Comprehensive Cancer Center
Tübingen-Stuttgart

Post EBMT 2026

GMP-Manufacturing, Point of care CAR-T

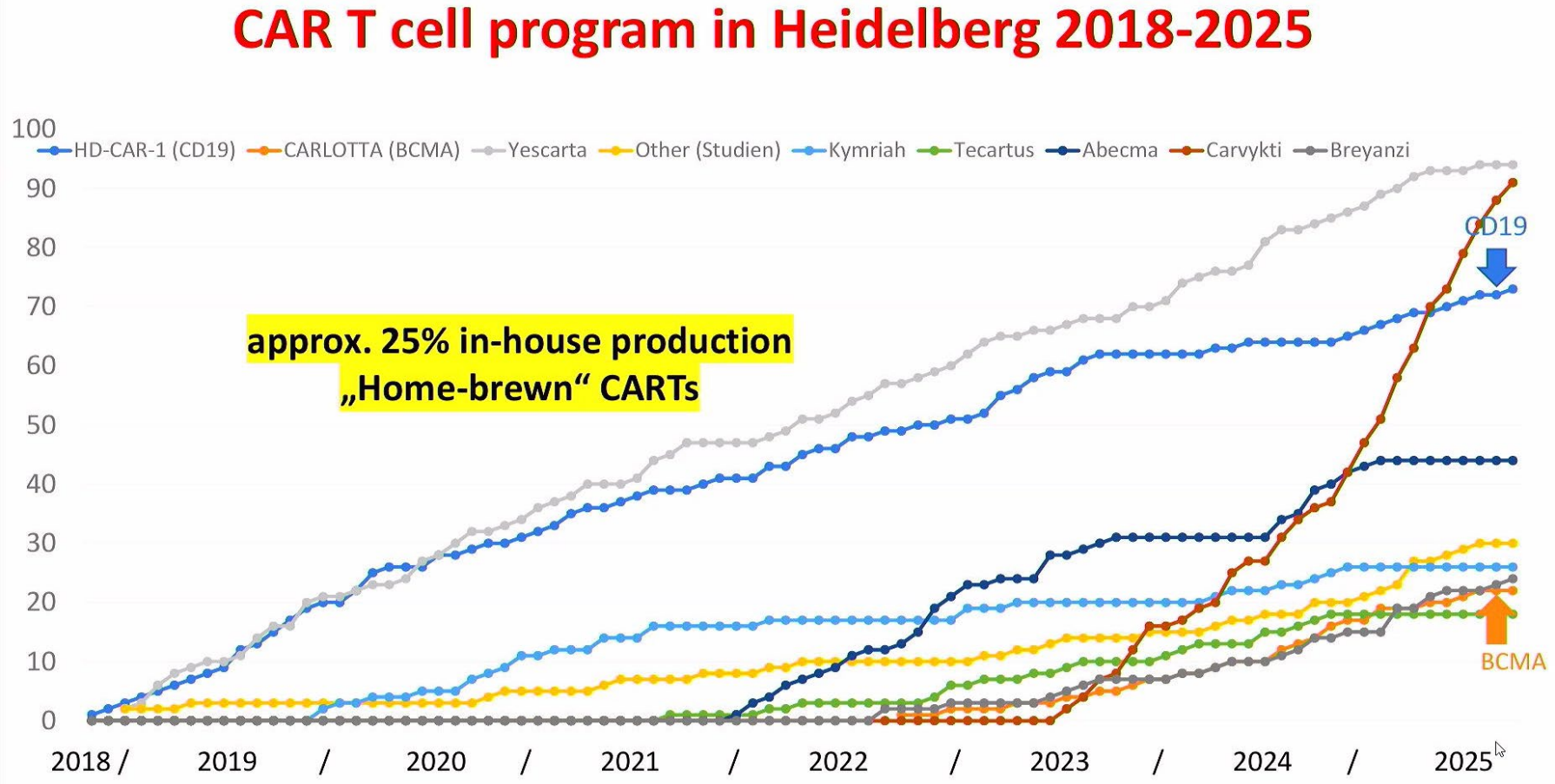
Dr. Luca Hensen, Gemeinsames Stammzell- und Immunlabor

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Comprehensive
Cancer Center
Tübingen - Stuttgart

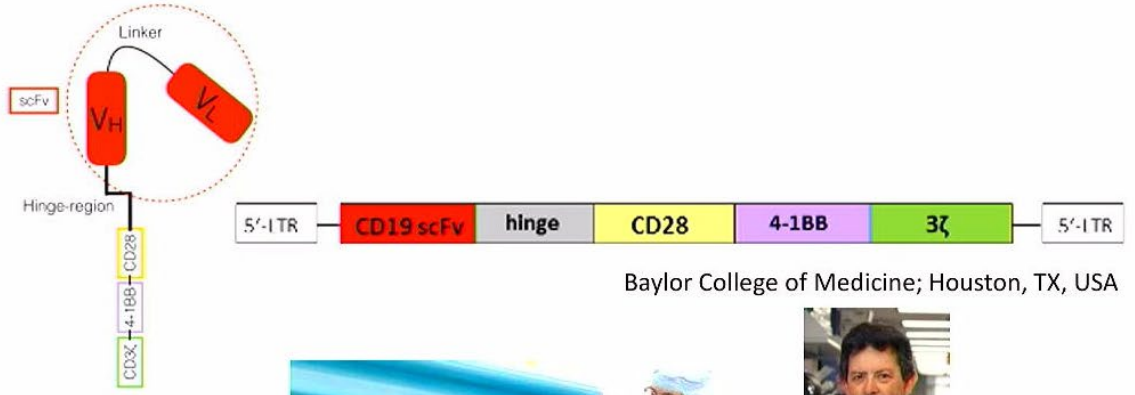
Universitätsklinikum
Tübingen

Hospital exemption for heidagenlecleucel (Heidi-cel), a third generation CD19. CAR T cell product in Germany- Michael Schmitt



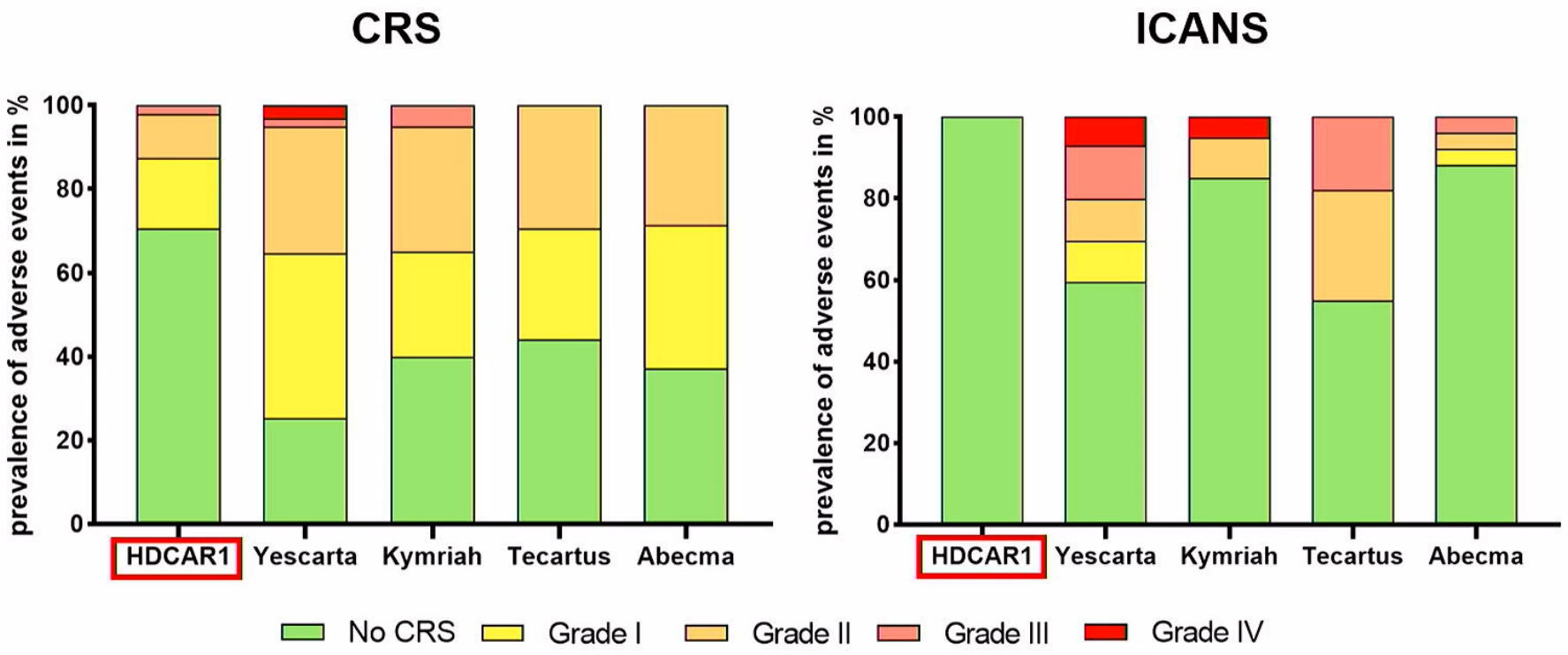
HD-CAR-1: Heidelberg CAR Trial 1 (Heidagen Lecleucel)

- **Third-generation** CD19 CAR
- Academic CAR T cell trial
- CAR T cell therapy ***in-house***
- Entities
  - ALL: 14
  - CLL: 11
  - Other NHL: 18
- Lymphodepleting therapy
- Initiated 09/2018



Baylor College of Medicine; Houston, TX, USA

HD-CAR-1: Exquisite safety profile



CRS and ICANS prevalence of different CAR-T products.
Incidence of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome depicted for patients who received commercially available CAR-T products Yescarta®, Kymriah® ,Tecartus®, Abecma® in comparison to heidagen lecleucel (depicted as HDCAR1).
Patient numbers: HDCAR1 n=44, Yescarta® n=68, Kymriah® n=28,Tecartus® n=13, Abecma® n=31

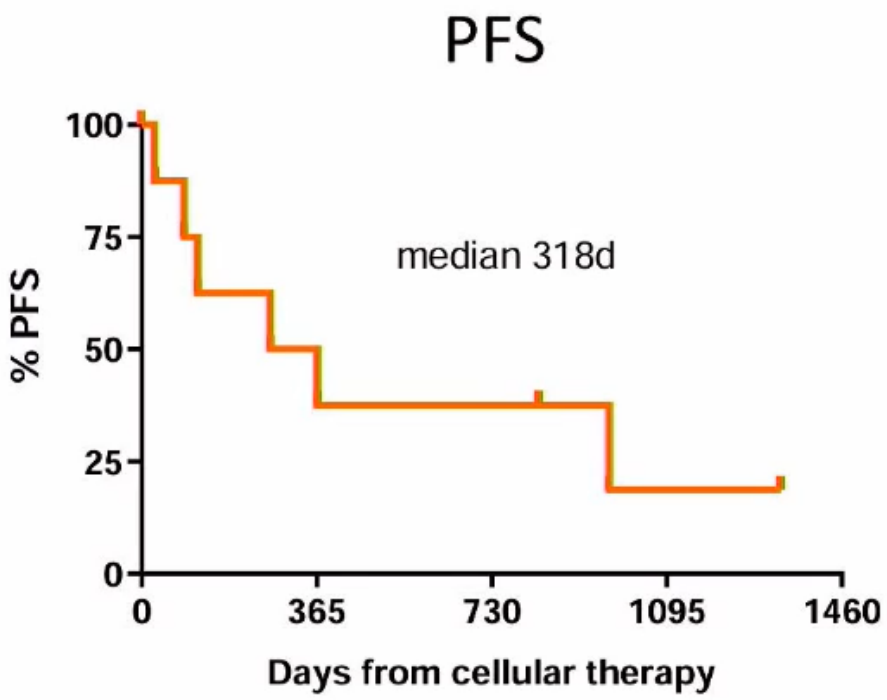
Kuhn H/Schmitt M, unpublished

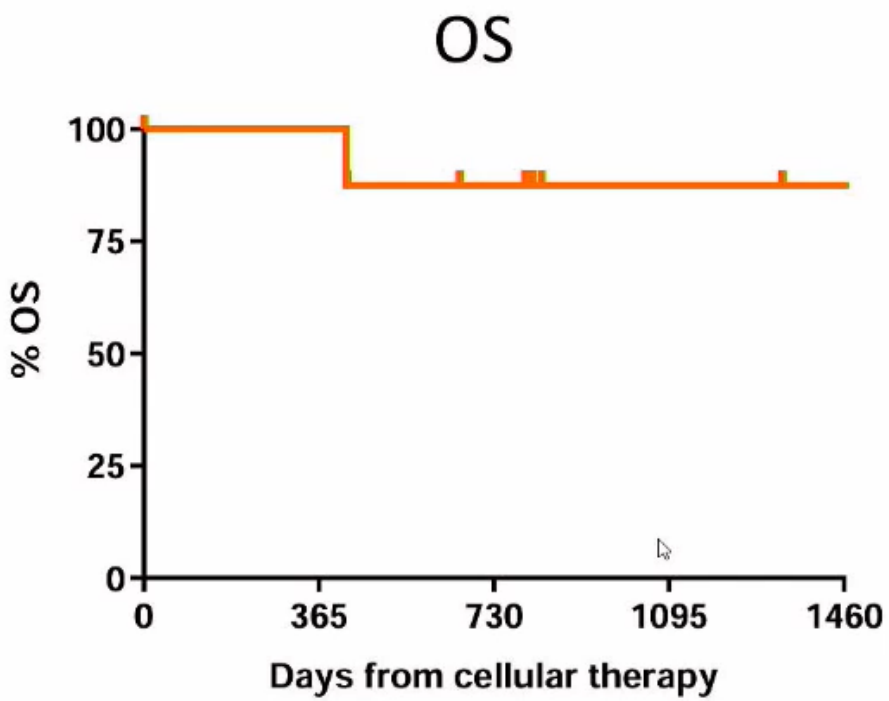
Leukemia (2024) 38:2419–2428; https://doi.org/10.1038/s41375-024-02392-7

UNIVERSITÄTS KLINIKUM HEIDELBERG

Third-generation anti-CD19 CAR T cells for relapsed/refractory chronic lymphocytic leukemia: a phase 1/2 study

Patrick Derigs[1✉], Maria-Luisa Schubert[1], Peter Dreger[1], Anita Schmitt[1], Schayan Yousefian[2,3,4], Simon Haas[2,3,4,5,6,7], Caroline Röthemeier[2,3,4], Brigitte Neuber[1], Angela Hückelhoven-Krauss[1], Monika Brüggemann[8], Helga Bernhard[9], Guido Kobbe[10], Albrecht Lindemann[11], Mathias Rummel[12], Birgit Michels[1], Felix Korell[1], Anthony D. Ho[1,5], Carsten Müller-Tidow[1,5] and Michael Schmitt[1,5]





Update 30 Sep 2025

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zuzustellen

18.09.2025

Antrag vom 30.05.2023, eingegangen am 31.05.2023

BESCHEID:

A. Das im Folgenden genannte Arzneimittel wird nach

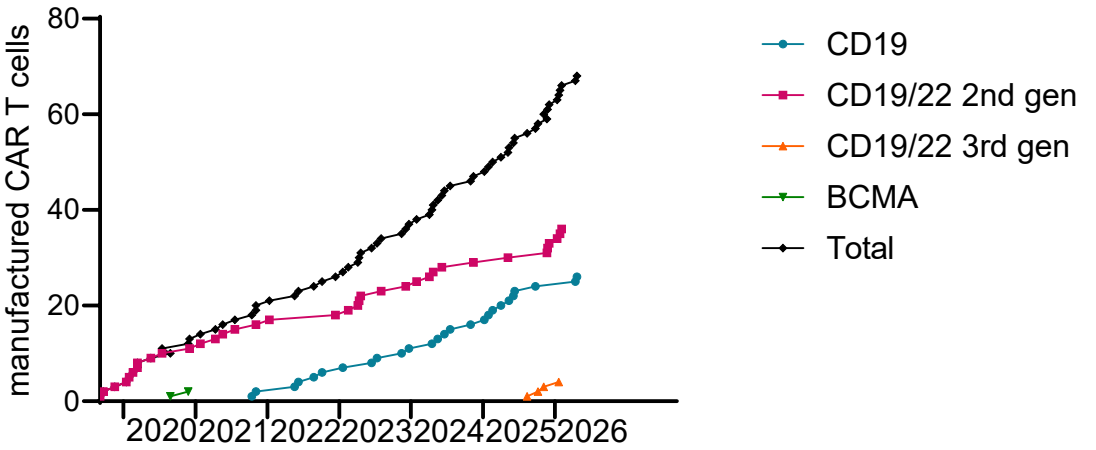
§ 4b Abs. 3 des Arzneimittelgesetzes (AMG)

für das Anwendungsgebiet „Erwachsene Patienten mit rezidivierten oder refraktären CD19+-Erkrankungen des lymphatischen Systems: chronische lymphatische Leukämie (CLL)"

genehmigt und erhält folgende Genehmigungsnummer:

Arzneimittelbezeichnung	Genehmigungsnummer
HD-CAR-19 (Heidagen-lecleucel)	PEI.A.12181.01.1

Academic CAR T manufacturing in Tübingen



§4b manufacturing license - Potential avenue for CAR T cells manufactured in Tübingen

Quo vadis CAR T manufacturing?

02 Advantages of In Vivo CAR-T

华中科技大学同济医学院附属协和医院
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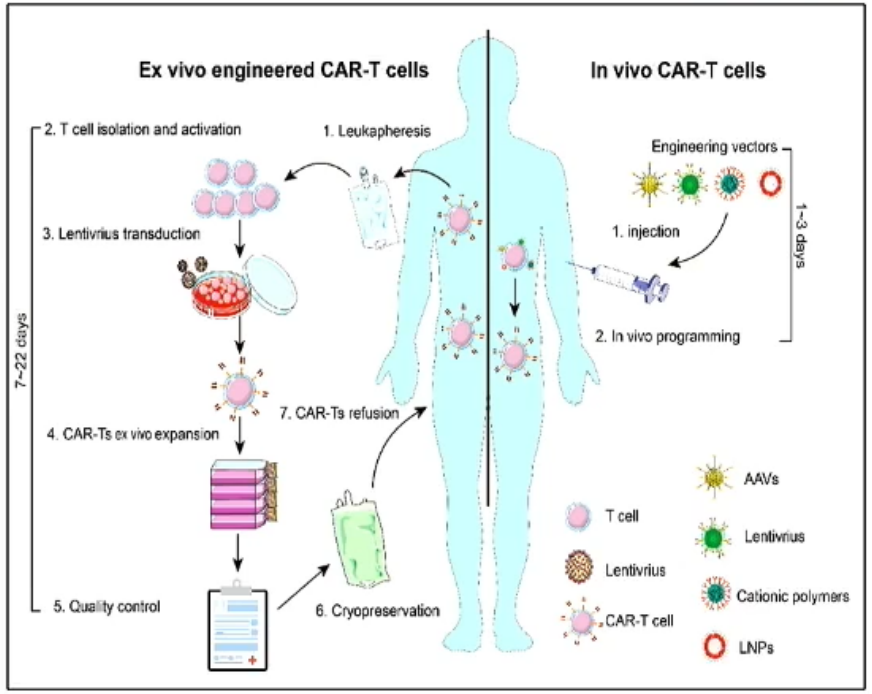
Novel Technology to Overcome the Limitations of Autologous CAR-T ——In Vivo CAR-T

T cells are directly edited in vivo into CAR-T cells within the patient's body using viral vectors or nanocarriers, establishing a new paradigm for CAR-T therapy.



	Autologous CAR-T	Universal CAR-T	In vivo CAR-T
Ex-vivo Customization	Required	Not Required	**Not Required**
Cell Source	Selected and Activated T Cells	Healthy Donors	**In vivo T Cell Repertoire**
Manufacturing timeline	3-4 Weeks	Short	**None**
Lymphodepletion Pretreatment	Required	Required	**Not Required**
Batch Yield	One Unit per Batch, Customized	Up to 100 Units per Batch	**Up to 1,000+ Units per Batch**
Drug Price	High	Low	**Low**
Clinical Accessibility	Relatively Low	High	**High**

Mei Heng et al. Adv Sci 2023

In-vivo B-cell maturation antigen CAR-T-cell therapy for relapsed or refractory multiple myeloma – Heng Mei

03 Wuhan Union Hospital In Vivo CAR-T — ESO-TO1

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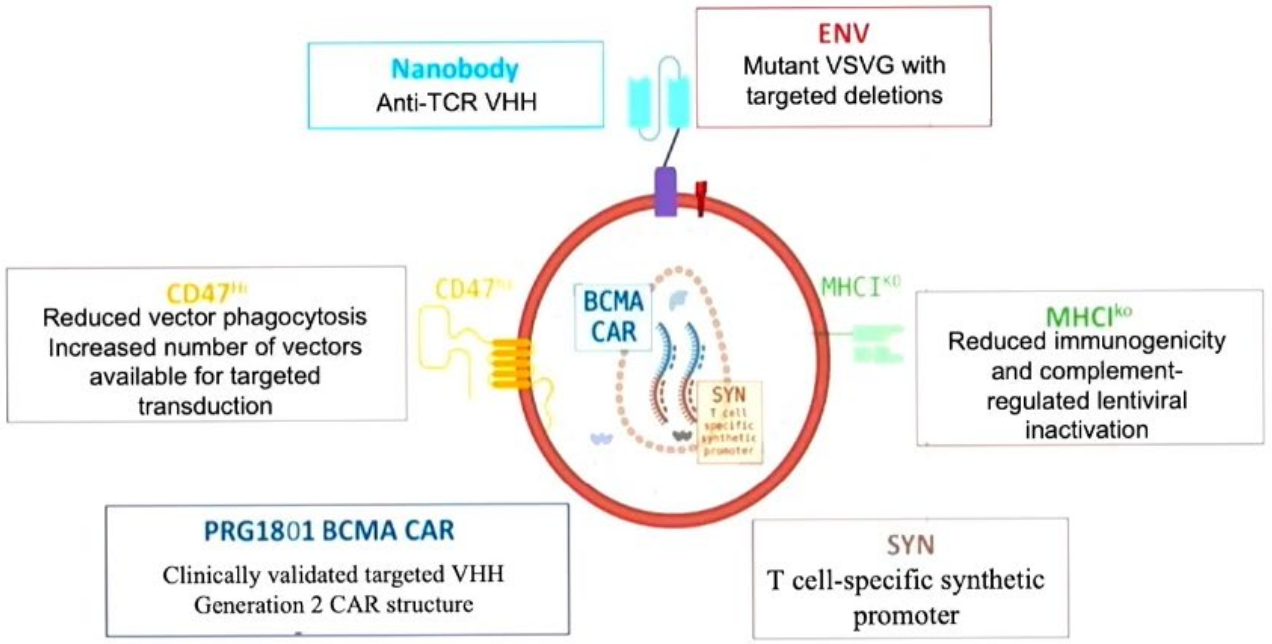
◆ **In Vivo CAR-T ESO-T01 is a third-generation, non-replicating, self-inactivating lentiviral vector.**

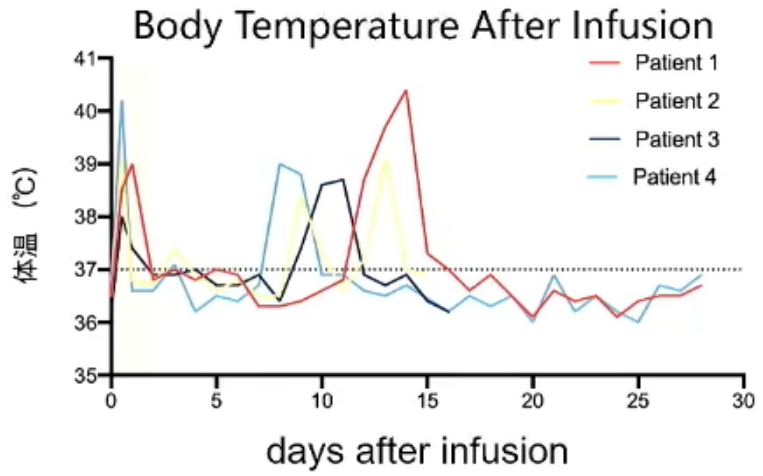


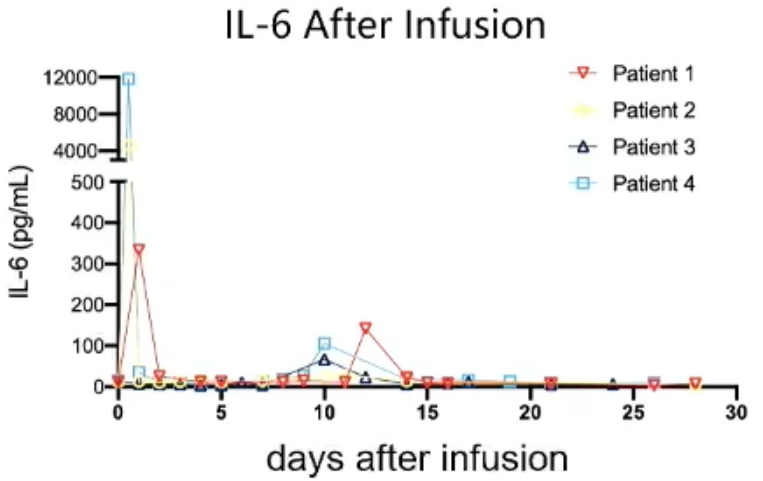
华中科技大学同济医学院附属协和医院 EsoBiotec PREGENE

03 Wuhan Union Hospital In Vivo CAR-T clinical trial — Characteristic

Patient Number	Patient 1	Patient 2	Patient 3	Patient 4
Age/Gender	69/Male	40/Female	67/Female	59/Male
ECOG Score	2	0	1	1
Disease Subtype	κ Light Chain Type	κ Light Chain Type	λ Light Chain Type	IgG-λ Type
R-ISS Stage	III	I	II	II
DS Stage	IIIA	IIIA	IIIA	IIIA
Genetic Abnormality	None	None	None	t (4;14), 1q21 Amplification
Frontline Treatment	4 (Pent-refractory)	2 (Sequential ASCT)	4	4 (BCMA-GPRC5D CAR-T)
Intramedullary Disease	0.5%	0%	20%	72.61%
Cerebrospinal Fluid Involvement	51.1%	0%	23.5%	97.28%
Extramedullary Involvement	Extensive	Left Parasternal, Left Paravertebral	Extensive	Left Dorsal Pleura
Largest Measurable Lesion	11.6 × 3.3 cm	5.5 × 5.2 cm	9.3 × 6.4 cm	7.1 × 3.7 cm
Time between Screening to Infusion	8 days	3 days	11 days	5 days

03 Wuhan Union Hospital In Vivo CAR-T clinical trial — Safety





Prophylactic Medications and Adverse Reactions

	Patient 1	Patient 2	Patient 3	Patient 4
Prophylactic medication	Diclofenac sodium suppository 25 mg p.r . Promethazine hydrochloride 25 mg i.m.	Diclofenac sodium suppository 25 mg p.r. Promethazine hydrochloride 25 mg i.m. Dexamethasone 20mg i.v.gtt	Diclofenac sodium suppository 25 mg p.r. Promethazine hydrochloride 25 mg i.m. Dexamethasone 20mg i.v.gtt	Diclofenac sodium suppository 25 mg p.r. Promethazine hydrochloride 25 mg i.m. Dexamethasone 20mg i.v.gtt
Early adverse reactions (D0 - D2)	Fever, hypotension, hypoxemia, disturbance of consciousness, tremor of both upper limbs (CRS grade 3)	Fever, hypotension, hypoxemia, headache (CRS grade 3)	Fever, muscle soreness (CRS grade 1)	Fever, hypoxemia, hypotension, epistaxis (CRS grade 3)
Late adverse reactions (D3 - D28)	CRS grade 1 Pleural effusion Edema of both lower limbs	CRS grade 1 Nausea Paresthesia	CRS grade 1	CRS grade 1 ICANS grade 1

“ Two Phase CRS ”

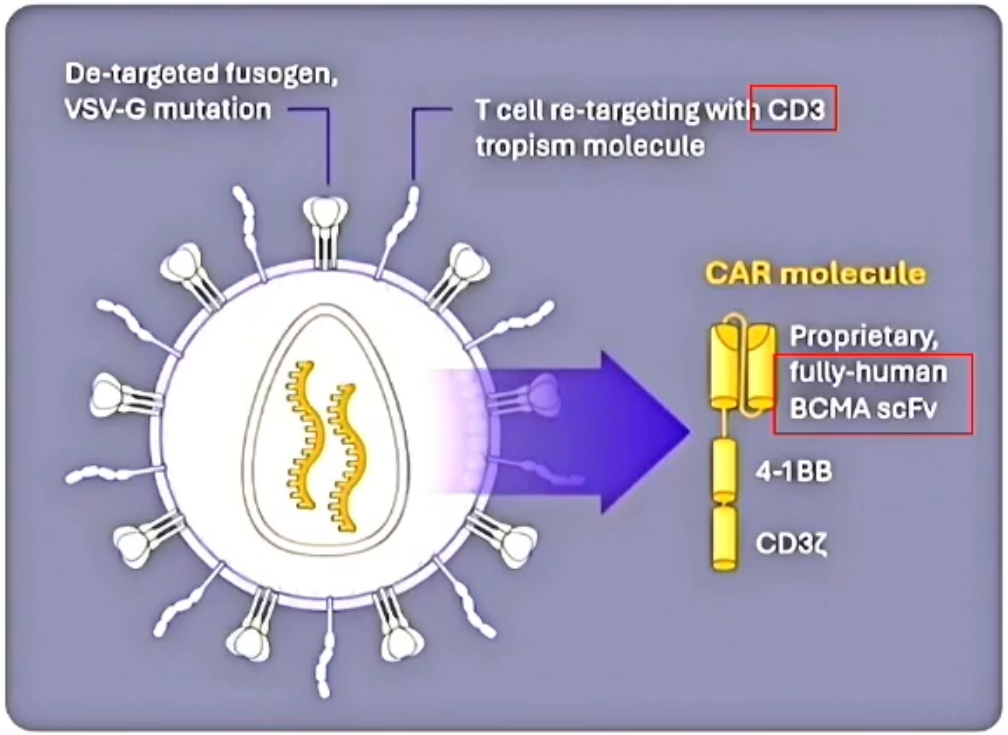
- **Early Phase:** Grade 3 CRS, onset within 3-6 hours after infusion, lasting for 6-18 hours
- **Late Phase:** Grade 1 CRS, onset 8-12 days after infusion, lasting for 1-4 days
- All the above symptoms improved after anti-inflammatory and symptomatic treatment

03 Wuhan Union Hospital In Vivo CAR-T clinical trial — Efficacy

Patient	H001	H002	H003	H004
D28	VGPR 1.Blood and urine electrophoresis and free light chains (-) 2. MRD: BM (-) , CSF (-) 3. EMD PR	sCR 1. Regression of paraosseous plasmacytoma	PR 1.Blood and urine electrophoresis and free light chains (-) 2. MRD: BM (-) , CSF (-) 3. EMD PR	PR 1.Blood and urine electrophoresis and free light chains (+) 2. MRD: BM (-) , CSF (+) 3. Regression of paraosseous plasmacytoma
M2	sCR 1.EMD (-)	sCR 1. Regression of paraosseous plasmacytoma	PR	PR
M3	sCR 1.EMD (-)	sCR	PR	PR
Longer Follow-up	Relapsed at 4M and withdrew to receive chemotherapy, but failed to achieve a response, died of disease progression at 7M	15M sCR 	Relapsed at 3M and withdrew to receive ex vivo BCMA/GPRC5D CAR-T therapy, then achieved VGPR at M1 post-infusion, but died of intracranial hemorrhage (6M)	Relapsed at 3M (MRD+ and CSF) and withdrew to chemotherapy, achieved sCR and (7M), died of disease progression at 10 M

KLN-1010: a modified LVV generating anti-BCMA CAR-T cells *in vivo*

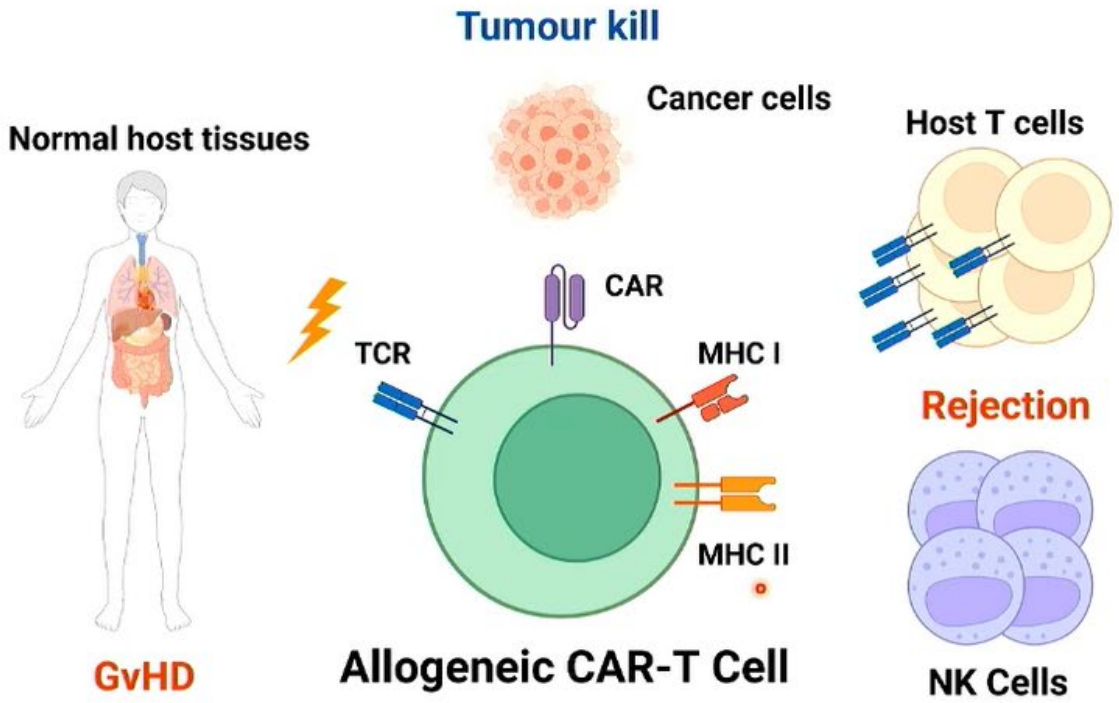
- **Envelope-modified, replication-incompetent, self-inactivating lentiviral vector**
- **De-targeted VSV-G fusogen** avoids delivery to LDL-expressing cells while maintaining high transduction efficiency
- **Precise re-targeting to T cells** with a CD3 scFv; avoids liver uptake and drug sinks
- Anti-BCMA CAR was **selected based on high levels of activity to BCMA-positive tumors**



Could allogeneic CAR-T cells reduce costs and increase global access to cellular therapy? – Paul Maciocia

UCL

Barriers to allogeneic CAR-T cells



Evolution of Studies – escalating complexity

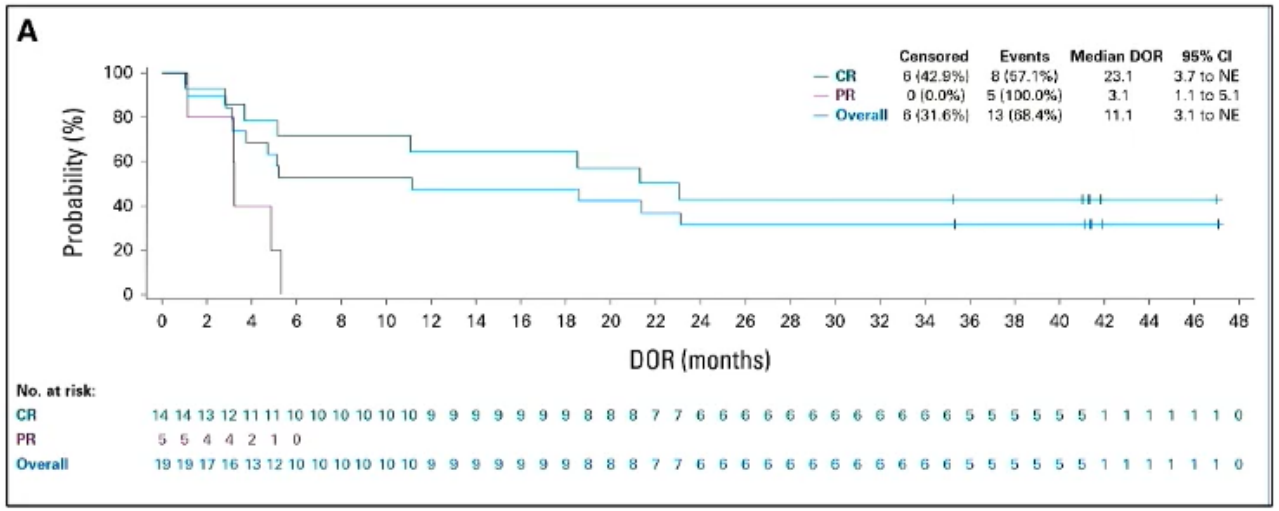
1. KO TCR only - GvHD
2. KO TCR + B2m – GvHD/CD8
3. KO TCR + B2M/ CIITA – GvHD/CD8/CD4
4. KO TCR + B2M/CIITA + HLA-E/CD47 – GvHD/ CD4/CD8/NK

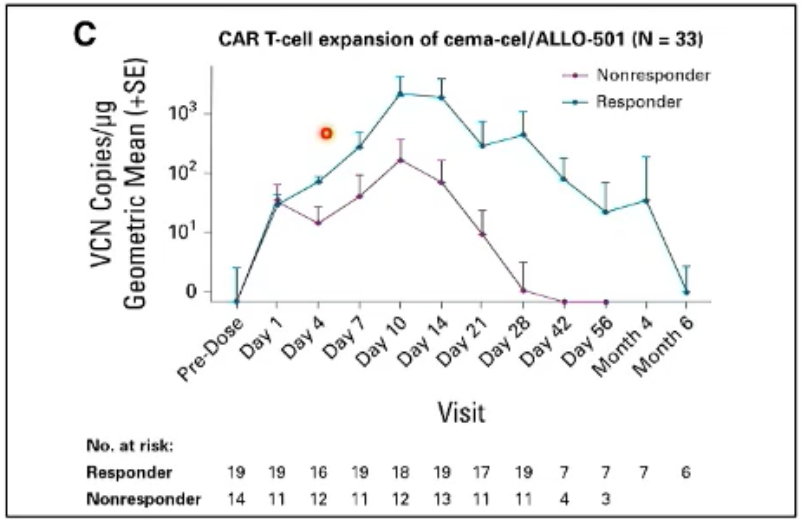
Early Clinical Data Summary

Product	Company	Target	Platform	Trial	N	Setting	ORR	CR	12m PFS	Gr≥3 CRS	GvHD	Status
Vispa-cel	Caribou	CD19	CRISPR chRDNA	ANTLER	22[1]	2L LBCL	82%	64%	51%	<5%	0%	Ph3 planned (best allo)
Cema-cel	Allogene	CD19	TALEN	ALPHA /ALPHA2	33[2]	≥2L LBCL	67%[3]	58%[3]	—	0%	0%	Pivotal Ph2 (ALPHA3)
CTX110	CRISPR Tx	CD19	CRISPR Cas9	CARBON	27[4]	≥2L LBCL	67%	41%	—	0%	0%	Ph1 (deprioritised)
Eti-cel	Cellectis	CD20 /CD22	TALEN	NATHALI	~8	R/R B-NHL	~88%	~63%	—	—	—	Ph1 (early)
Azer-cel	Precision	CD19	ARCUS	Ph1/2a	11[5]	Post-CAR NHL	100%	73%	—	0%	0%	Stalled
FT819	Fate	CD19	iPSC	Ph1	10	≥3L LBCL	38%	25%	—	0%	0%	Pivoting to SLE
CTX130	CRISPR Tx	CD70	CRISPR Cas9	COBALT	31[6]	R/R TCL	52%	19%	—	5%	0%	Ph1 (RMAT)
BE-CAR7	UCL/GOSH	CD7	Base editing	Ph1	11	R/R T-ALL	82%[7]	82%[7]	—	9%	0%	Ph1 (NEJM 2025)

Cemacabtagene Ansegedleucel in DLBCL (Alpha Studies)

- CAR-naïve, DLBCL in 3rd line+, 33 patients at P2 dose
- Flu/Cy/ anti-CD52. TRAC and CD52 edits (TALEN)
- 120M CAR-T





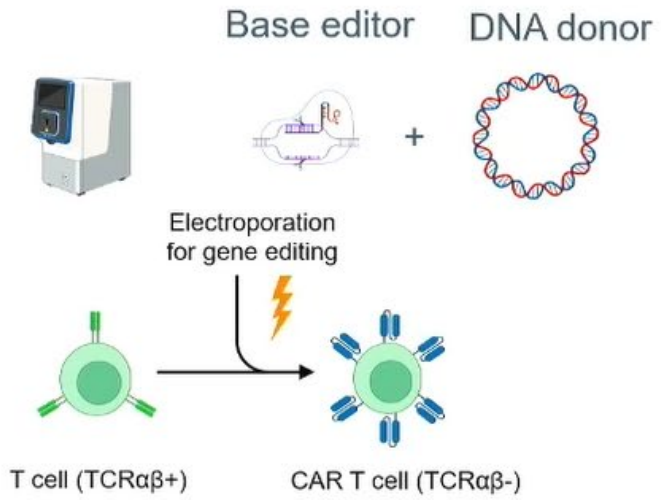
- ALPHA3 – '7th cycle', no FC, target 240 patients – futility analysis due Q1 2026
- Remainder moved to TRAC/B2M/CD70 CAR platform

- Locke et al JCO 2025

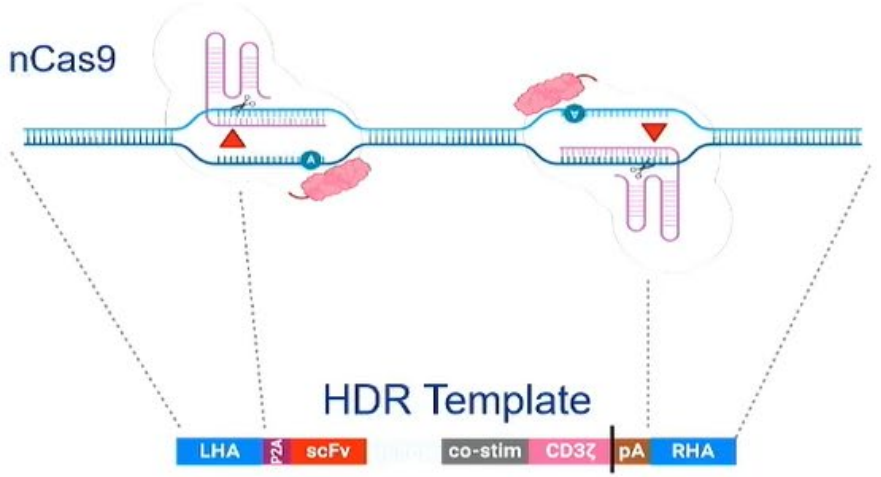
Repurposing base editors for targeted knock-in and simultaneous knockouts to generate multiplex-edited allogeneic CAR-T cells with minimal translocations – Dimitros Laurin Wagner

Could this be achieved with a single intervention / without viruses?

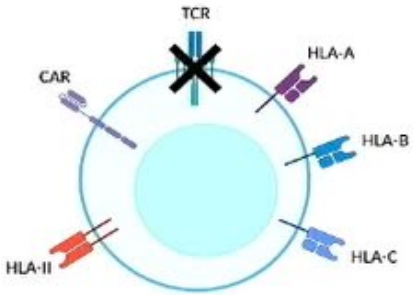
Viktor Glaser



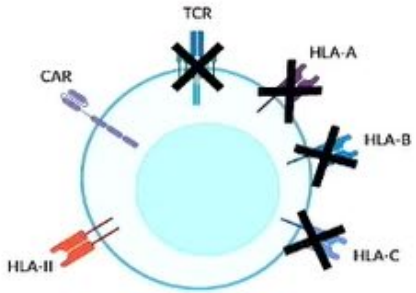
Base Editor mediated Knock-In (BEKI)



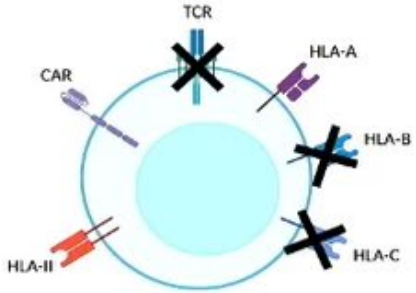
BE-mediated KO of HLA-B and -C for hypoimmunogenic CAR T cells



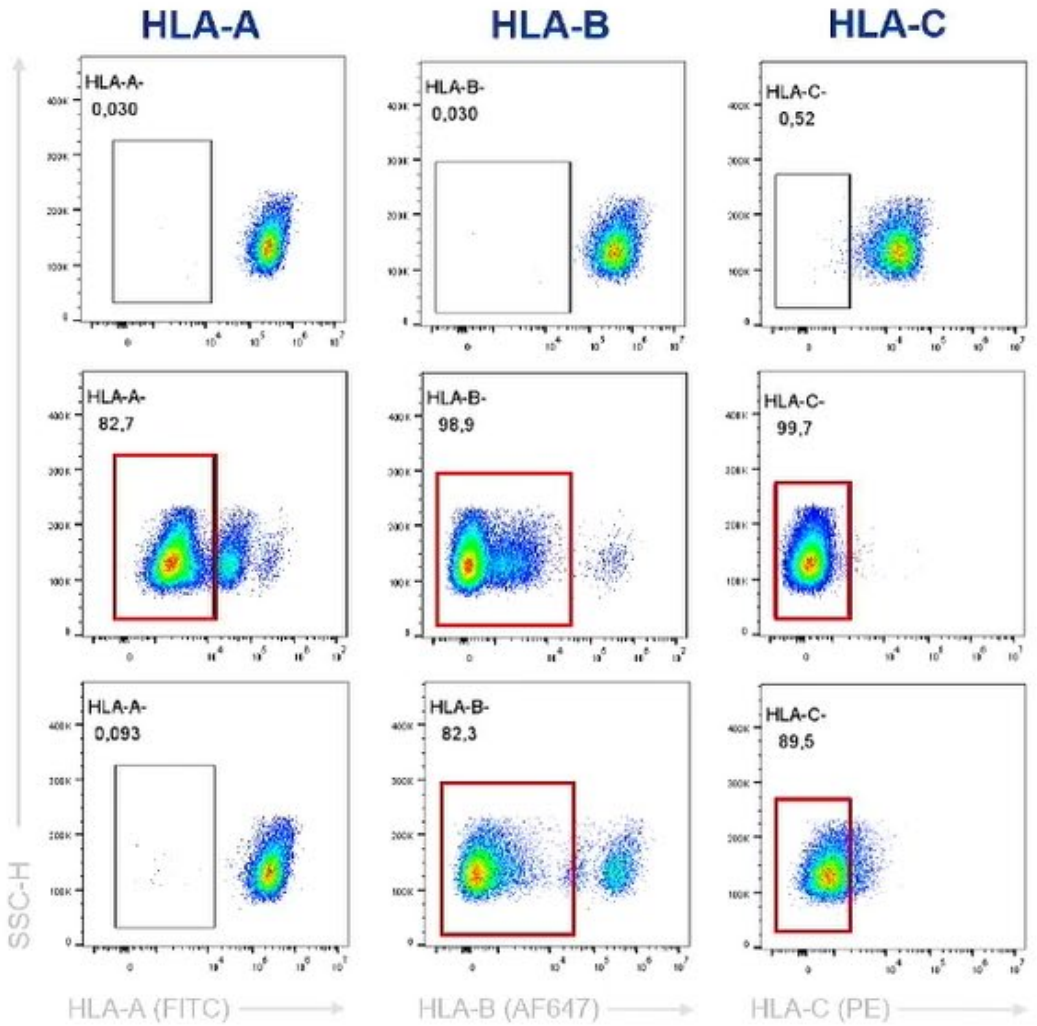
zeta CAR



zeta CAR
+B2M KO



zeta CAR
+HLA-B/C KO



Lily Becker

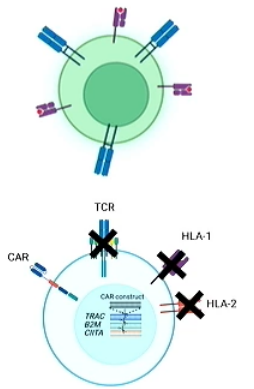
Viktor Glaser

- Complete KO of MHC-I
- Partial KO of MHC-I with retained HLA-A

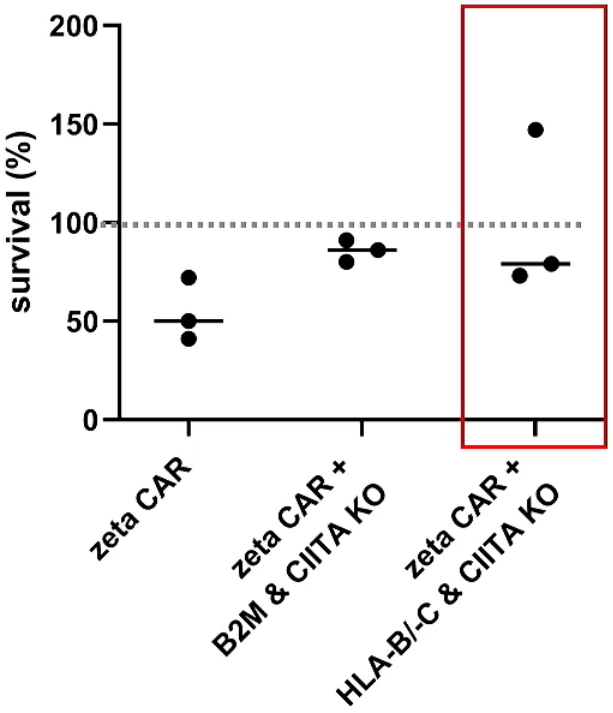
Retaining HLA-alleles protects CAR T cells from both allo-T cell and NK cell rejection

Viktor Glaser

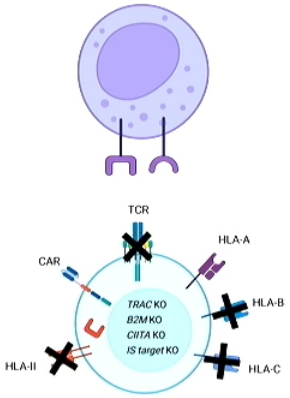
Allo-reactive T cell



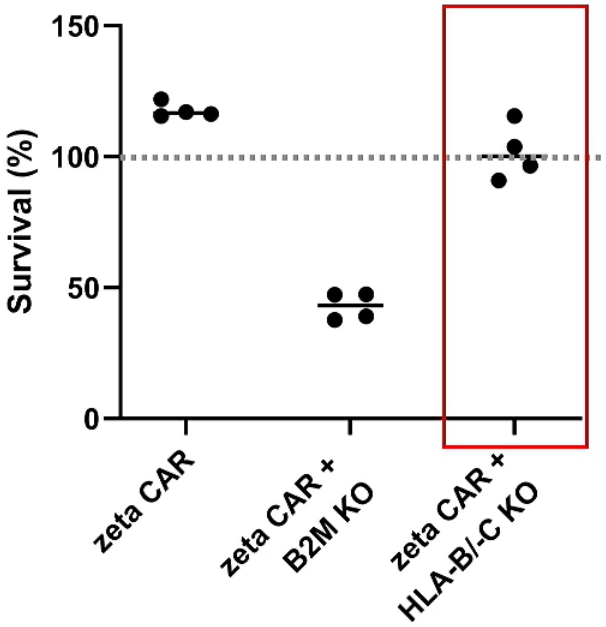
Edited CAR T cell



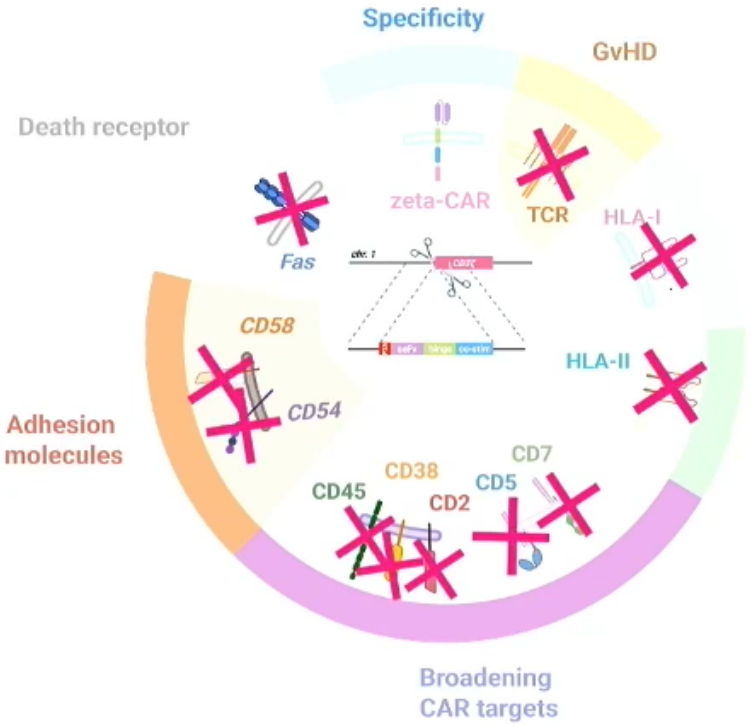
NK cell

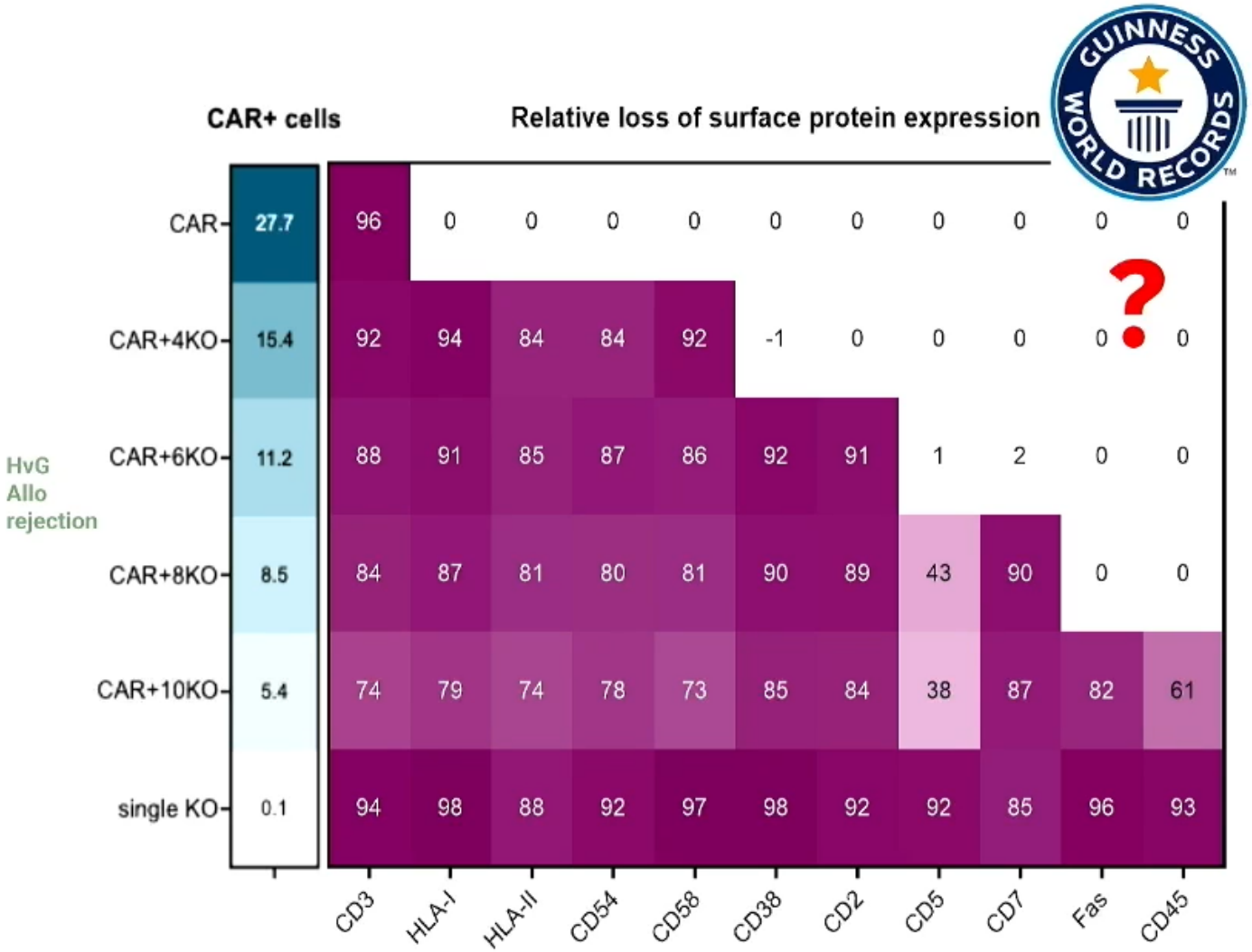


Edited CAR T cell



What is the limit of multiplex editing with base editors?





und am Ende....

Vielen Dank für Ihre Aufmerksamkeit

Universitätsklinikum Tübingen