INSTITUT DE RECERCA CONTRA LA LEUCÈMIA JOSEP CARRERAS
Per un futur sense leucèmia

Adoptive T-cell Immunotherapies for T-cell malignancies

Pablo Menendez
ICREA Research Professor
Josep Carreras Leukemia Research Institute
Barcelona - Spain

November 4th 2021,
FLS Science Immunotherapy and Hemopathies

Per molt anys Josep María!

Disclosures

PM is co-founder of OneChain Immunotherapeutics S.L, a IJC spin-off devoted to advance cancer immunotherapies

T-cell malignancies

T-cell leukemias

- ✓ T-cell acute Lymphoblastic leukemia (T-ALL)

  15% of childhood AL
  25% of adulthood AL

- ✓ T-cell Lymphoblastic lymphoma (TLLy)

  Rare and no BM involvement

- ✓ Adult T-cell leukemia/Lymphoma (ATLL)

  Rare and fatal outcome. HTLV1-driven.

- ✓ T-cell large granular lymphocytic leukemia (T-LGL)
- ✓ T-prolymphocytic leukemia (T-PLL)

  Very rare

T-cell Lymphomas

- ✓ Cutaneus T-cell Lymphoma (CTCL)

  Mycosis Fungoide
  Sezary Syndrome

- ✓ Peripheral T-cell Lymphoma (PTCL)

  Anaplastic large T-cell lymphoma (ALCL)
  Angioimmunoblastic T-cell lymphoma (AITL)
  Extranodal (NK)-T-cell lymphoma (ENKTL)
  Enteropathy-associated T cell lymphoma (EATL)
  Hepatosplenic T-cell lymphoma (HSTCL)
  PTCL-not otherwise specified

R/R patients wit T-cell tumors have few therapeutic options beyond allogeneic HSC transplant (25% TRM)

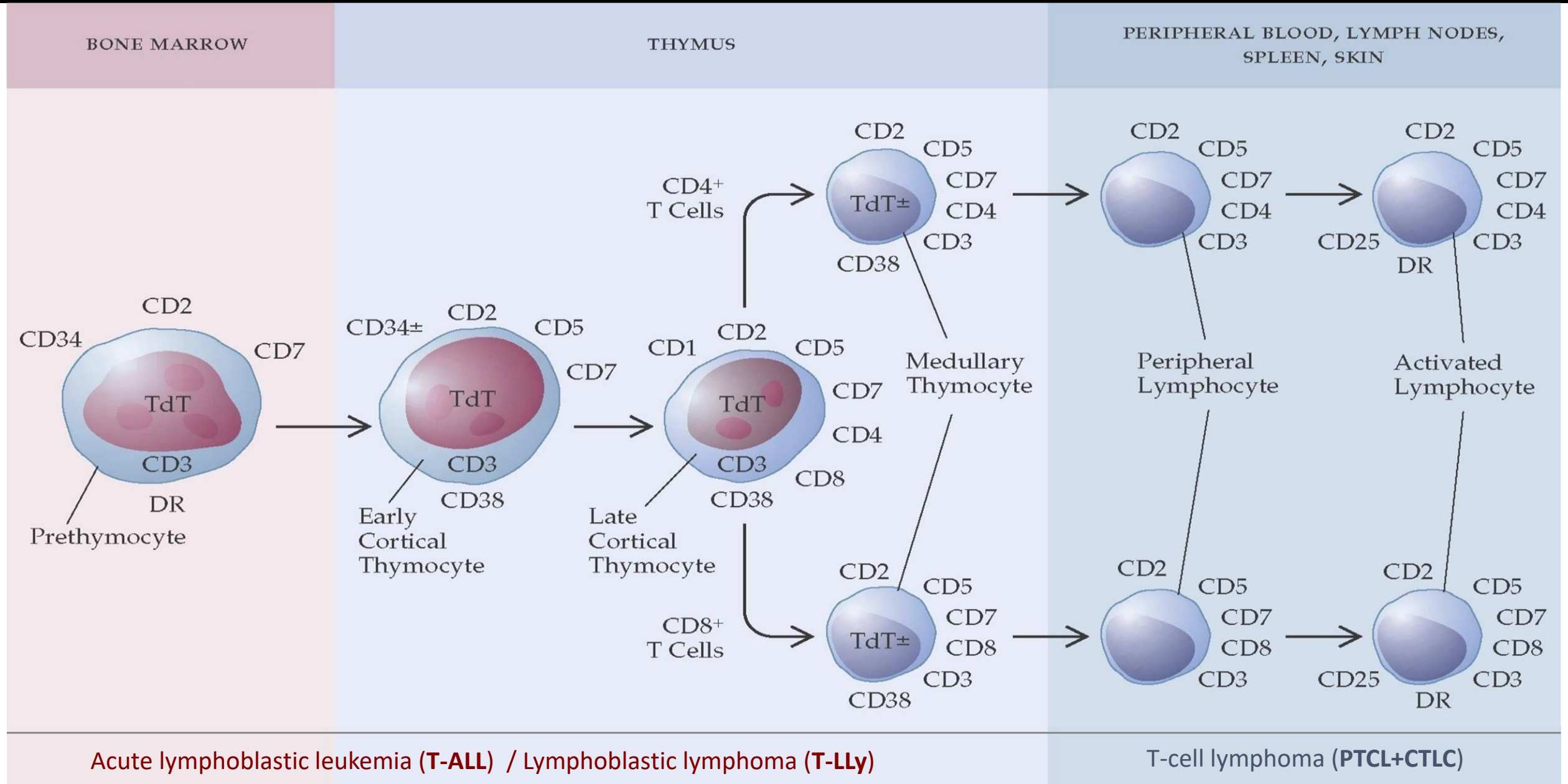
Current MoAb-based IT efficiency remains modest

☺☺ : GOOD
☺ : MODEST
☹ : NONE/LITTLE

- Toxin-conjugated anti-CD5 or toxin-anti-CD7 MoAb
  - T-ALL ☹
  - TCL ☹
- Immunecheckpoint Inhibitors in:
  - ENKTL ☺☺
  - TCL ☹
- Mogamulizumab (anti-CCR4 MoAb) in:
  - Peripheral TCL ☹
  - Cutaneous TCL ☺

These agents could even increase disease progresion and induce severe autoinmune symptoms in T-ALL due to tumor over-activation

Most targetable Ag are co-expressed in leukemic & normal T-cells

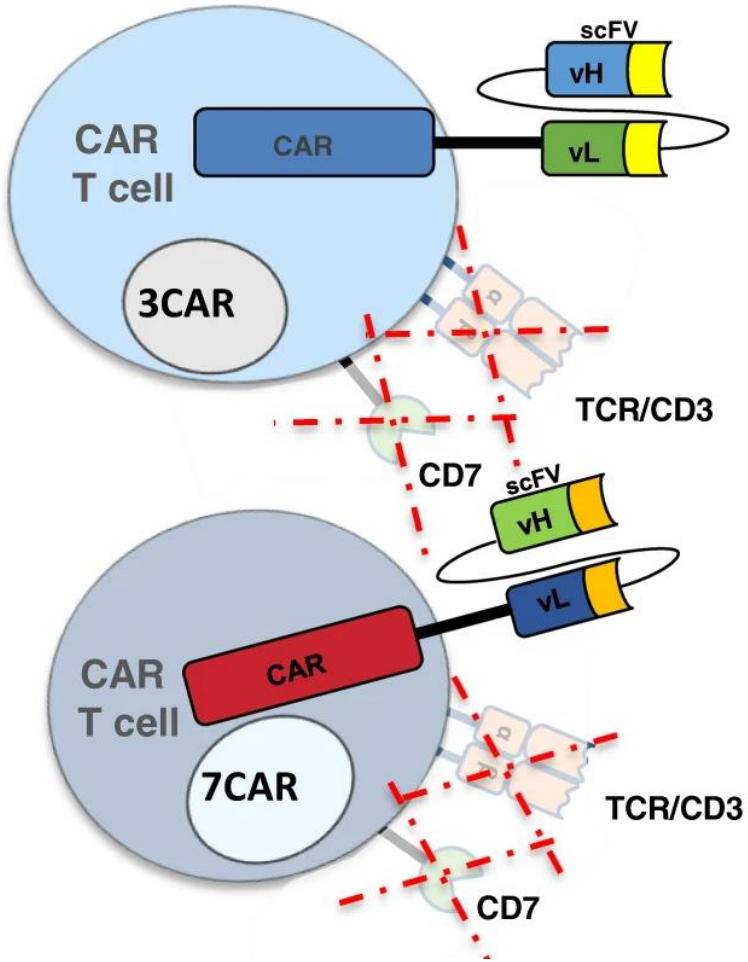


Acute lymphoblastic leukemia (**T-ALL**) / Lymphoblastic lymphoma (**T-LLy**)

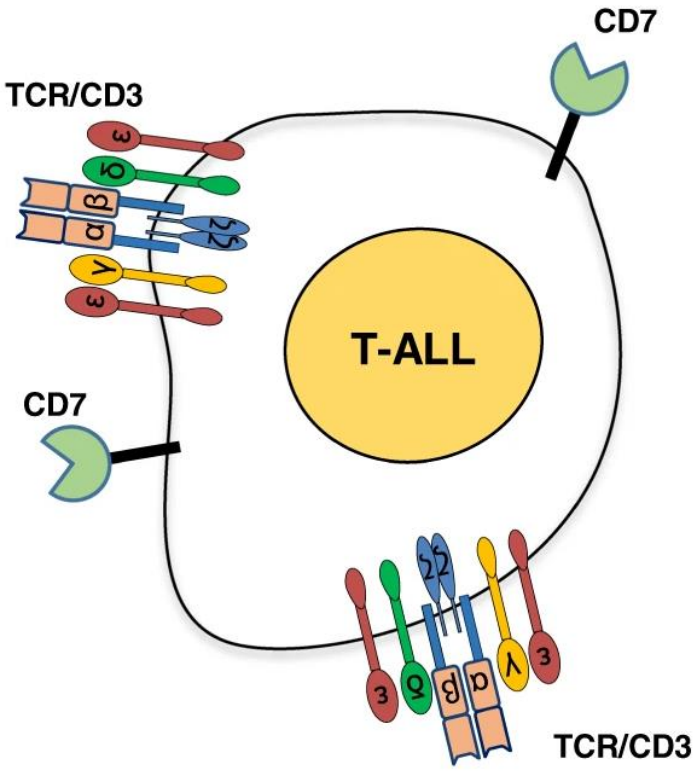
T-cell lymphoma (**PTCL+CTLC**)

Not only T-cells Ags but also TCR/CD3 and HLA-II

Healthy T-cells



Tumoral T-cells



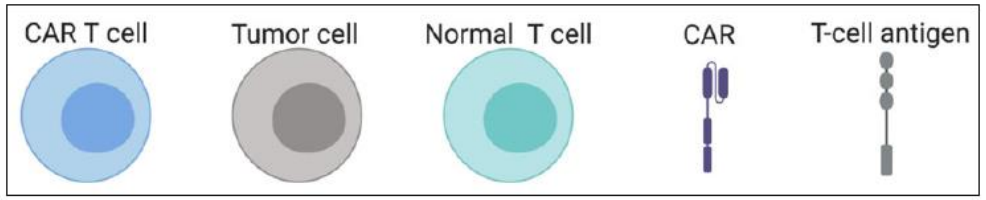
TCR/CD3/TRCA

HLA-II

CD3, CD2, CD5, CD7
CD4/CD8 etc

T-cell-based immunotherapies for T-cell tumors – major challenges

There is no a known T-cell tumor-specific Ag

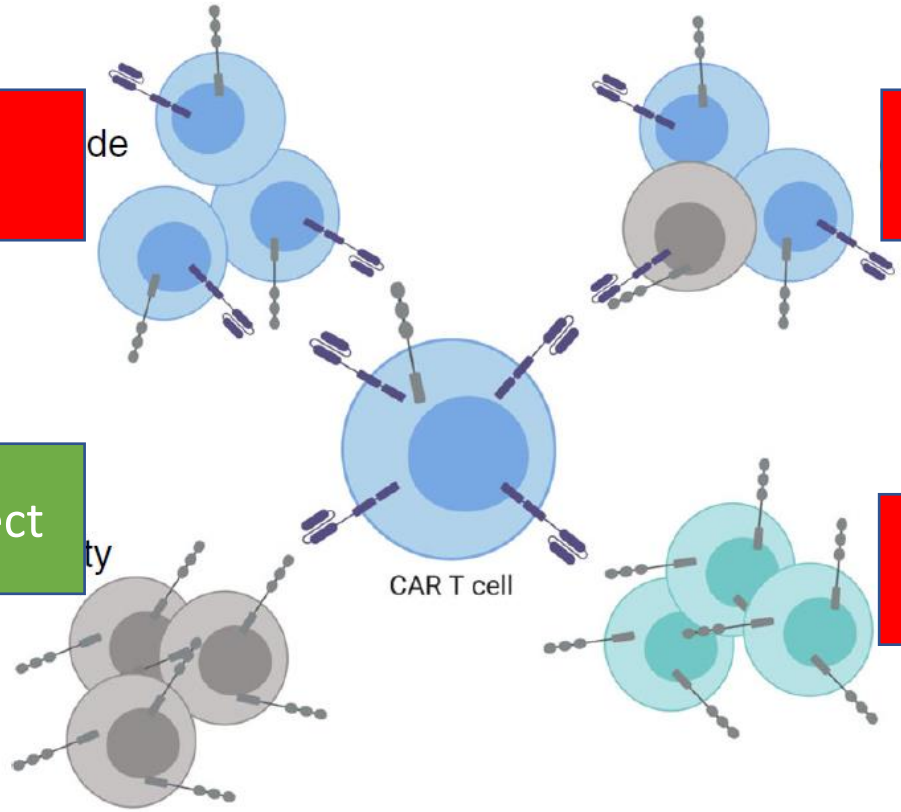


☹ T-cell fratricide

☺☺ Anti-leukemic effect

Product contamination ☹

T-cell aplasia - immunodeficiency ☹



Adopted from Fleischer LC JH&O 2019

Main limitations in developing IT for T-malignancies

1. Fratricide of CAR T cells → Impaired / Exhausted expansion of therapeutic T-cells
2. Targeting normal T cells → Immune deficiency
3. Modification of malignant blasts → Tumor escape

How to overcome limitations of CAR T-cells in T-cell tumors?

Fratricide

- Targeting downregulated Ags

A T-cell–directed chimeric antigen receptor for the selective treatment of T-cell malignancies

Maksim Mamonkin, Rayne H. Rouce, Haruko Tashiro, and Malcolm K. Brenner

Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital and Houston Methodist Hospital, Houston, TX

Key Points

- T cells transduced with a CD5 CAR demonstrate limited and transient fratricide and expand ex vivo.
- CD5 CAR T cells eliminate T-ALL blasts in vitro and control disease progression in xenograft T-ALL mouse models.

Options for targeted therapy of T-cell malignancies remain scarce. Recent clinical trials demonstrated that chimeric antigen receptors (CARs) can effectively redirect T lymphocytes to eradicate lymphoid malignancies of B-cell origin. However, T-lineage neoplasms remain a more challenging task for CAR T cells due to shared expression of most targetable surface antigens between normal and malignant T cells, potentially leading to fratricide of CAR T cells or profound immunodeficiency. Here, we report that T cells transduced with a CAR targeting CD5, a common surface marker of normal and neoplastic T cells, undergo only limited fratricide and can be expanded long-term ex vivo. These CD5 CAR T cells effectively eliminate malignant T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoma lines in vitro and significantly inhibit disease progression in xenograft mouse models of T-ALL. These data support the therapeutic potential of CD5 CAR in patients with T-cell neoplasms. (*Blood*. 2015;126(8):983-992)

CD5 gets downregulated upon exposure to CD28-based CAR but not 41BB-based CAR

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Extra genetic manipulation of the effector cells

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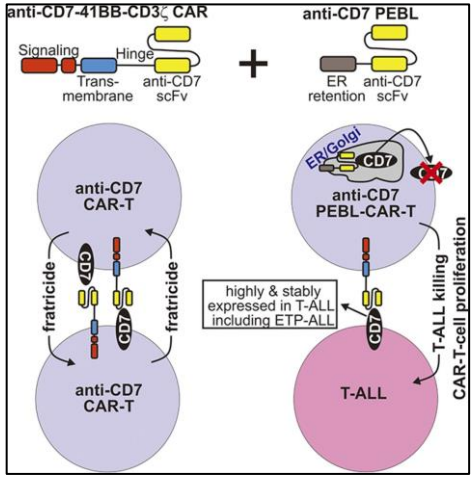

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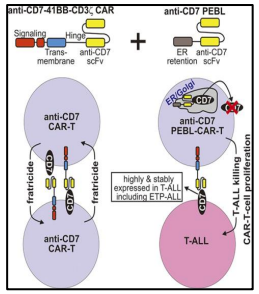

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CD7-edited T cells expressing a CD7-specific CAR for the therapy of T-cell malignancies

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Key Points

- Genomic disruption of CD7

Extending the success of chimeric antigen receptor (CAR) T cells to T-cell malignancies is problematic because most target antigens are shared between normal and malignant cells, leading to CAR T-cell fratricide. CD7 is a transmembrane protein highly expressed in acute

JCI insight

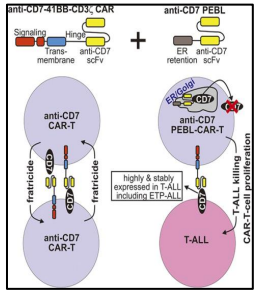
TCRαβ/CD3 disruption enables CD3-specific antileukemic T cell immunotherapy

Jane Rasaiyaah, … , Ulrike Mock, Waseem Qasim

How to overcome limitations of CAR T-cells in T-cell tumors?

Fratricide

- Targeting downregulated Ags
- Protein expression blockers
- Genome editing of the target Ag
- Ag with no expression in normal T-cells: CD1a, TRCB, γδ, etc
- NK cells as effector cells (except CD7….)



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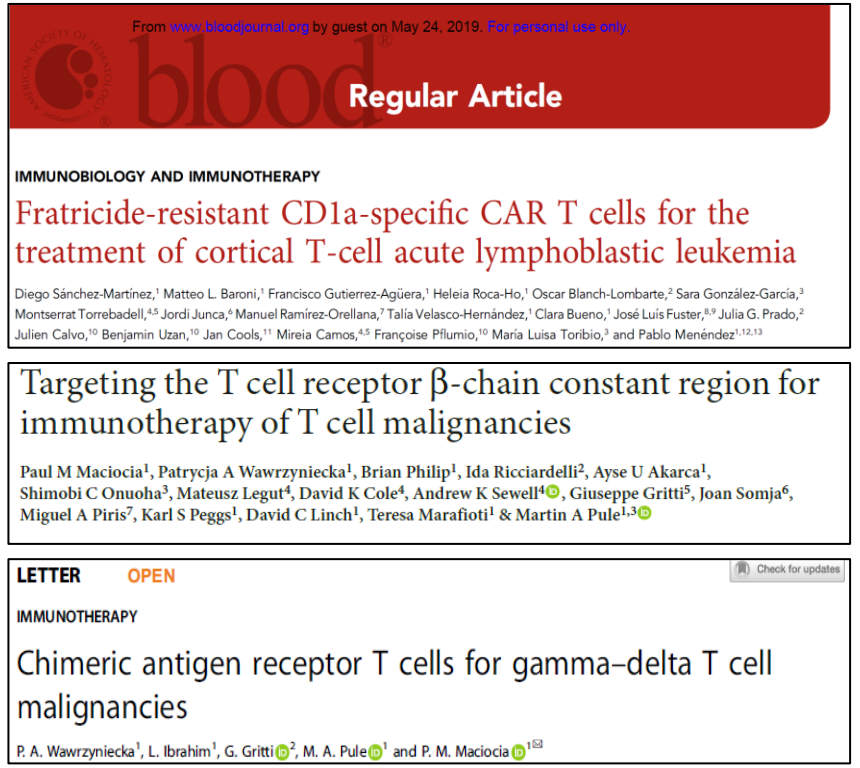
T-cell aplasia

- Ag with no expression in normal T-cells:
  (CD1a, TRCB, γδ, etc)

- Low persisting NK cells or γδ T-cells as effector cells
  (multiple infusion – stop infusion as a safety switch)

- Bridge as HSCT and/or genetic safety switches



blood
Regular Article

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Fratricide-resistant CD1a-specific CAR T cells for the treatment of cortical T-cell acute lymphoblastic leukemia

Diego Sánchez-Martínez,[1] Matteo L. Baroni,[1] Francisco Gutierrez-Agüera,[1] Heleia Roca-Ho,[1] Oscar Blanch-Lombarte,[2] Sara González-García,[3] Montserrat Torrebadell,[4,5] Jordi Junca,[6] Manuel Ramírez-Orellana,[7] Talía Velasco-Hernández,[1] Clara Bueno,[1] José Luís Fuster,[8,9] Julia G. Prado,[2] Julien Calvo,[10] Benjamin Uzan,[10] Jan Cools,[11] Mireia Camos,[4,5] Françoise Pflumio,[10] María Luisa Toribio,[3] and Pablo Menéndez[1,12,13]

Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies

Paul M Maciocia[1], Patrycja A Wawrzyniecka[1], Brian Philip[1], Ida Ricciardelli[2], Ayse U Akarca[1], Shimobi C Onuoha[3], Mateusz Legut[4], David K Cole[4], Andrew K Sewell[4], Giuseppe Gritti[5], Joan Somja[6], Miguel A Piris[7], Karl S Peggs[1], David C Linch[1], Teresa Marafioti[1] & Martin A Pule[1,3]

LETTER OPEN

Check for updates

IMMUNOTHERAPY

Chimeric antigen receptor T cells for gamma–delta T cell malignancies

P. A. Wawrzyniecka[1], L. Ibrahim[1], G. Gritti[2], M. A. Pule[1] and P. M. Maciocia[1]

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- Bridge as HSCT and/or genetic safety switches

- KO the target Ag in HSPC –tough to implement

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

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Cell

Genetic Inactivation of CD33 in Hematopoietic Stem Cells to Enable CAR T Cell Immunotherapy for Acute Myeloid Leukemia

CD7-deleted hematopoietic stem cells can restore immunity after CAR T cell therapy

Miriam Y. Kim, Matthew L. Cooper, Miriam T. Jacobs, Julie K. Ritchey, Julia Hollaway, Todd A. Fehniger, and John F. DiPersio

How to overcome limitations of CAR T-cells in T-cell tumors?

Product contamination

- Inclusion criteria and clinical decisions
  (conditioning regimen, disease burden allowed to enter the treatment, apheresis purging, etc)

- Allogenic MHC-unrestricted NK- or γδ T-cells as effector cells (no GvHD).

- Genome modification of TRCA, TCR/CD3 in allogenic αβT-cells.


JCI insight

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Jane Rasaiyaah, … , Ulrike Mock, Waseem Qasim


An "off-the-shelf" fratricide-resistant CAR-T for the treatment of T cell hematologic malignancies

Matthew L Cooper[1] · Jaebok Choi[1] · Karl Staser[1,2] · Julie K Ritchey[1] · Jessica M Devenport[1] · Kayla Eckardt[1] · Michael P Rettig[1] · Bing Wang[1] · Linda G Eissenberg[1] · Armin Ghobadi[1] · Leah N Gehrs[1] · Julie L Prior[3] · Samuel Achilefu[3] · Christopher A Miller[1,4] · Catrina C Fronick[4] · Julie O'Neal[1] · Feng Gao[5] · David M Weinstock[6] · Alejandro Gutierrez[6,7] · Robert S Fulton[4] · John F DiPersio[1]

Current fears with genome edited CAR T-cells

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Endogenous TCR promotes in vivo persistence of CD19-CAR-T cells compared to a CRISPR/Cas9-mediated TCR knockout CAR

Dana Stenger,[1,2] Tanja A. Stief,[1,3] Theresa Kaeuferle,[1] Semjon Willier,[1] Felicitas Rataj,[4] Kilian Schober,[3,5] Binje Vick,[1,2,6] Ramin Lotfi,[7,8] Beate Wagner,[9] Thomas G. P. Grünewald,[2,10,11] Sebastian Kobold,[4] Dirk H. Busch,[3,5,12] Irmela Jeremias,[1,2,6] Franziska Blaeschke,[1,*] and Tobias Feuchtinger[1-3,*]

Current fears with genome edited CAR T-cells

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results

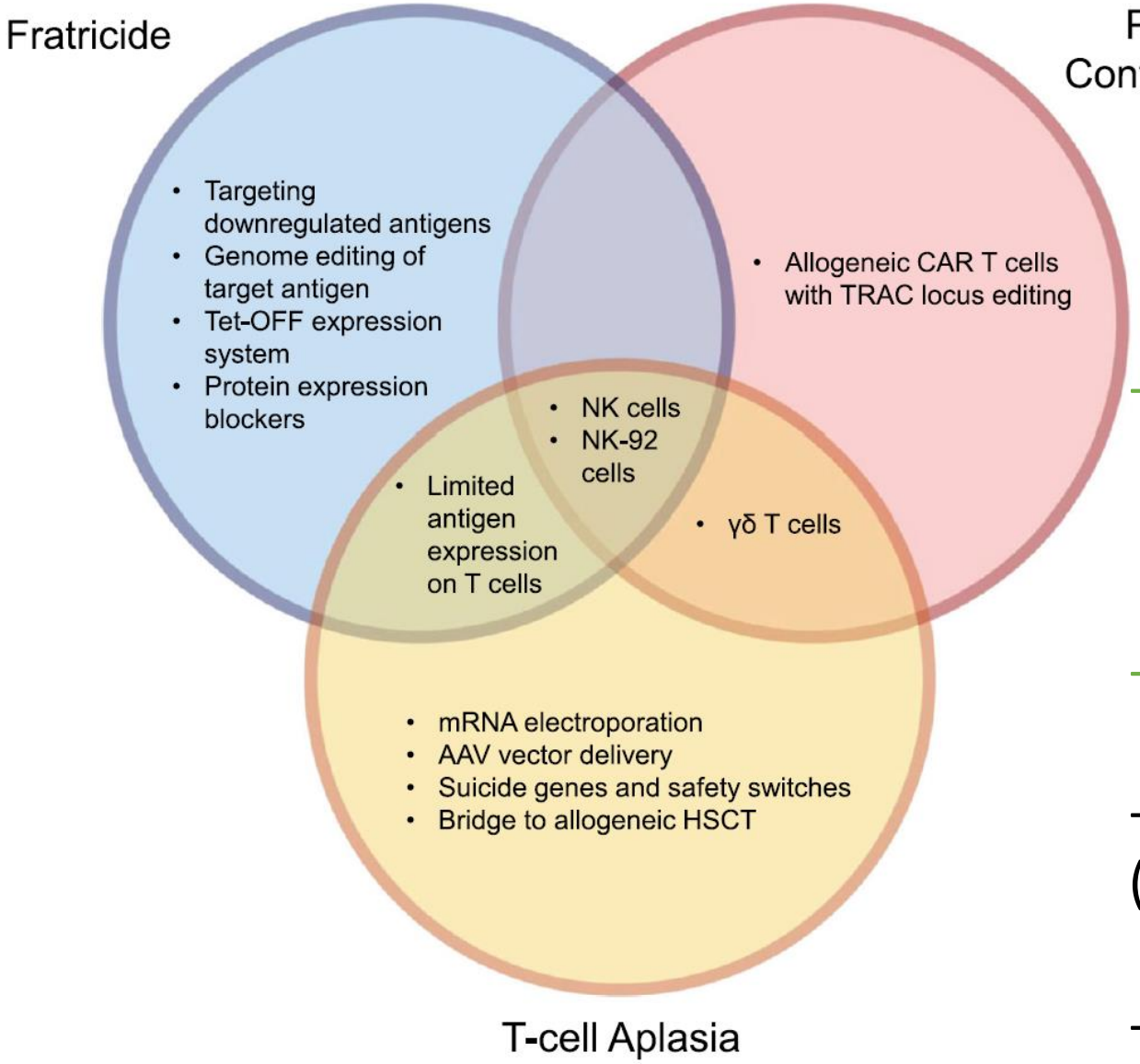
Follow this preprint

Frequent Aneuploidy in Primary Human T Cells Following CRISPR-Cas9 cleavage

A.D. Nahmad, E. Reuveni, E. Goldschmidt, T. Tenne, M. Liberman, M. Horovitz-Fried, R. Khosravi, H. Kobo, E. Reinstein, A. Madi, U. Ben-David, A. Barzel

doi: https://doi.org/10.1101/2021.08.20.457092

SUMMARY on how overcome limitations of CAR T-cells in T-cell tumors



-Universal HLA-unrestricted effector cells

NK cells

γδ T-cells

-Find a target Ag with no expression in T-cells

-Genome editing target Ag in autologous T-cells (overcome fratricide).

-Genome editing TCR & MHC in allogenic αβ T-cells (overcome GvHD and receptor rejection)

CLINICAL CURRENT SCENARIO

CAR T-cells targeting a Pan T-cell Ag

CAR T-cells targeting a non Pan Pan-cell Ag

CLINICAL CURRENT SCENARIO

CAR T-cells targeting a Pan T-cell Ag

CD5-directed unmanipulated T-cells

Trial overview and inclusion criteria

- R/R T-ALL or TCL with >50% of blasts CD5+
- Inclusion: suitable for alo-HSCT (donor available) **or** availability of alo-HSCT donor T-cells for CARTs manufacture
- Autologous (GROUP A) or allo-HSCT donor-derived (GROUP B) $\alpha\beta$T-cells.
- CD5-CAR-CD28-CD3z
- Fludarabine + cytoxan conditioning
- CART dose: $1x10^7/m^2$ - $5x10^7/m^2$ - $1x10^8/m^2$
- Primary endpoint: Dose Limiting Toxicity (safety)
- Secondary endpoint: Overall Response Rate (efficacy)
- N=50 pts up to 75 yo (first 6 pts, >18yo)

Reported data in ASH 2020

- **No/limited immunodeficiency/toxicity**
- **60% ORR**
- CD5 CAR T-cell persistence unknown

MAGENTA TRIAL (NCT03081910)
BCM/MD ANDERSON

T-Cells Expressing a Second Generation CAR for Treatment of T-Cell Malignancies Expressing CD5 Antigen

CD7-directed unmanipulated T-cells

Trial overview and inclusion criteria

- R/R T-ALL or TCL with >20% of blasts CD7+
- Inclusion: suitable for alo-HSCT (donor available) **or** availability of alo-HSCT donor T-cells for CARTs manufacture
- Autologous
- CD7-CAR-CD28-CD3z
- Fludarabine + cytoxan conditioning
- CART dose: $1x10^7/m^2$ - $3x10^7/m^2$ - $1x10^8/m^2$
- Primary endpoint: Dose Limiting Toxicity (safety)
- Secondary endpoint: Overall Response Rate (efficacy)
- N=50 pts up to 75 yo (first 6 pts, >18yo)

CRIMSON TRIAL (NCT03690011)
BCM/MD ANDERSON

No data reported as of today

Cell Therapy for High Risk T-Cell Malignancies Using CD7-Specific CAR Expressed On Autologous T Cells

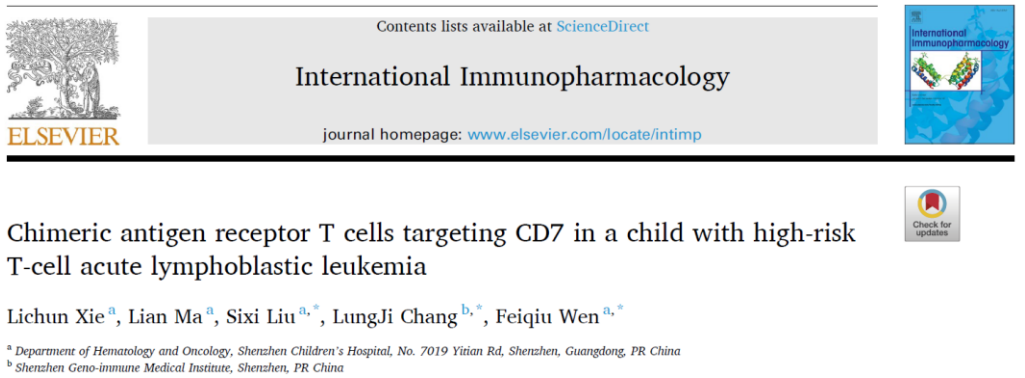
CD7-directed unmanipulated T-cells

Ad hoc treatment of one children with R/R T-ALL

- 11 yo refractory T-ALL with KTM2A-MLLT1
- Treatment proposal: CD7-CAR followed by allo-HSCT
- Autologous
- CD7-CAR-41BB-CD3z
- Fludarabine + cytoxan conditioning
- CART dose: $2x10^6$/Kg

Clinical data reported

- CR on day 17
- CARTs disappear by day 35
- CRS grade 1
- No ICANS
- T-cell immunodeficiency and high neutropenia was overcome with allo-HSCT



Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Chimeric antigen receptor T cells targeting CD7 in a child with high-risk T-cell acute lymphoblastic leukemia

Lichun Xie [a], Lian Ma [a], Sixi Liu [a,*], LungJi Chang [b,*], Feiqiu Wen [a,*]

[a] Department of Hematology and Oncology, Shenzhen Children's Hospital, No. 7019 Yitian Rd, Shenzhen, Guangdong, PR China
[b] Shenzhen Geno-immune Medical Institute, Shenzhen, PR China

Chinese Children Cancer Group-ALL

Cell Therapy for High Risk T-Cell Malignancies Using CD7-Specific CAR Expressed On Autologous T Cells

CD7-directed unmanipulated T-cells

Trial overview and inclusion criteria

- R/R T-ALL with >20% of blasts CD7+ ; N=20 pts
- CD7-CAR-CD28-CD3z
- Donor derived T-cells (previous alo-HSCT) or new donors
- Fludarabine + cytoxan conditioning
- CART dose: 0.5-1x10^6/Kg
- Primary endpoint: Dose Limiting Toxicity (safety)
- Secondary endpoint: Overall Response Rate (efficacy)

Donor-Derived CD7 Chimeric Antigen Receptor T Cells for T-Cell Acute Lymphoblastic Leukemia: First-in-Human, Phase I Trial

Jing Pan [1], Yue Tan [2], Guoling Wang [2], Biping Deng [3], Zhuojun Ling [4], Weiliang Song [4], Samuel Seery [5 6], Yanlei Zhang [7], Shuixiu Peng [7], Jinlong Xu [4], Jiajia Duan [4], Zelin Wang [4], Xinjian Yu [8], Qinlong Zheng [8], Xiuwen Xu [8], Ying Yuan [9], Fangrong Yan [10], Zhenglong Tian [11], Kaiting Tang [4], Jiecheng Zhang [12], Alex H Chang [7 13], Xiaoming Feng [2 14]

Chinese Academy of Medical Sciences (NCT04689659)

T-Cells Expressing a Second Generation CAR for Treatment of T-Cell Malignancies Expressing CD7 Antigen

Clinical data reported in JCO 2021

- 18/20 (90%) CR.
- 15/18 (88%) in CR after 6,5 months
- 7/18 (40%) went to allo-HSCT
- CRS 3-4 (10%) and ICANS 1-2 (10%).
- CD7+ T-cells were depleted BUT CD7- T-cells expanded & alleviated treatment-related T-cell immunodeficiency.
- Rest adverse effects were all reversible.

CD7-directed CD7/TCR/HLA/E-Cad/γc T-cells

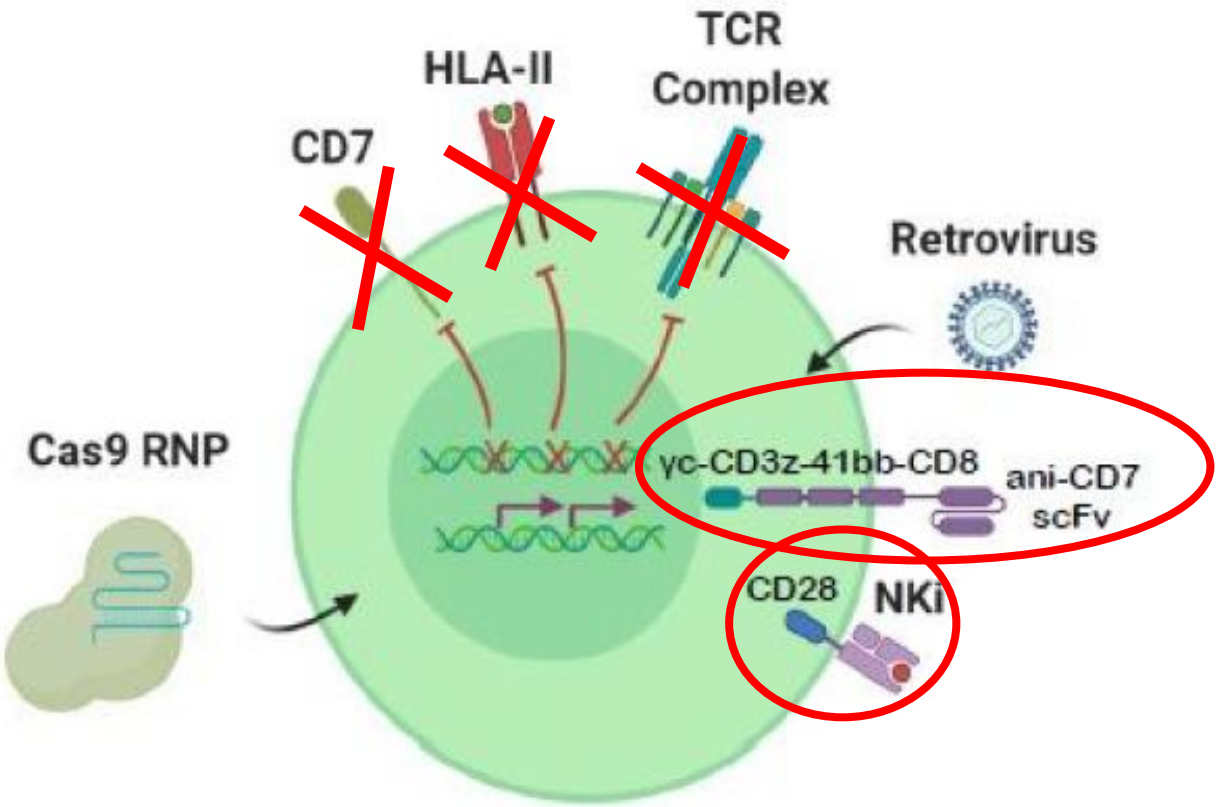
KO CD7 → overcomes T-cell fratricide

HLA-II KO → overcomes alloreactivity host to donor

KO TCR → overcomes GvHD (donor→host rejection)

E-cad-CD28 (NKi) → enhances NK cell immunosurveillance

γc → bypasses IL2 requirement



BIOHENG TRIAL (NCT04538599)
Zhejiang First Affiliated Hospital

Cell Therapy for High Risk CD7+ Malignancies Using CD7-Specific CAR Expressed on allogenic T Cells KO for CD7/TCR/HLA-II and expressing NKi and γc

CD7-directed CD7/TCR/HLA/E-Cad/γc T-cells

Trial overview and inclusion criteria

- R/R CD7+ tumors, mainly T-ALL and TCL with >20% of blasts CD7+
- Inclusion: not clearly stated
- Allogeneic, third-party
- γc-Nki-CD7.CAR-41BB-CD3z - triple KO for TCR/MHC-II, CD7
- Fludarabine + cyclophosphamide conditioning
- CART dose: $1x10^7/m^2$ - $2x10^7/m^2$ – $3x10^7/m^2$
- Primary endpoint: Dose Limiting Toxicity (safety)
- Secondary endpoint: Overall Response Rate (efficacy)
- N=12 pts up to 75 yo

Clinical data reported (ResearchSquare)

- No dose-limiting toxicity
- No GvHD
- No ICANS ; No CRS > grade
- 82% objective response; CCR: 75% T-ALL and 33% TCL

CLINICAL CURRENT SCENARIO

CAR T-cells targeting a non Pan T-cell Ag

Non pan-T cell CAR T-cells: CD30, TRBC1, CD1a…

ANTIGENS WITH RESTRICTED EXPRESSION					
CD30	17%*	16% (PTCL-NOS) 32–50%* (AITL) 93% (ALCL) 64%* (NK-T) 39% (ATLL) 18% (CTCL)	Activated T and B cells	Clinical Trial NCT02917083° NCT02690545° NCT03602157° NCT03383965° NCT03049449° NCT02958410°	(22–24)
TRBC1 (TCR)	7–11%	27% (PTCL-NOS) 34% (AITL) 25% (ALCL)	~35% of T cells	NCT03590574°	(20, 25–28)
CCR4	~0%	34% (PTCL) 88% (ATLL) 31–100% (CTCL)	Tregs, Th2 and Th17 cells Platelets Kidney		(29–32)
CD4	12%	60% (PTCL-NOS) 86% (AITL) 63% (ALCL) 29%* (NK-T) 94% (ATLL) 92% (CTCL)	$CD4^+$ T cells Some monocytes and Dendritic cells		(33, 34)
CD37	~0%	82%	Mature B cells At a low level in plasma cells Low levels in dendritic cells		(35, 36)

TRBC1 (T-cell R Beta Chain)-directed CAR T cells

- ✓ In contrast to T-ALL, many TCLs are TCR+ and depend on TCR for leukomogenesis.
- ✓ Malignant TCL cells are clonal while normal T-cells are bi-clonal for TRBC1 and TRBC2.
- ✓ Maciocia et al used TCRB1-directed CARTs….sparing normal T-cells.
- ✓ Fear of crosslinking of normal TCR decreasing persistence, anti-tumor activity and even inducing autoimmune symptoms.

Autolous (NCT03590574)
UCL, UK

Cell Therapy for T-cell Malignancies Using TRBC1-Specific CAR Expressed on autologous T Cells

Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies

Paul M Maciocia[1], Patrycja A Wawrzyniecka[1], Brian Philip[1], Ida Ricciardelli[2], Ayse U Akarca[1], Shimobi C Onuoha[3], Mateusz Legut[4], David K Cole[4], Andrew K Sewell[4], Giuseppe Gritti[5], Joan Somja[6], Miguel A Piris[7], Karl S Peggs[1], David C Linch[1], Teresa Marafioti[1] & Martin A Pule[1,3]

CD1a-directed CAR T-cells

blood®

Regular Article

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Fratricide-resistant CD1a-specific CAR T cells for the treatment of cortical T-cell acute lymphoblastic leukemia

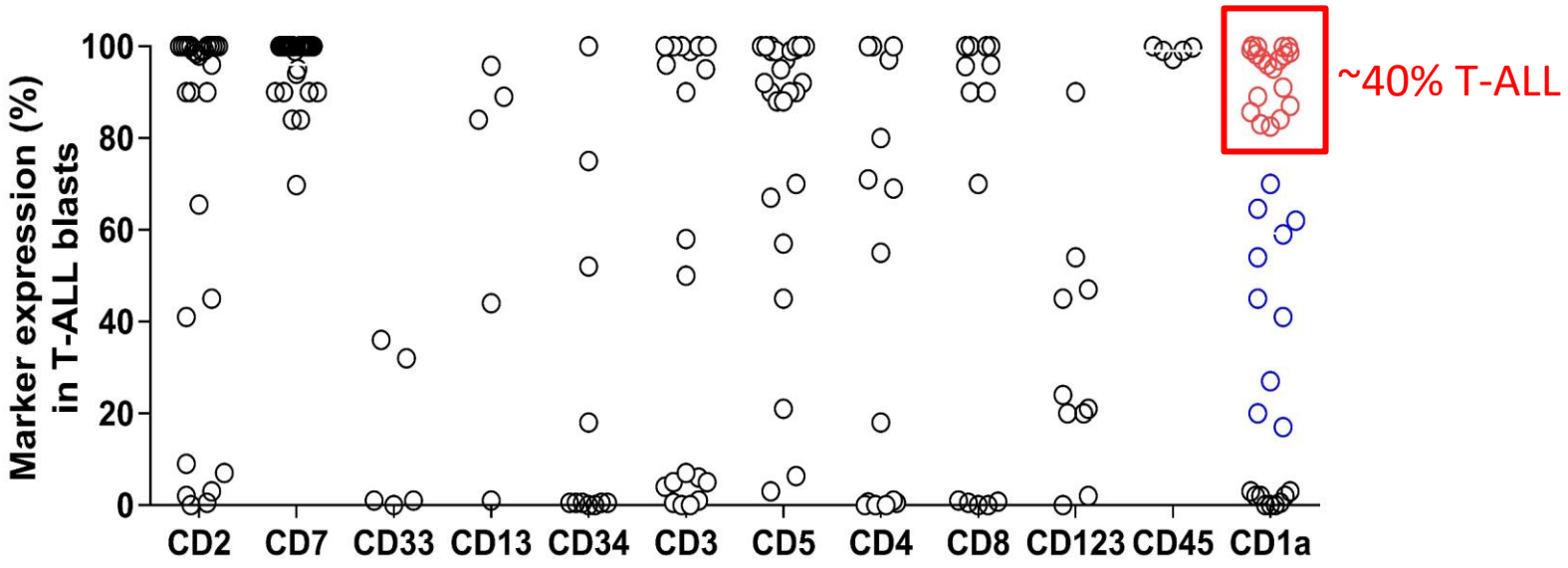
Diego Sánchez-Martínez,[1] Matteo L. Baroni,[1] Francisco Gutierrez-Agüera,[1] Heleia Roca-Ho,[1] Oscar Blanch-Lombarte,[2] Sara González-García,[3] Montserrat Torrebadell,[4,5] Jordi Junca,[6] Manuel Ramírez-Orellana,[7] Talía Velasco-Hernández,[1] Clara Bueno,[1] José Luís Fuster,[8,9] Julia G. Prado,[2] Julien Calvo,[10] Benjamin Uzan,[10] Jan Cools,[11] Mireia Camos,[4,5] Françoise Pflumio,[10] María Luisa Toribio,[3] and Pablo Menéndez[1,12,13]

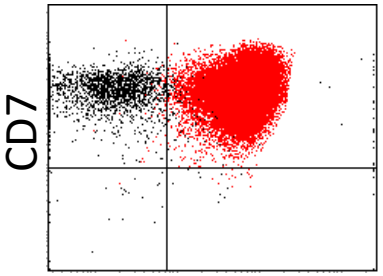
OneChain Tx, Barcelona. Spain (EudraCT 2021-002333-42)

Adoptive CD1a-directed CAR T cells for R/R CD1a+ tumors (cortical T-ALL and CD1a+ Ly-TCL)

Considerations on CD1a CAR T-cells

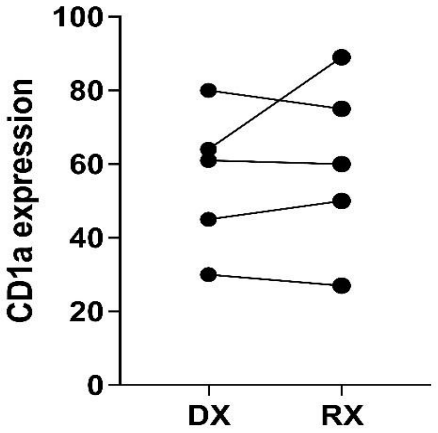
✓ CD1a is specifically expressed in cortical T-ALL and some TCLs and highly retained at relapse.



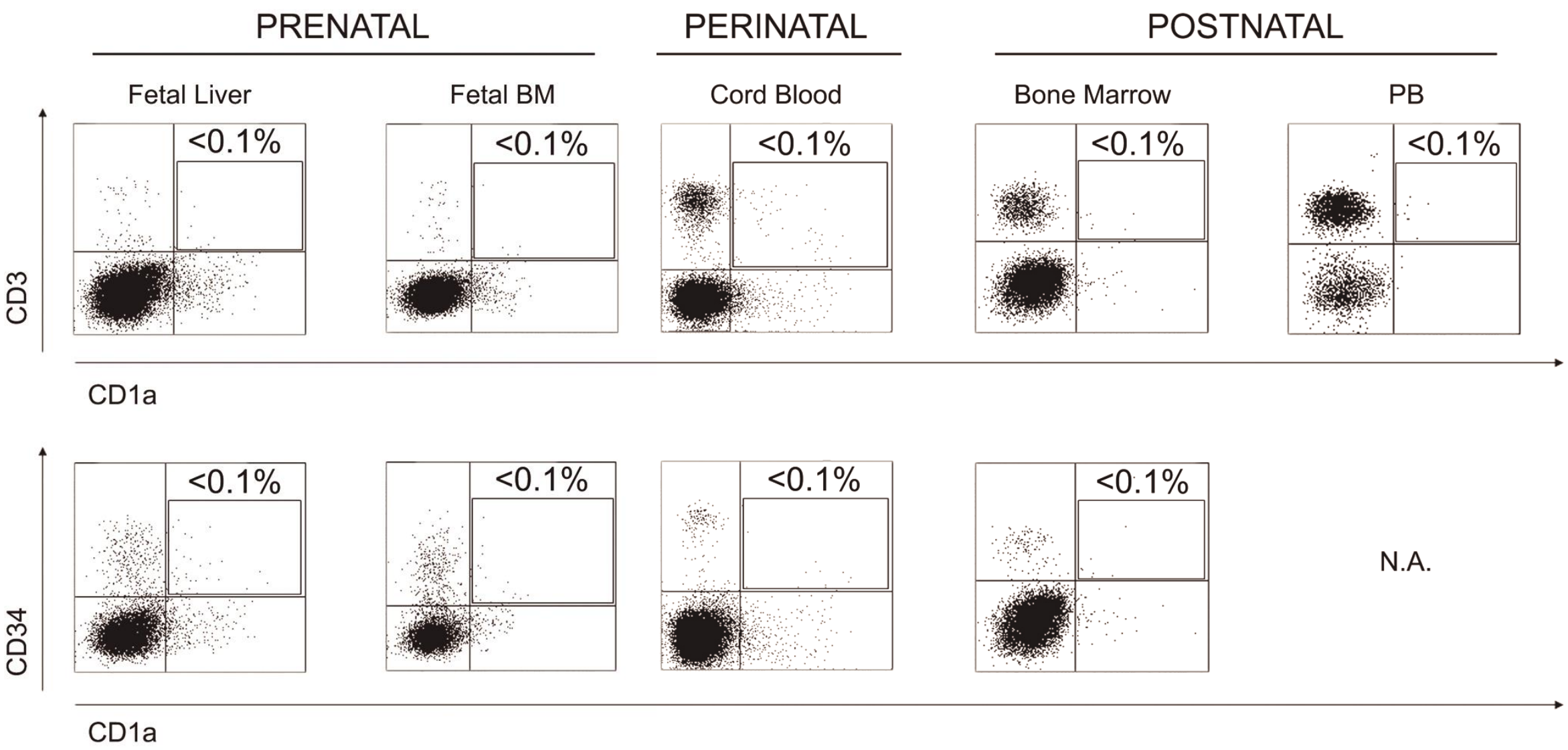


coT-ALL blasts
Normal T cells

No fratricide

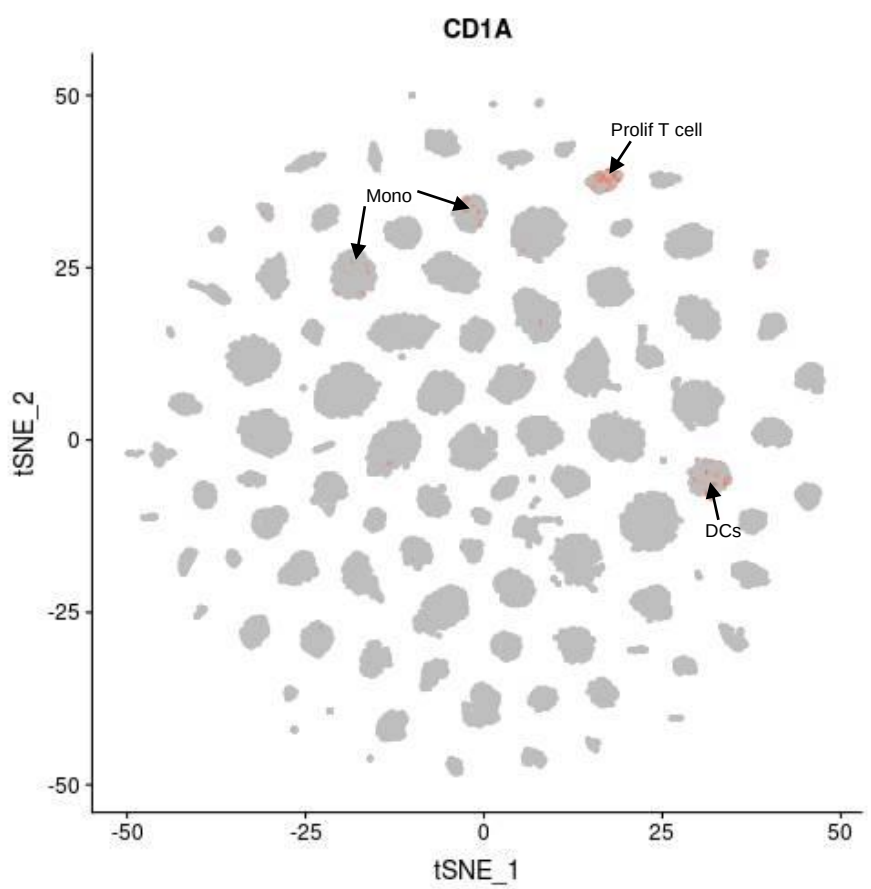


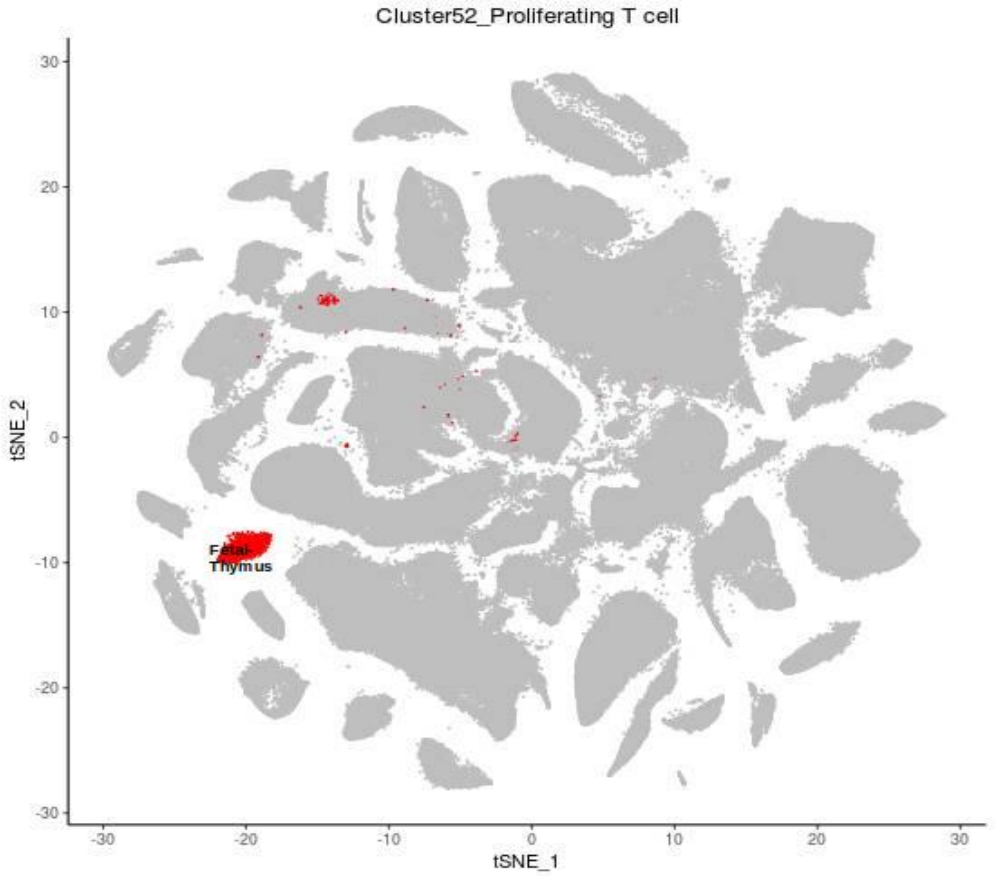
Considerations on CD1a CAR T-cells



Human single cell atlas reveals very restricted expression for CD1a

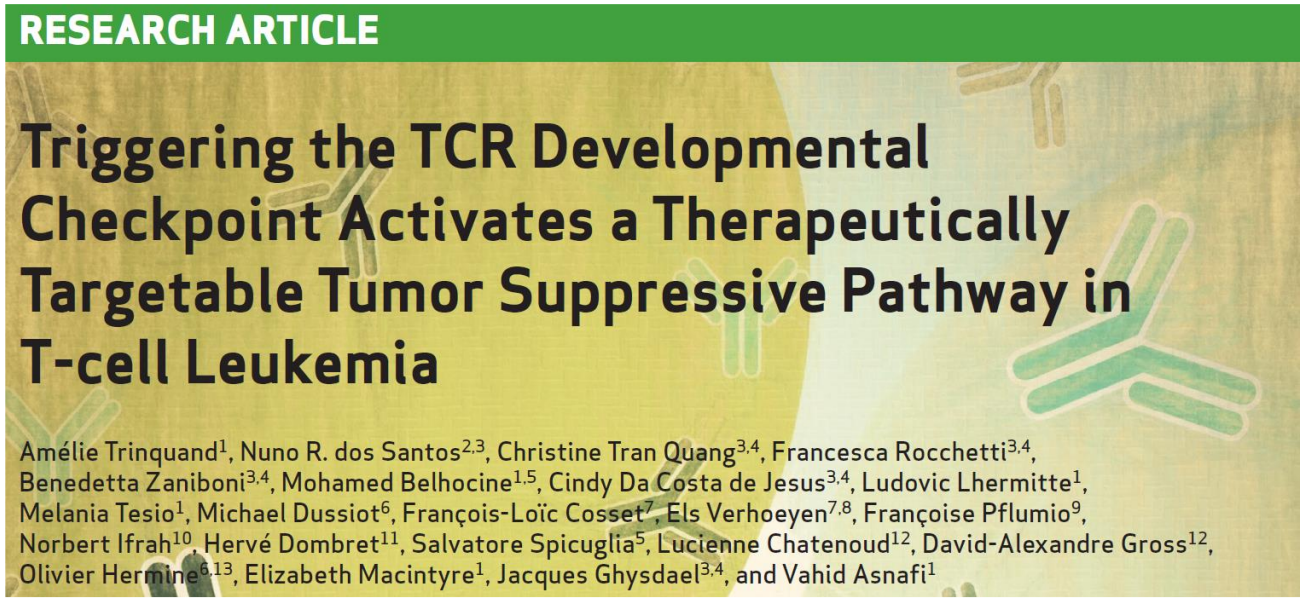
Nature vol 581, 303–309 (2020)





- Normalized expression across **700k** cells on **50** human tissues
- Mostly expressed in prolif thymocytes
- Some expression in skin DCs.

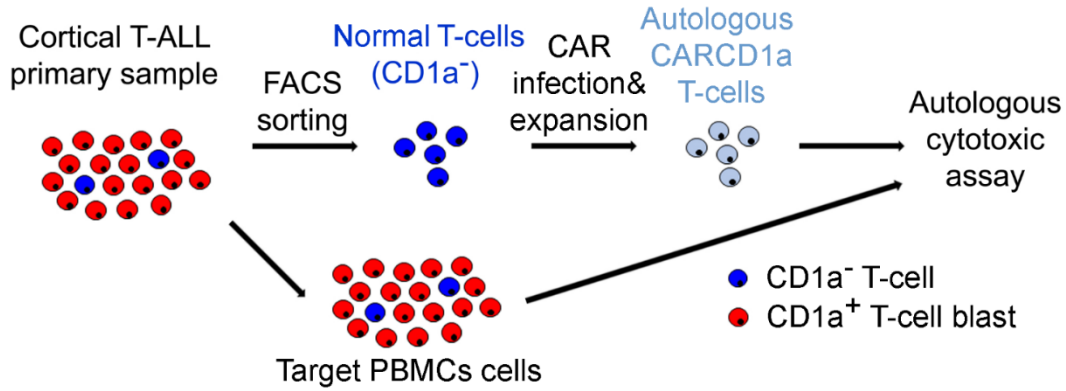
TCR stimulation eliminates T-cell blasts: safe manufacturing

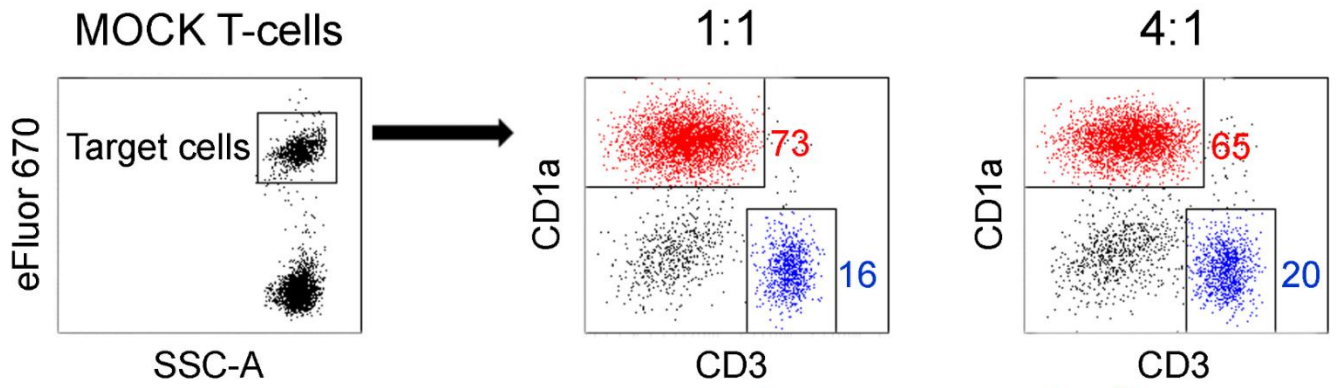


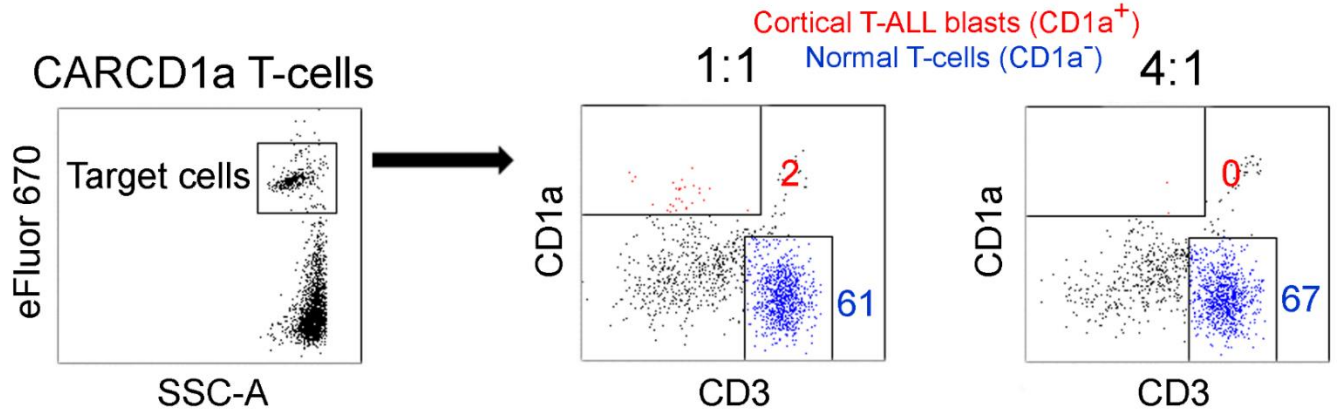
A TCR-switchable cell death pathway in T-ALL

Christine Tran Quang, Benedetta Zaniboni, Jacques Ghysdael

Autologous CARCD1a T-cells eliminates coT-ALL blasts







European recruitment network needed

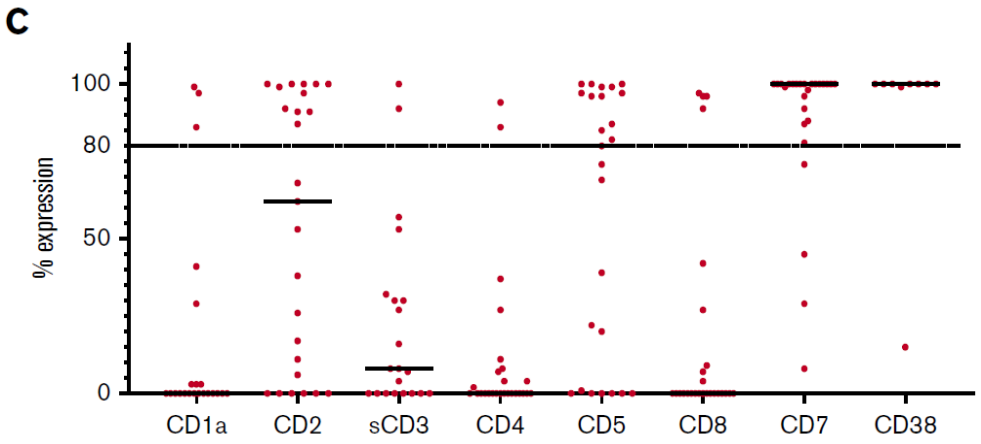
COMMENTARY

blood advances

TO THE EDITOR:

CD1a is rarely expressed in pediatric or adult relapsed/refractory T-ALL: implications for immunotherapy

Sarah Leong,[1] Sarah Inglott,[2] Foteini Papaleonidopoulou,[3] Karen Orfinada,[4] Philip Ancliff,[2] Jack Bartram,[2] Ben Carpenter,[1] Adele K. Fielding,[1,3] Sara Ghorashian,[2] Victoria Grandage,[1] Rajeev Gupta,[1,3] Rachael Hough,[1] Asim Khwaja,[1,3] Vesna Pavasovic,[2] Anupama Rao,[2] Sujith Samarasinghe,[2] Ajay Vora,[2] Marc R. Mansour,[1,3] and David O'Connor[2,3]



OneChain IMMUNOTHERAPEUTICS

CLÍNIC BARCELONA Hospital Universitari

SJD Sant Joan de Déu Barcelona · Hospital

Clinical design CD1a Phase I – EU open

- ✓ **Humanized CD1ascFv – 41BB** (Kanamycin rather than Amp)
- ✓ **Autologous T-cells**
- ✓ **Exploratory, open-label, single-arm, multicentre, non-competitive, dose escalation study to assess the safety and efficacy.**
- ✓ **Indication: Children and adults with R/R CD1a+ T-ALL/LL after a minimum of two standard therapy lines**
- ✓ **Blast expression ≥20% at inclusion**
- ✓ **Conditioning treatment: Fludarabine+cyclophosphamide**
- ✓ **Dose: $5x10^5$ to $5x10^6$ cells/kg body weight (4 cohorts; 3 +3 design)**
- ✓ **Split dose (10%-30%-60%) in three days in a row – will avoid CRS/ICANS**

Clinical design CD1a Phase I – EU open

Main Safety Endpoints

- Incidence and severity of severe CRS and ICANS
- Assessment of overall toxicity
- Non-relapse, treatment-related mortality (NRM)
- Number of Adverse events of especial interest (AESI)
- Assessment of the Immunological homeostasis
- Assessment of the treatment-related dermatological effects

Main Efficacy endpoints

- Remission rate
- Duration of Response (DOR) after CAR infusion
- Progression-free Survival (PFS) after administration
- Overall survival
- MRD response in CR patients
- Genomic copy number of CAR in PB T-cells and % of CAR-expressing T cells

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Talía Velasco
Meritxell Vinyoles

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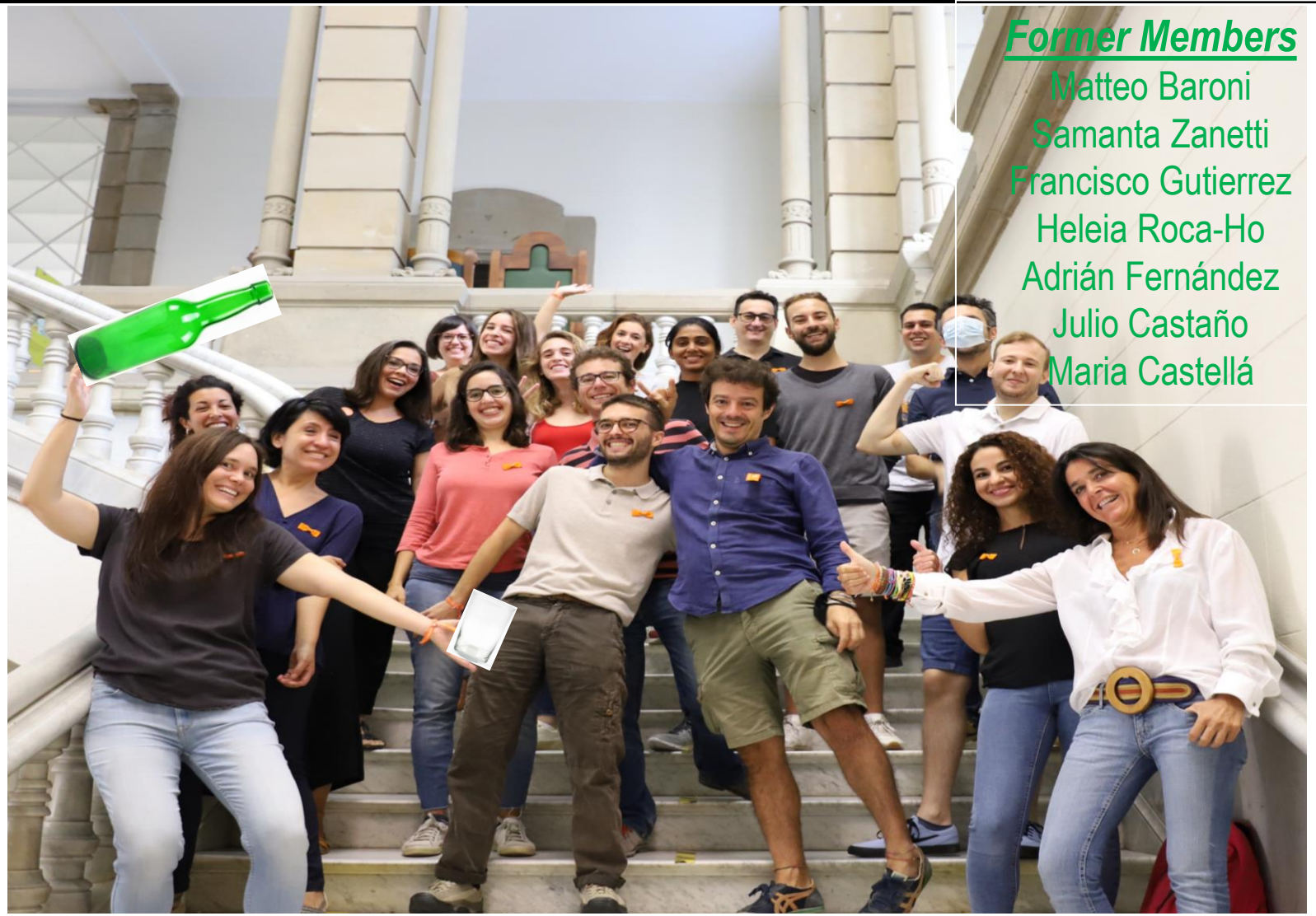
Jorge Alemany
Wilmar Castillo
Victor Díaz
Laura García



Former Members

Matteo Baroni
Samanta Zanetti
Francisco Gutierrez
Heleia Roca-Ho
Adrián Fernández
Julio Castaño
Maria Castellá

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