4th Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2024

CUNEO
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Spazio Incontri Fondazione CRC

CAR-T in AML: ready for prime time?

Sarah Tettamanti, PhD

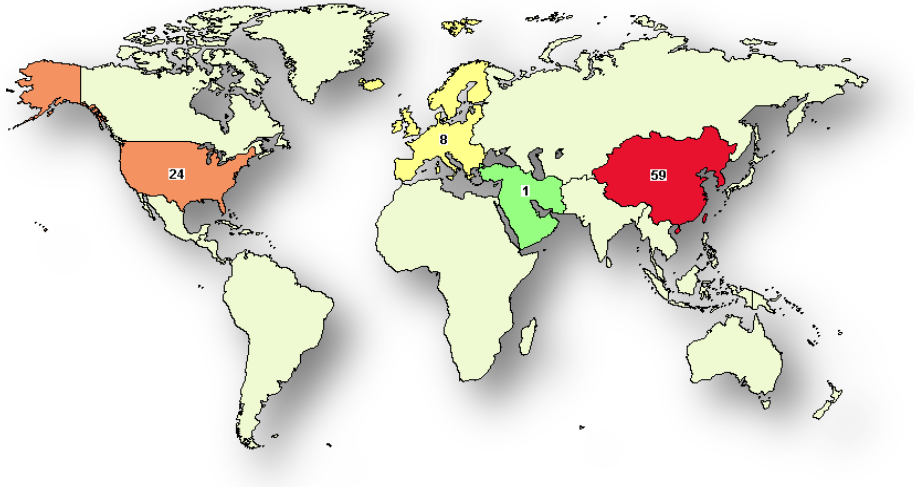
Tettamanti Center, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy

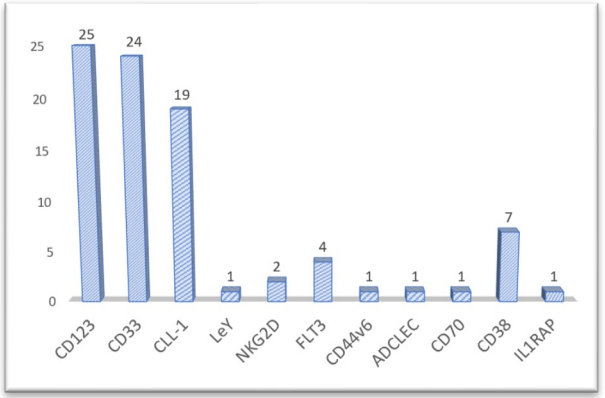
Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo - Italy and
Centro Interdipartimentale di Biotecnologie Molecolari "Guido Tarone" (MBC), Torino - Italy

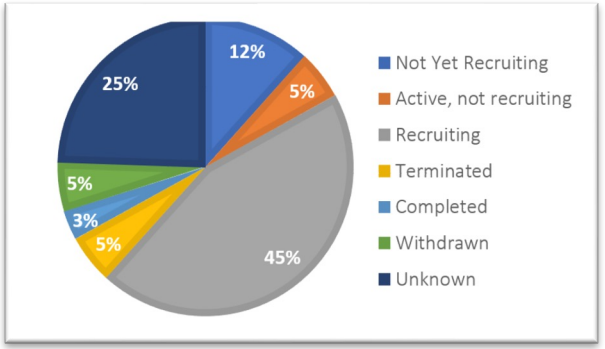
Disclosures of Sarah Tettamanti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
N/A							

CAR T cells in AML: clinical trials







ClinicalTrials.gov Search Results 13/02/2024

CAR T cells in AML: clinical trials

- Active trials

NCT Number	Interventions	Study Title	Sponsor
NCT03927261	PRGN-3006 T Cells	PRGN-3006 Adoptive Cellular Therapy for CD33-Positive Relapsed or Refractory AML, MRD Positive AML or Higher Risk MDS	Precigen, Inc
NCT02159495	Autologous CD123CAR-CD28-CD3zeta-EGFRt	Genetically Modified T-cell Immunotherapy in Treating Patients With R/R AML and Persistent/Recurrent BPDCN	City of Hope Medical Center
NCT03766126	CART123 cells	Lentivirally Redirected CD123 Autologous T Cells in AML	University of Pennsylvania

ClinicalTrials.gov Search Results 09/10/2024

CAR T cells in AML: clinical trials

- Recruiting trials

NCT Number	TARGET	Interventions	Sponsor
NCT05748197	ADCLEC	ADCLEC.syn1 CAR T cells	Memorial Sloan Kettering Cancer Center
NCT05457010	ARC	ARC-T Cells	Arcellx, Inc.
NCT06118788	BG1805	BG1805	Guangzhou Bio-gene Technology Co., Ltd
NCT06420063	CD123	CD123/CD33 CART	Essen Biotech
NCT04318678	CD123	CD123-CAR T	St. Jude Children's Research Hospital
NCT04265963	CD123	CD123 CAR-T cells	Chongqing Precision Biotech Co., Ltd
NCT04272125	CD123	CD123 CAR-T cells	Chongqing Precision Biotech Co., Ltd
NCT06006403	CD123	CD123 CAR-NK cells	Chongqing Precision Biotech Co., Ltd
NCT04678336	CD123	CART123 cells	University of Pennsylvania
NCT04230265	CD123	UCART + TMCD123	AvenCell Europe GmbH
NCT03190278	CD123	UCART123v1.2	Cellectis S.A.
NCT05949125	CD123	DRUG: R-TM123|DRUG: Allo-RevCAR01-T	AvenCell Europe GmbH
NCT04257175	CD19	CAR-T CD19	Sheba Medical Center
NCT03896854	CD19	CART-19	Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd
NCT05942599	CD33	BE CAR33 T Cells (BE752TBTTBCAR33PBL)	Great Ormond Street Hospital for Children NHS Foundation Trust
NCT05672147	CD33	CD33 CAR T-cells	City of Hope Medical Center
NCT05984199	CD33	VCAR33	Vor Biopharma
NCT05945849	CD33	CD33KO-HSPC; CART33	University of Pennsylvania
NCT05665075	CD33	CD33CAR NK	Zhejiang University
NCT05105152	CD33	SC-DARIC33	Seattle Children's Hospital
NCT03971799	CD33	CD33CART autologous	Center for International Blood and Marrow Transplant Research
NCT06017258	CD371	CD371-specific/YSNVz/I-18 CAR T cells	Memorial Sloan Kettering Cancer Center
NCT05239689	CD38	CD38 CAR T-cells	Zhejiang University
NCT05442580	CD38	CART-38 cells	University of Pennsylvania
NCT06197672	CD4	CD4CAR	Huda Salman
NCT06326463	CD70	CD70-CAR T cell	St. Jude Children's Research Hospital
NCT05454241	CD70	CD7 CAR-T	Ying Wang
NCT05995028	CD70	Universal CD7-specific CAR gene-engineered T cells	Shenzhen Geno-Immune Medical Institute
NCT04662294	CD70	CD70 CAR T-cells	Zhejiang University
NCT05377827	CD70	CD7 Allogeneic CAR T-Cells	Washington University School of Medicine
NCT05266950	CI-135	CI-135 CAR-T cells	Beijing Boren Hospital
NCT05252572	CLL1	CLL1 CAR T-cells	Zhejiang University
NCT06307054	CLL1	CLL-1 CAR NK cells	Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine
NCT04219163	CLL1	CLL-1.CAR T cells	Baylor College of Medicine
NCT04923919	CLL1	CLL1 CART cells	920th Hospital of Joint Logistics Support Force of People's Liberation Army of China
NCT06110208	CLL1	CLL1 and CD38 dual-target CAR-T injection	920th Hospital of Joint Logistics Support Force of People's Liberation Army of China
NCT04884984	CLL1	CLL1 CART	The First Affiliated Hospital of Soochow University
NCT06128044	CLL1	CLL1 CAR T	Caribou Biosciences, Inc.
NCT05995041	CLL1, CD33, CD38, CD123	CLL-1, CD33, CD38 and/or CD123-specific universal CAR- T cells	Shenzhen Geno-Immune Medical Institute
NCT06492304	CTX131	CTX131	CRISPR Therapeutics
NCT04167696	CYAD	CYAD-02	Celyad Oncology SA
NCT06326021	FL-33	autologous FL-33 CAR T	Beijing GoBroad Hospital
NCT05023707	FLT3	FLT3 CAR-T	The First Affiliated Hospital of Soochow University
NCT05445011	FLT3	FLT3 CAR T	Wuhan Union Hospital, China
NCT05432401	FLT3	FLT3 CAR T	PersonGen BioTherapeutics (Suzhou) Co., Ltd.
NCT04803929	ILT3	ILT3 CAR-T	Carbiogene Therapeutics Co. Ltd.
NCT05488132	SIGLEC 6	Siglec-6 CAR-T cells	Xuzhou Medical University
NCT05017883	TAA05	TAA05 cell injection	PersonGen BioTherapeutics (Suzhou) Co., Ltd.
NCT06125652	TIM-3/CD123	Tim-3/CD123 CAR-T cell	Xuzhou Medical University
NCT03291444		CAR T cells|BIOLOGICAL: peptide specific dendritic cell	Zhujiang Hospital

ClinicalTrials.gov Search Results 09/10/2024

First wave of Anti-AML CARs in clinic: 2013-2022

AML clinical results – published & abstracts

Agent	Patients	Responses	Toxicity	Correlatives
CD123				
Donor CART123 [1]	1	PR (?)	CRS gr. 4	Not reported
UniCART-123 [2]	3	1 PR, 2 CRi	CRS gr.1 n = 2. Myelosuppression.	Expansion, persistence. IL6/TNF/IFNγ
CART-123 [3]	7 (18 enrolled)	2 MLFS, 1 CRi	CRS gr.1-2.	Peak expansion D14. No CD123 loss.
CD33				
UltraCART-33 [4]	9 (no LD) 6 (with LD)	ORR = 3, 2 early relapse and 1 bridged to allo	CRS gr. 1-3 n = 7	No detectable increase in cytokines. Mean VCN ~1x10⁴ (no LD) vs 1.2x10⁵ (LD cohort)
CART-33 [5]	1	PR	CRS, pan[illegible]	IL6/IL8/TNF/IFNγ. Peak VCN ~ 1x10⁵
CART-33 [6]	3	0	[illegible] (1)	IL6/TNF/IFNγ elevation
CLL-1 (CLEC12A)				
CART-CLL1 [7] (pediatric)	8	[illegible] (MRD+ve), 1 MLFS (MRD+ve), 1 CRi (MRD+ve) 1 PD, 1 SD	CRS gr. 1-2 n = 8	Not reported
CLL1/CD33 CART [8]	11	8 CR, 1 PR	CRS gr. 1-3 n = ?	Not reported
CART-CLL1 [9]	10	7 CR/CRi; 6 underwent HSCT at median 20d post CART	CRS mild (4); severe (6). Severe pancytopenia (10)	IL6 elevation

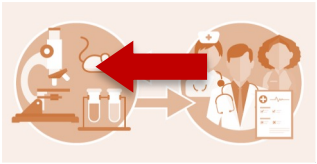
~30% response rate

[1] Yao *Front Oncol* 2019;9:1358
[2] Wermke Blood 2021
[3] Budde AACR 2020
[4] Sallman ASH 2021
[5] Wang *Mol Ther* 2014
[6] Tambaro *Leukemia* 2021
[7] Zhang Leukemia 2022
[8] Zhang ASCO 2021
[9] Jin J. Heme Onc 2022

American Society *of* Hematology

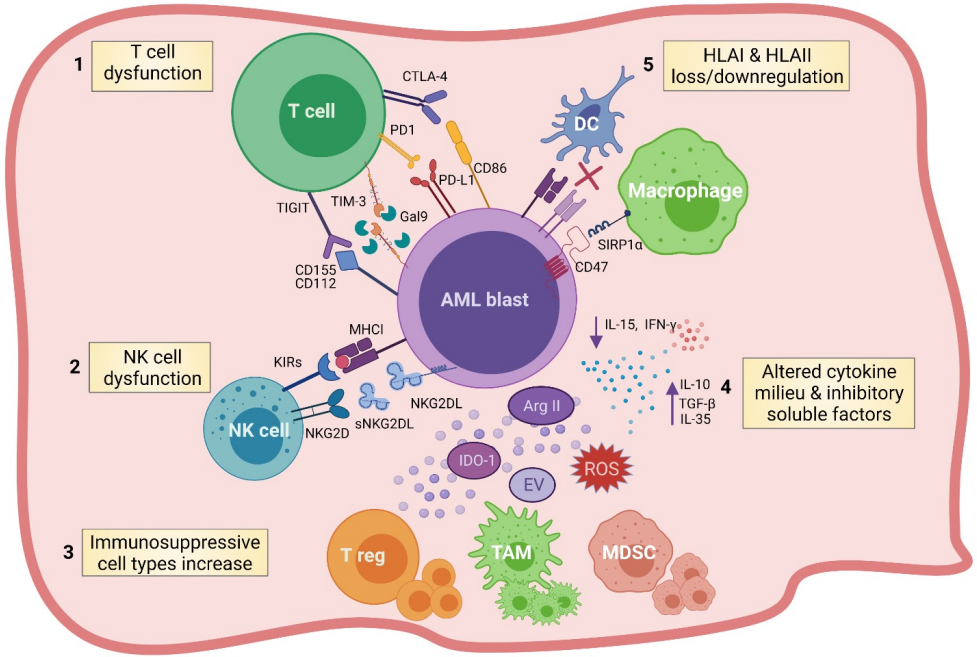
Limited persistence
&
Activity

Why ?



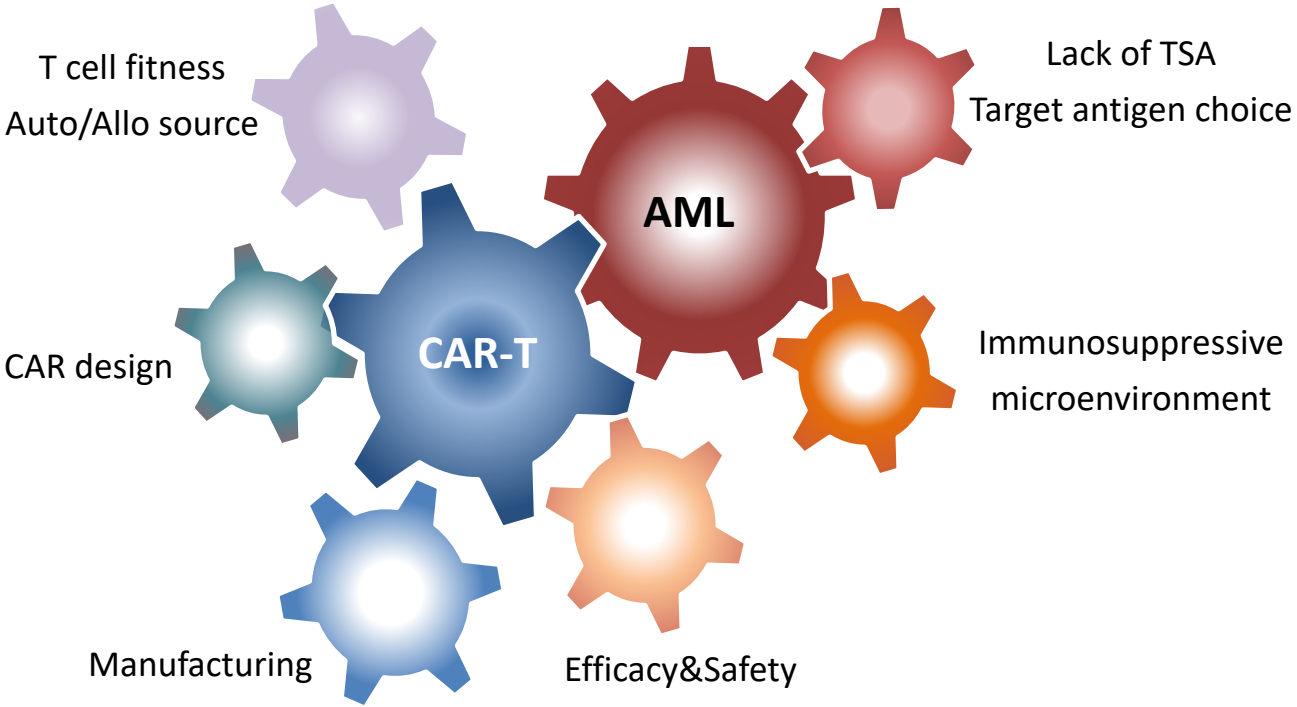
ASH 2022 Dr. Gill, Upenn SPOT LIGHT SESSION

The bone marrow AML niche: the sanctuary of LSCs

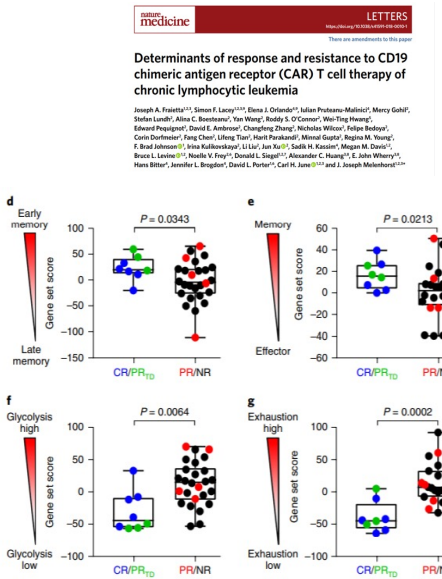


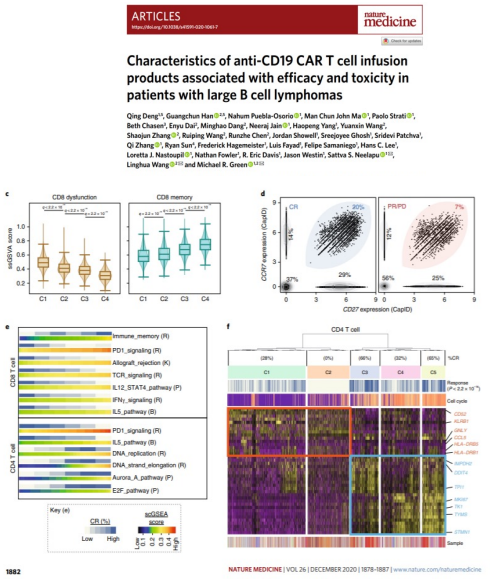
Tettamanti S, Pievani A, et al., Leukemia 2021

Challenges in CAR T cell therapy for AML



T Cell Fitness and Autologous CAR T Cell Therapy in AML



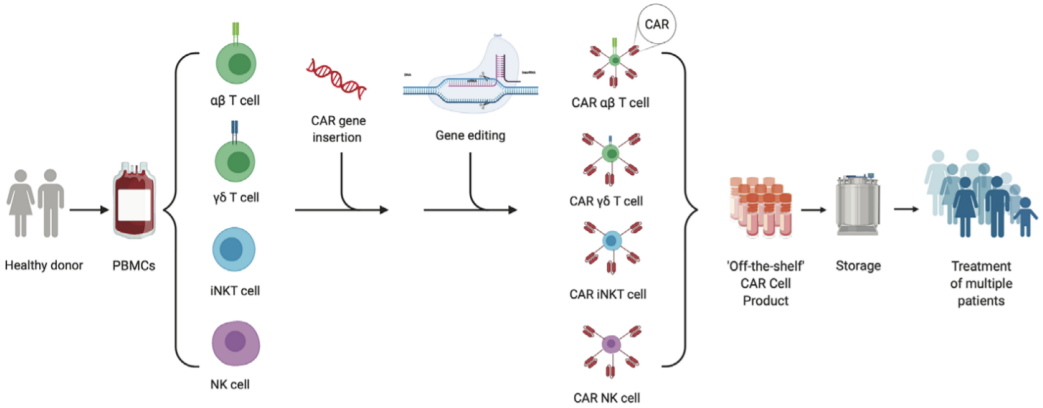


Quality of CAR T cell product → CLINICAL RESPONSE

CD33CAR
NCT03126864
University of Texas MD Anderson Cancer Center

- 10 R/R AML pts enrolled, **only 3** pts treated
- Second generation CAR (41BB), autologous T cells
- **All three patients who received CD33-CAR-T cells have died, due to disease progression; study closed;**
- The sponsors have transitioned to a platform that facilitates **more rapid production and in vivo expansion** with a product referred to as PRGN-3006 (NCT03927261)

Allogeneic source

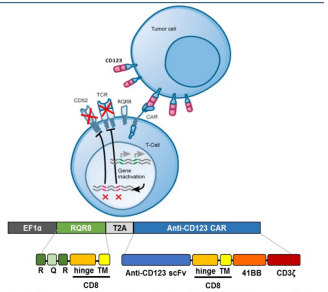


CD123 CAR-adult, multicentric phase I, **United States**

- AMELI-01
- **Allogeneic UCART-123v1.2 (41BB)**
- **FC or FCA (Alemtuzumab)** lymhodepleting regimen (8pts + 8 pts)
- **FCA regimen → improved LD and significantly higher UCART123v1.2 cell expansion**
- 1 pt in the DL2 **(6.25x10^5 cells/kg) FCA arm** achieved >90% blast reduction at Day 28
- 1 pt in the DL2 FCA arm achieved a long term durable MRD negative CR (now past 12 months)
- Based on observed UCART123v1.2 expansion patterns and cytokine profiles, **the study will be enrolling patients in the FCA 2-dose regimen arm (DL2)**

UCART123v1.2 (anti-CD123 scFv-41BB-CD3ζ):

- CD123 is a validated therapeutic target in AML
- Genetically modified allogeneic T-cell product manufactured from non-HLA–matched healthy donor cells
- *TRAC* disrupted using TALEN® to eliminate TCRαβ from the cell surface and reduce risk of GvHD
- *CD52* disrupted using TALEN® to eliminate sensitivity to LD with alemtuzumab



Allogeneic source

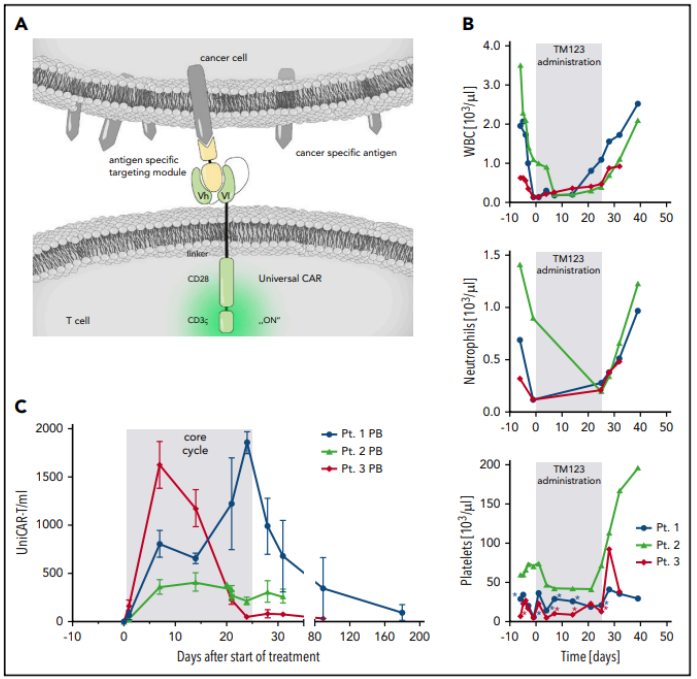
Switch on/off system: UniCAR T cells

ASH 2022:
N=14
CRS 12/14
4 PR, 2 CRi, 1 CR

Allogeneic CD123-Directed Switchable CAR-T

AVENCELL NCT05949125

AVC-201 is the world's first CRISPR-engineered switchable allogeneic CAR-T designed to fully avoid rejection by both the innate and adaptive host immune system.



Wermke et al., *Blood* 2021;

CAR NK Cell Therapy in AML

Table 4. Completed CAR-NK cell clinical studies with reported outcomes in relapsed/refractory acute myeloid leukemia. PD: progressive disease, CR: complete response, RD: relapsed disease, PB: peripheral blood, N/A: information not available.

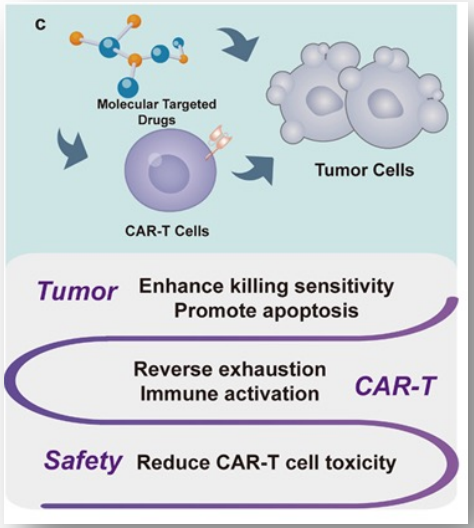
Target Antigen	Phase	NK Cell Source	CAR Construct/Genetic Modifications	Reported Outcomes
CD33	I	NK92	[62] Tang et al.: N/A	3/3 PD.
	I	PB	[89] Huang et al.: N/A	4/10 PD, 4/10 RD after CR, 2/10 CR

Table 5. Active/recruiting CAR-NK cell trials in acute myeloid leukemia. r/r: relapsed/refractory, AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, iPSCs: induced pluripotent stem cells.

NCT Identifier	Phase	NK Cell Source	Target Antigen	CAR Construct/Genetic Modifications	Disease	Location
NCT05574608	I	Unknown	CD123	Unknown CAR design	r/r AML	The 5th Medical Center of Chinese PLA General Hospital, Beijing, China
NCT05215015	I	Unknown	CD33, CLL-1	Unknown CAR design	r/r AML	Wuxi People's Hospital, Wuxi, China
NCT04623944 [90]	I	Peripheral blood of haplo-matched, related, or unrelated donors	NKG2D ligands	NKG2D-OX40-CD3ζ, Additional modification membrane-bound IL15	- r/r AML - intermediate, high and very high-risk r/r MDS	Multicenter, Nkarta Inc., San Fransisco, CA, USA

Christodoulou et al., Cancers 2023

Molecular targeted drugs & CAR T cells



Dasatinib + CD123CAR T

pediatric- St.Jude Children's Research Hospital, **United States**

- Bridge to allo-HSCT Phase 1 study
- **Lenti-CD123-CD28 CAR and a CD20 safety switch, autologous CD4/CD8 T cells**
- Upcoming CD123-CAR T cell products will be manufactured in the presence of **dasatinib** to limit T-cell differentiation and exhaustion

Azacitidine

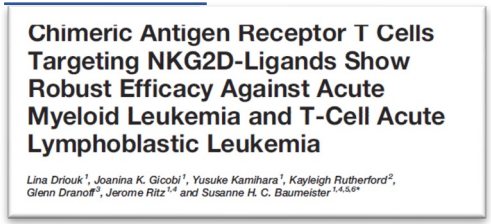
ARTICLE

OPEN

Demethylating therapy increases anti-CD123 CAR T cell cytotoxicity against acute myeloid leukemia

Nadia El Khawanky[1,2,3,4], Amy Hughes[2], Wenbo Yu[5], Renier Myburgh[6], Tony Matschulla[7], Sanaz Taromi[3,8], Konrad Aumann[9], Jade Clarson[1,10], Janaki Manoja Vinnakota[3], Khalid Shoumariyeh[3], Cornelius Miething[3], Angel F. Lopez[2,5], Michael P. Brown[2,5,11], Justus Duyster[3], Lutz Hein[7], Markus G. Manz[6], Timothy P. Hughes[1,2,10], Deborah L. White[1,2,12], Agnes S. M. Yong[1,2,13,14,16]✉ & Robert Zeiser[3,15,16]✉

HDAC inhibitors

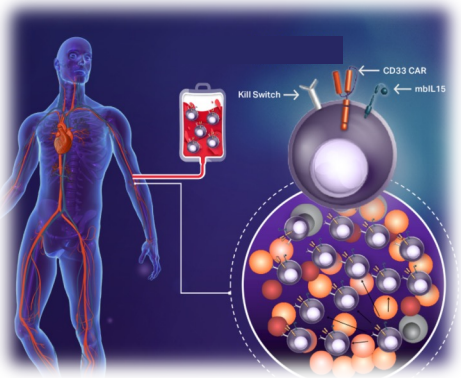


Chimeric Antigen Receptor T Cells Targeting NKG2D-Ligands Show Robust Efficacy Against Acute Myeloid Leukemia and T-Cell Acute Lymphoblastic Leukemia

Lina Driouk[1], Joanina K. Gicobi[1], Yusuke Kamihara[1], Kayleigh Rutherford[2], Glenn Dranoff[3], Jerome Ritz[1,4] and Susanne H. C. Baumeister[1,4,5,6]

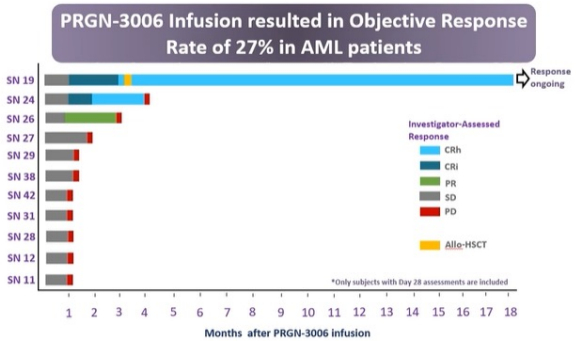
“Fast” CAR T cells in AML

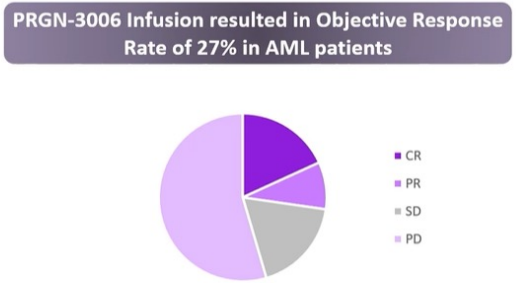
Manufactured Overnight for Next Day Infusion



NCT03927261

A single infusion of PRGN-3006 led to objective responses in AML patients

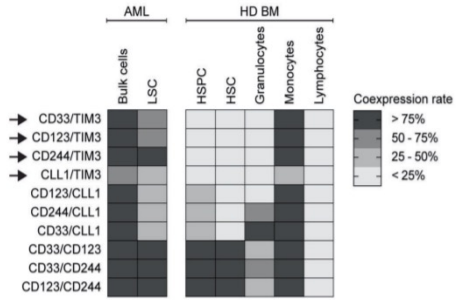




Dual CAR combinatorial strategies to gain specificity and safety

Coexpression profile of leukemic stem cell markers for combinatorial targeted therapy in AML

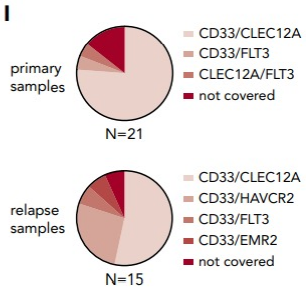
S. Haubner[1,2,3] · F. Perna[3] · T. Köhnke[1,2] · C. Schmidt[1,2] · S. Berman[3] · C. Augsberger[1,2] · F. M. Schnorfeil[1,2] · C. Krupka[1,2] · F. S. Lichtenegger[1,2] · X. Liu[1,2] · P. Kerbs[1,4,5] · S. Schneider[1] · K. H. Metzeler[1] · K. Spiekermann[1] · W. Hiddemann[1] · P. A. Greif[1,4,5] · T. Herold[1] · M. Sadelain[3] · M. Subklewe[1,2,4,5]



IMMUNOBIOLOGY AND IMMUNOTHERAPY

CLEC12A and CD33 coexpression as a preferential target for pediatric AML combinatorial immunotherapy

Semjon Willier,[1] Paula Rothämel,[1] Maximilian Hastreiter,[1] Jonas Wilhelm,[1] Dana Stenger,[1] Franziska Blaeschke,[1] Meino Rohlfs,[1] Theresa Kaeuferle,[1] Irene Schmid,[1] Michael H. Albert,[1] Vera Binder,[1] Marion Subklewe,[1,2] Christoph Klein,[1,2] and Tobias Feuchtinger[3]



Haubner et al., *Leukemia* 2019; Willier, Blood 2021

Dual CARs: first clinical data

EHA 2020

FIRST-IN-HUMAN CLL1-CD33 COMPOUND CAR (CCAR) T CELL THERAPY IN RELAPSED AND REFRACTORY ACUTE MYELOID LEUKEMIA

Fang Liu, Hongyu Zhang, Lihua Sun, Yecheng Li, Shan Zhang, Guangcui He, Hai Yi, Masayuki Wada, Kevin G Pinz, Kevin H Chen, Yu Ma, Yisong Xiong, Yi Su, Yupo Ma

	Age/sex Dx	Prior treatment	BM Blast%	CD33/CLL1 expression	Cytogenetic /molecular	Origin of car-t cells	CAR-T Dose	response
P1	44/m AML	4 chemo	47%	CD33$^+$/CLL1$^+$	ASXL1,TP53	auto	0.7x10^6/kg	MRD$^-$
P2	6/f JMML-AML	5 chemo	81%	CD33$^+$/CLL1$^+$	Complex FLT3-ITD	auto	2x10^6/kg	MRD$^-$
P3	23/F CML AP	3 TKIs for 5 years	1.63%	CD33$^+$/CLL1$^+$	t(9;22) T315mut	auto	1.1x10^6/kg	MRD$^-$
P4	43/F M2	3 chemo	42%	CD33$^+$/CLL1$^+$	NK FLT3-ITD	auto	2.8x10^6/kg	MRD$^-$
P5	32/F AML	3 chemo	19%	CD33$^+$/CLL1$^+$	NK MLL	auto	2x10^6/kg	MRD$^-$
P6	48/F AML	5 chemo	94%	CD33$^+$/CLL1$^+$	t(8;21) AML1/ETO CKIT	auto	1.3x10^6/kg	MRD$^-$
P7	23/F AML	4 chemo	74%	CD33$^+$/CLL1$^+$	t(8;21) AML1/ETO CKIT	auto	1x10^6/kg	NR
P8	27/F AML	5 chemo	93%	CD33$^+$/CLL1$^-$	NA MLL AF9	auto	2.3x10^6/kg	NR
P9	42/f AML	2 chemo	7%	CD33$^+$/CLL1+	T(3;3) RUNX1	MSD donor	3.7x10^6/kg	MRD$^-$

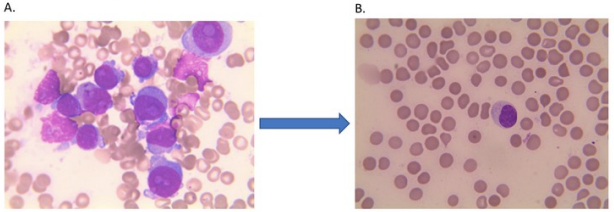
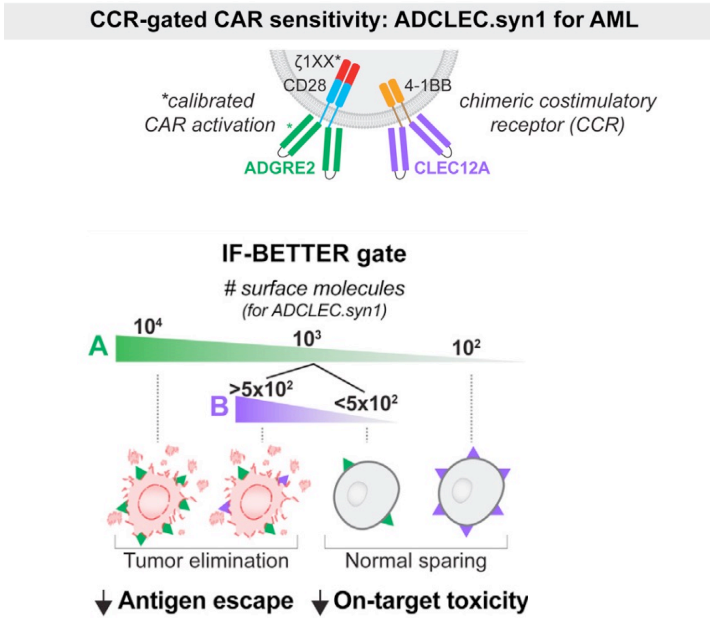
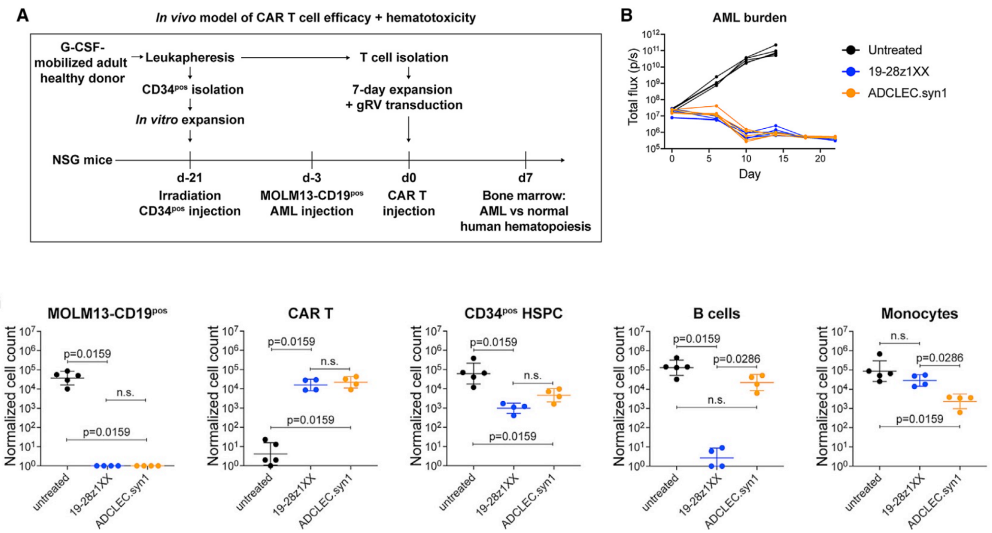


Figure 1. Patient treated with cCAR achieved complete remission. A. 12 days post cCAR infusion, leukemia blasts comprised 98% of the bone marrow. **B.** 19 days post cCAR infusion, total myeloid ablation had taken place in patient's bone marrow with only CAR T cells existing. Results were confirmed by flow cytometry showing the absence of blasts. Sternal bone marrow aspiration also showed similar findings.

- cCAR carrying two fully equipped CARs (costimulus and CD3z domains)
- All CRS, neurotoxicity and other adverse events were resolved after treatment;
- 7 MRD-, 6 underwent HSCT→ 5 pts successfully engrafted with a persistent full chimerism (1 died of sepsis before engraftment)

Boolean Logic-gated CARs: IF-better CAR T



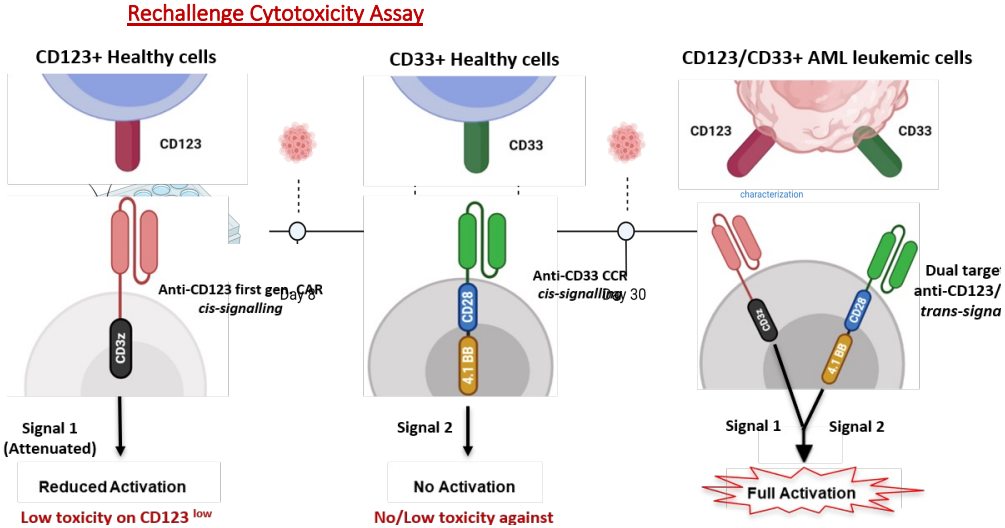


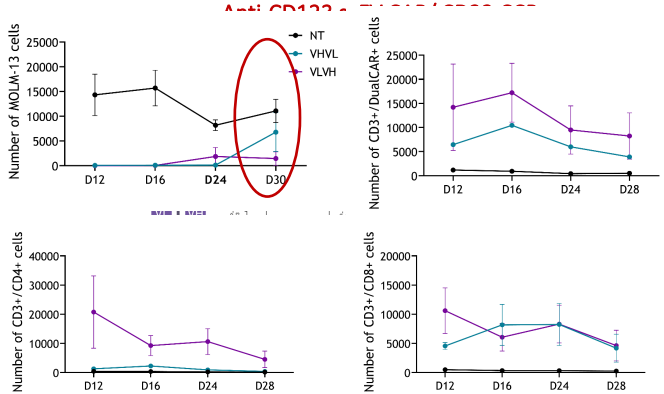
NCT05748197 Memorial Sloan Kettering Cancer Center, USA

A Phase I Study of ADCLEC.syn1 CAR T cells in Adult Patients with Relapsed or Refractory Acute Myeloid Leukemia

Boolean Logic-gated CARs: Dual AND-gated CD123-CD33 CARCIK cells

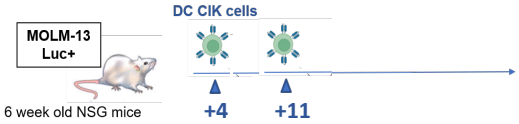
- Split **IL3 zetakine CAR** and **anti-CD33 CCR** to improve safety (*Perriello V, Rotiroti M et al., Blood Adv 2022)*
- Ongoing preclinical characterization of **scFv derived anti-CD123 CAR** (Collaboration with Prof. Falini, University of Perugia)

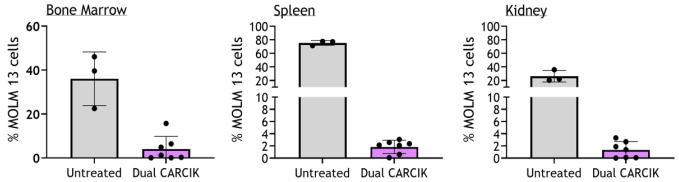




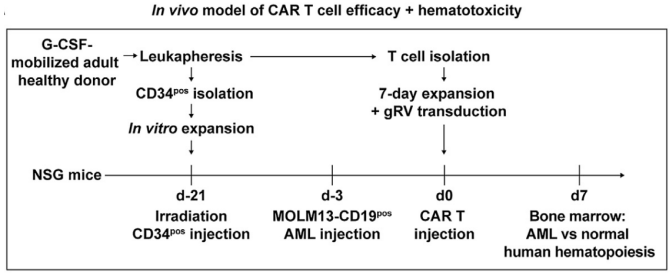
Boolean Logic-gated CARs: Dual AND-gated CD123-CD33 CARCIK cells

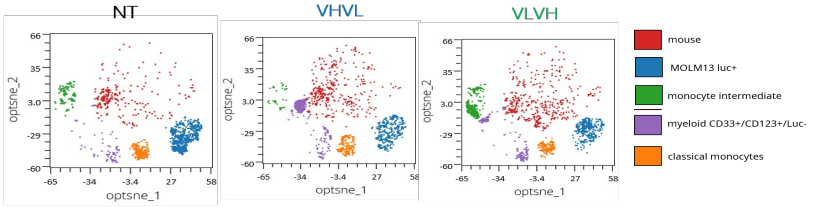
- In vivo efficacy of Dual CARCIK cells



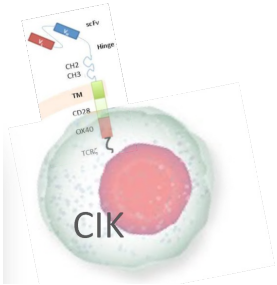


- Developing humanized NSG mice model to assess efficacy and toxicity





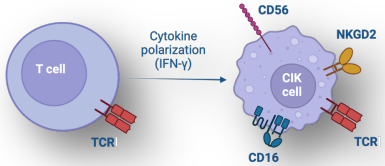
Non-viral Transposon based CAR-CIK cell engineering



Cytokine-Induced killer (CIK) cells

- Basal antitumor activity
- Low GvHD
- Safe and well tolerated

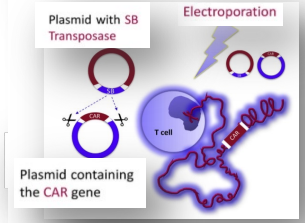
Introna M et al., Haematologica 2007
Pievani A et al., Blood 2011
Introna M et al., BBMT 2017
Gotti et al., Cytotherapy 2022



Sleeping Beauty transposon system

- Random pattern of integration→ reduced genotoxicity
- Cost effective

Magnani CF et al., Oncotarget. 2016 .
Magnani CF et al., Hum Gene Ther. 2018
Arcangeli S…Tettamanti S et al, Mol Ther 2017
Rotiroti MC…Tettamanti S et al., Mol Ther 2020.



Donor derived cells

- Healthy T cells

Magnani CF et al., JCI 2020
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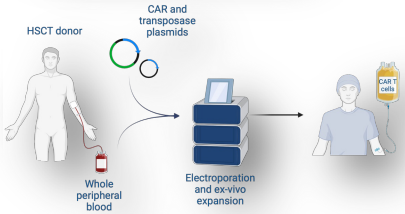
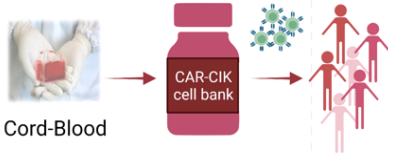
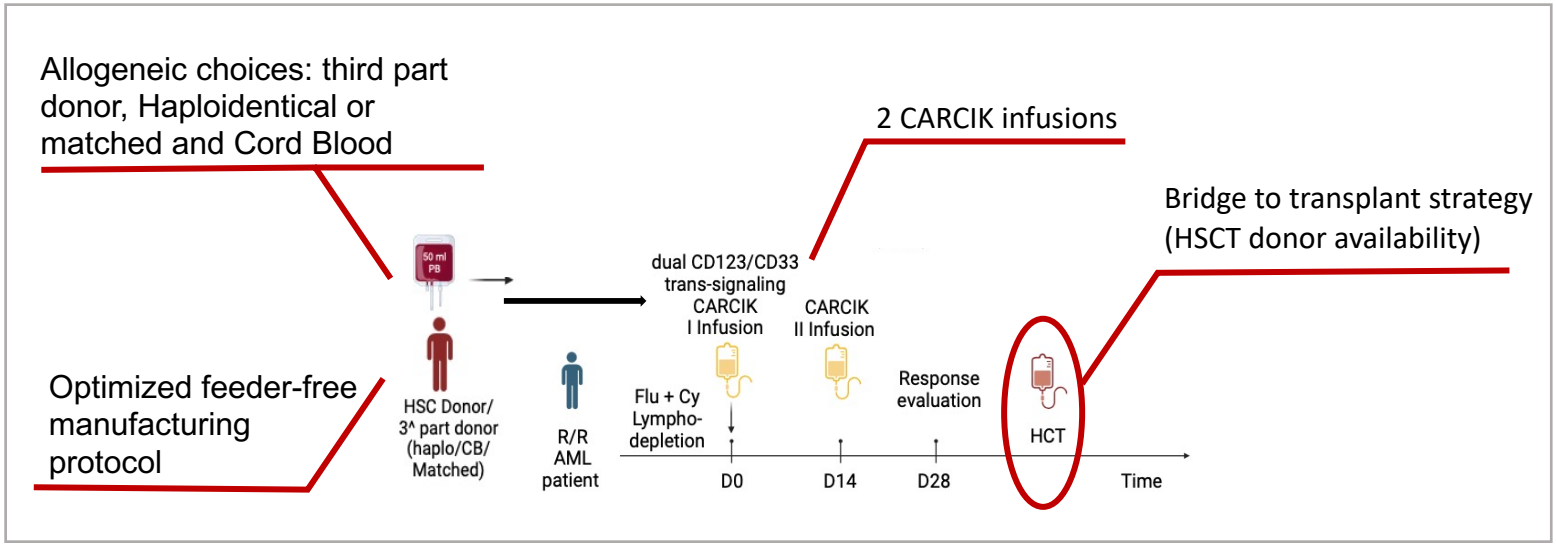




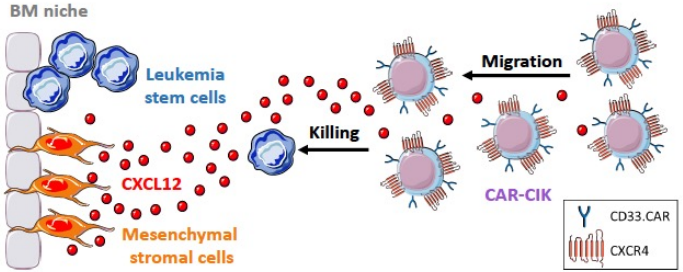
CD123/CD33 Dual CARCIK from Lab to Clinic: Translating Research into Clinical Trials

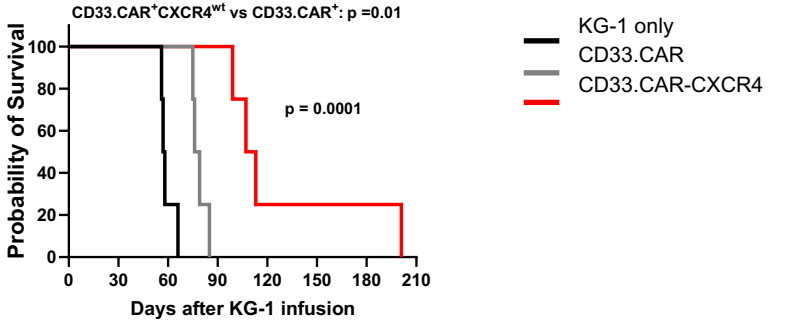
A phase I/II single-arm, clinical trial to evaluate the safety and preliminary efficacy of CD123/CD33 dual CARCIK cell for relapsed/refractory acute myeloid leukemia

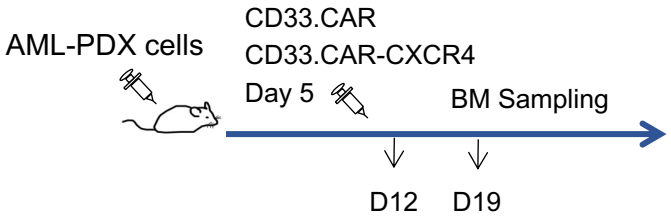


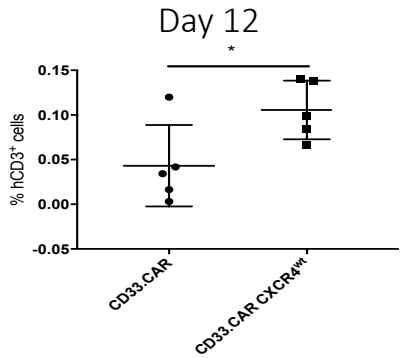
Armored CXCR4-CD33 CARCIK cells to boost the homing to the bone marrow niche

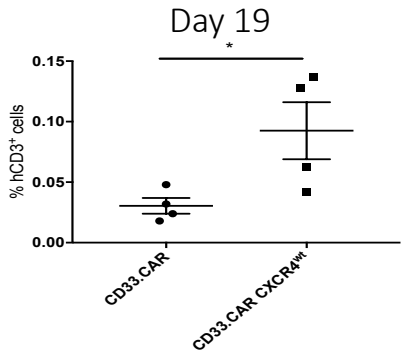
Improved antileukemic activity and maximize the presence of CARCIK in the BM in AMLPDX









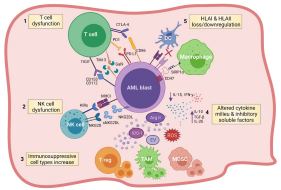


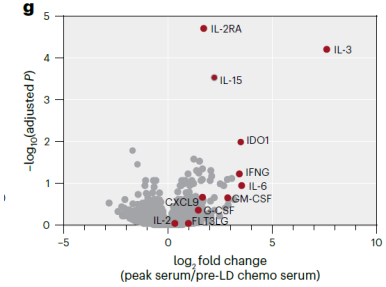
Cytokine-mediated CAR T therapy resistance in AML

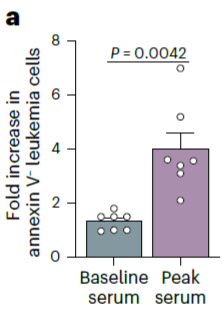
- Autologous CD123 CAR T
- 10/12 patients developed CRS
- Of the six patients evaluated for response, 2 CR, 1CRi, and 3 PD
- The overall response rate was 25%.
- The median duration of remission for responding patients: 84 to 381 days, with a median OS from infusion of 160 days.

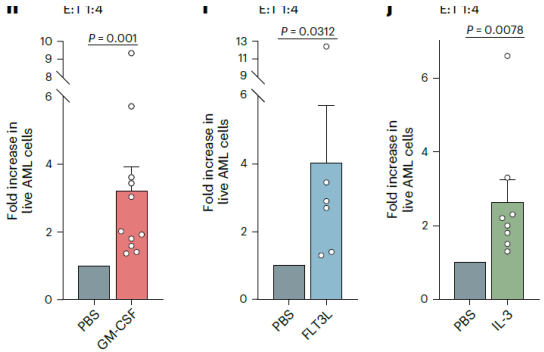
Bhagwat A et al., Nature Medicine (2024)

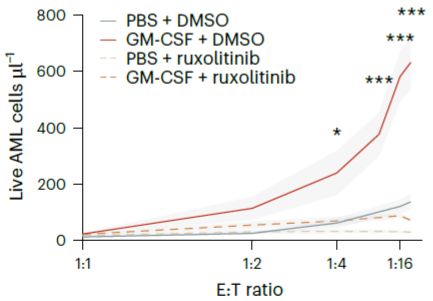
- Cytokines produced by activated CART cells and other immune cells in the marrow microenvironment stimulated cognate receptors on AML blasts, leading to JAK/STAT signaling, increased blast viability and resistance to CART cell killing











IL-3, GM-CSF, and FLT3L were secreted during the CART-123 therapy, promoting AML blast survival via JAK-STAT signaling.

Conclusions

- CAR T therapy can be a potent immunotherapy approach for AML treatment
- Barriers that limit the full therapeutic potential of CAR T cells (i.e. AML complexity, challenging CAR T manufacture, the cross talk with the immunosuppressive TME)
- The main issues are related to low CAR T cell persistence and transient anti-leukemic activity
- Need to implement anti-AML CAR T therapy with more fit T cells, smarter CARs and combinatorial strategies → Active preclinical research ongoing (i.e. CD33KO CD34+ or epitope edited CD34+; targeting of the TME)
- Careful and rationally- designed clinical trials are warranted to increase the therapeutic index of CAR T therapy in AML

How to foster CAR T cell therapy for AML

International AML working group

18 September 2023

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Laboratorio di Terapia Cellulare e Genica Stefano Verri

Daniela Belotti
Benedetta Cabiati
Stefania Cesana
Valentina Colombo
Michele Quaroni
Giada Matera

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Josee Golay
Martino Introna

Charles A. Nicolette, CEO
Mark DeBenedette, VP of R&D
Irina Tcherepanova, COO
Lori R. Harrelson, CFO