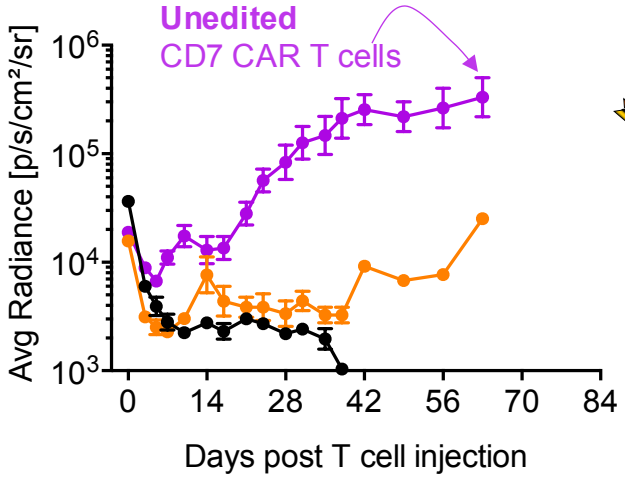
CAR T-cell expansion



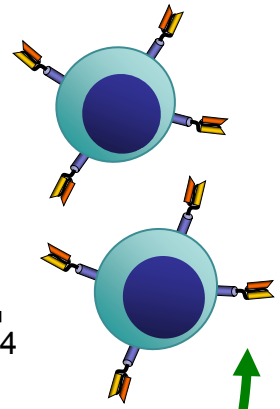
Cytotoxicity (Jurkat)



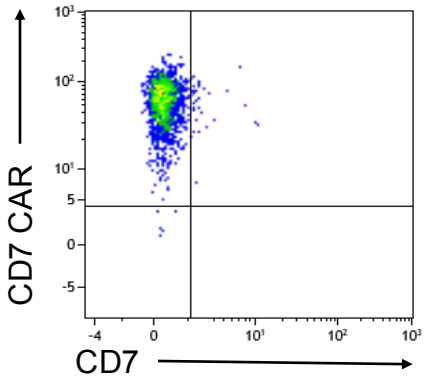
In vivo persistence



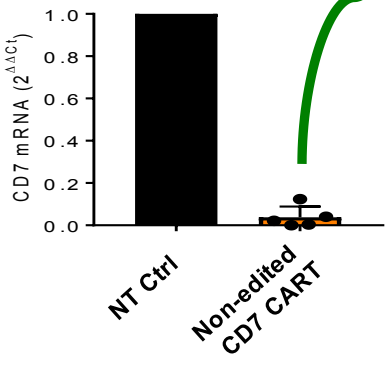
Gradual selection in vivo for naturally CD7^{-} CART



CD7 CART (day 60)

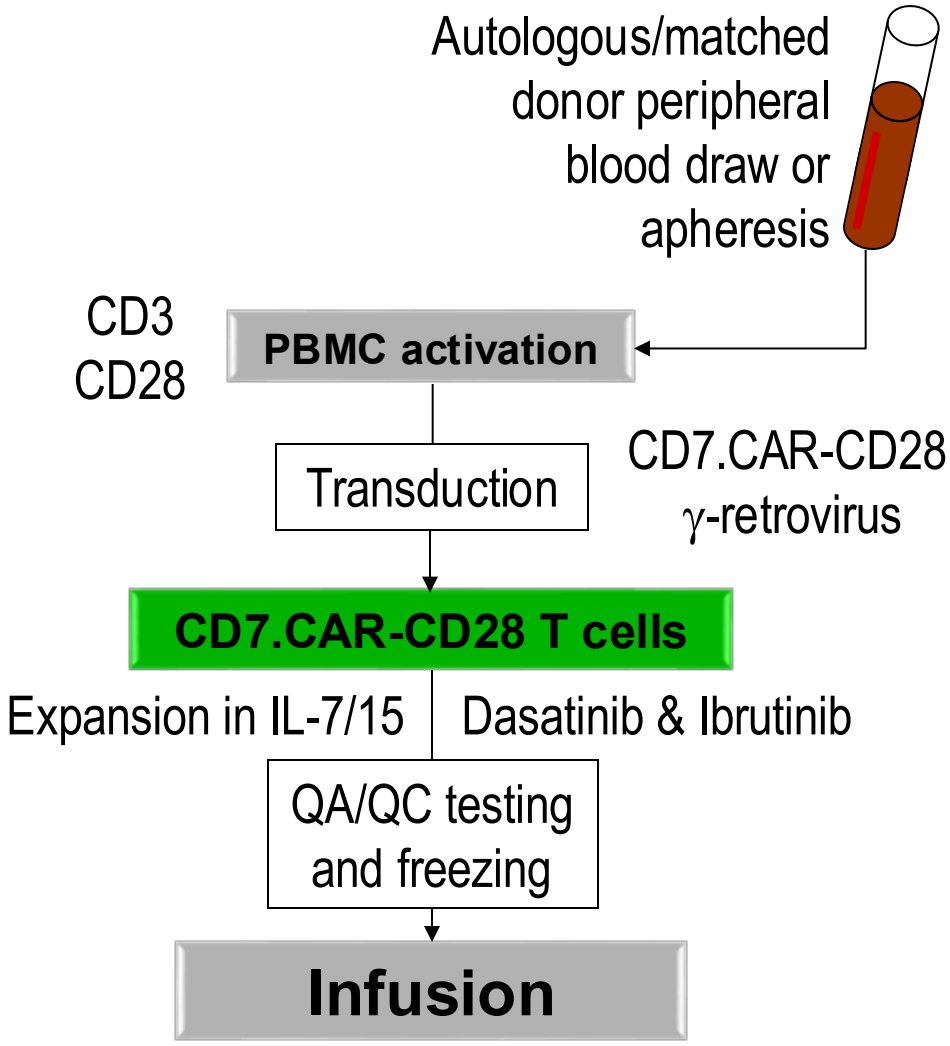


CD7 mRNA (day 60)



(Watanabe *et al.*, Mol Ther 2023)

NE-CD7.CART – CRIMSON trial (NCT03690011)



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Other CD7.CART studies for TCL/ALL

Study	Number of patients	CART source	Strategy	CR Rate
Y Hu et al.[1]	11	Random allo donor	Multiple (CD7 KO, TRAC KO, …)	64%
Y Tan et al.[2]	40	Matched allo donor	CD7 ER retainer	85%
S Li et al.[3]	12	Random allo donor	Multiple (CD7 KO, TRAC KO, …)	92%
X Zhang et al.[4]	60	Autologous	Spontaneous CD7 retention	94% (BM) 56% (EMD)
A Ghobadi et al.[5]	18	Random allo donor	CD7 KO, TRAC KO	39%
B Oh et al.[6]	17	Autologous	CD7 ER retainer	94%

- ~95% CRS, but mostly G1; ICANS ~5%, and mostly G1
- Multiple different strategies to avoid fratricide, GVHD, rejection, …

[1]Cell Res 2022, [2]Blood 2022 & J Hematol Oncol 2023, [3]Leukemia 2023, [4]Am J Hematol 2023, [5]Blood 2023, [6]Nat Med 2024

Conclusions

- Adoptive transfer of autologous (and allogeneic) CD5.CAR-T and CD7.CAR-T cells is feasible, safe, and potentially clinically effective in TCL
  - Several strategies can be exploited to circumvent fratricide and other potential challenges
  - CAR-T cells can be detected at sites of disease and expand in peripheral blood
  - No persistent T cell aplasia seen in most studies, but many use CART as bridge to HSCT
- More patients and longer follow-up are needed for validation

Acknowledgments

Max Mamonkin
Royce Ma
Tyler Smith
Lina Yang
Madhuwanti Srinivasan
Phillip Burkhardt
Diogo Gomes-Silva

Cliona Rooney
Malcolm Brenner
Helen Heslop

Clinical Research
LaQuisa Hill
Rayne Rouce
Premal Lulla
George Carrum
Rammurti Kamble
Martha Arredondo
Bambi Grilley

Statistics
Tao Wang
Jessie Wu

GMP Laboratories
Adrian Gee
Huimin Zhang
Birju Mehta
Silvana Perconti
Sreerekha Venu
Ka Liu

GLP Laboratories
Sachin Thakkar
Maria Isabel
Ana Elizondo

QA
Natasha Lapteva
Sara Richman

QC
Debbie Lyon

NGVL for RCR

All donors & patients

CAGT CENTER FOR CELL AND GENE THERAPY

Baylor College of Medicine · Texas Children's Hospital · Houston Methodist

Funding: NIH Lymphoma SPORE (Heslop), NIH Cancer Center grant (Heslop/Reddy), National Gene Vector Repository (Indiana University)