TEDDY – European Network of Excellence for Paediatric Clinical Research

Cell and advanced therapies for children with cancer "Cells4kids"

Antonio Pérez-Martínez[1,2,3,4]

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Cell and advanced therapies for children with cancer

1. A dream comes true: “Immunotherapy as reality”

2. Immune effector cells as old new drugs for childhood cancer
   a) The killer cells
   b) The memory cells
   c) The cell engineering

3. Hospital needs transformation: Research University Hospital

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Cytotoxic lymphocyte

James A Sullivan. Quill Graphics. Charlottesville, VA, USA

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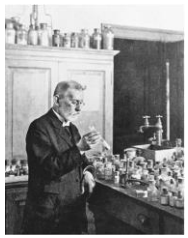
"From immune hypothesis to drug development"



Paul Ehrlich: Hypothesis that host defense forces may prevent neoplastic cells from developing tumors.

Gross and Foley: first clear demonstration of specific capability of tumours to stimulate immune response.

1909 | 1953 | 1957 | 2002 | 2012 | 2018

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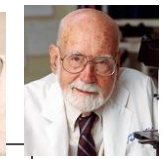

Innovative Therapies for Children with Cancer ITCC European Consortium

Next generation sequencing

Immunotherapy

Total chemotherapy	HSCT	Clinical trials	Personalized medicine	Cell therapy and advances therapies
1955-1990	1990	2000	2005	2010

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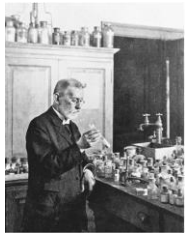
"From immune surveillance to cancer immunoediting"



Paul Ehrlich: Hypothesis that host defense forces may prevent neoplastic cells from developing tumors.

Gross and Foley: first clear demonstration of specific capability of tumours to stimulate immune response.

Lewis Thomas and MacFarlane Burnet: *The theory of immune surveillance.*

Ralph Schrelber: *The theory of immunoediting.*

Tasuku Honio and James P Allison: *The checkpoint inhibitors*

1909 1953 1957 2002 2012 2018

MILESTONES IN IMMUNOTHERAPY OF CANCER

1957 Bone Marrow Trasplant

1984 IL-2 Immunotherapy

1988 Adoptive T cell

1997 Antibody therapy
2002 NK cell alloreactivity

2012 Dendritic cell vaccines
2013 Checkpoint inhibitor
2017 CART cell therapies

Donald Thomas

Premio Nobel

1990

Tasuku Honjo James P Allison

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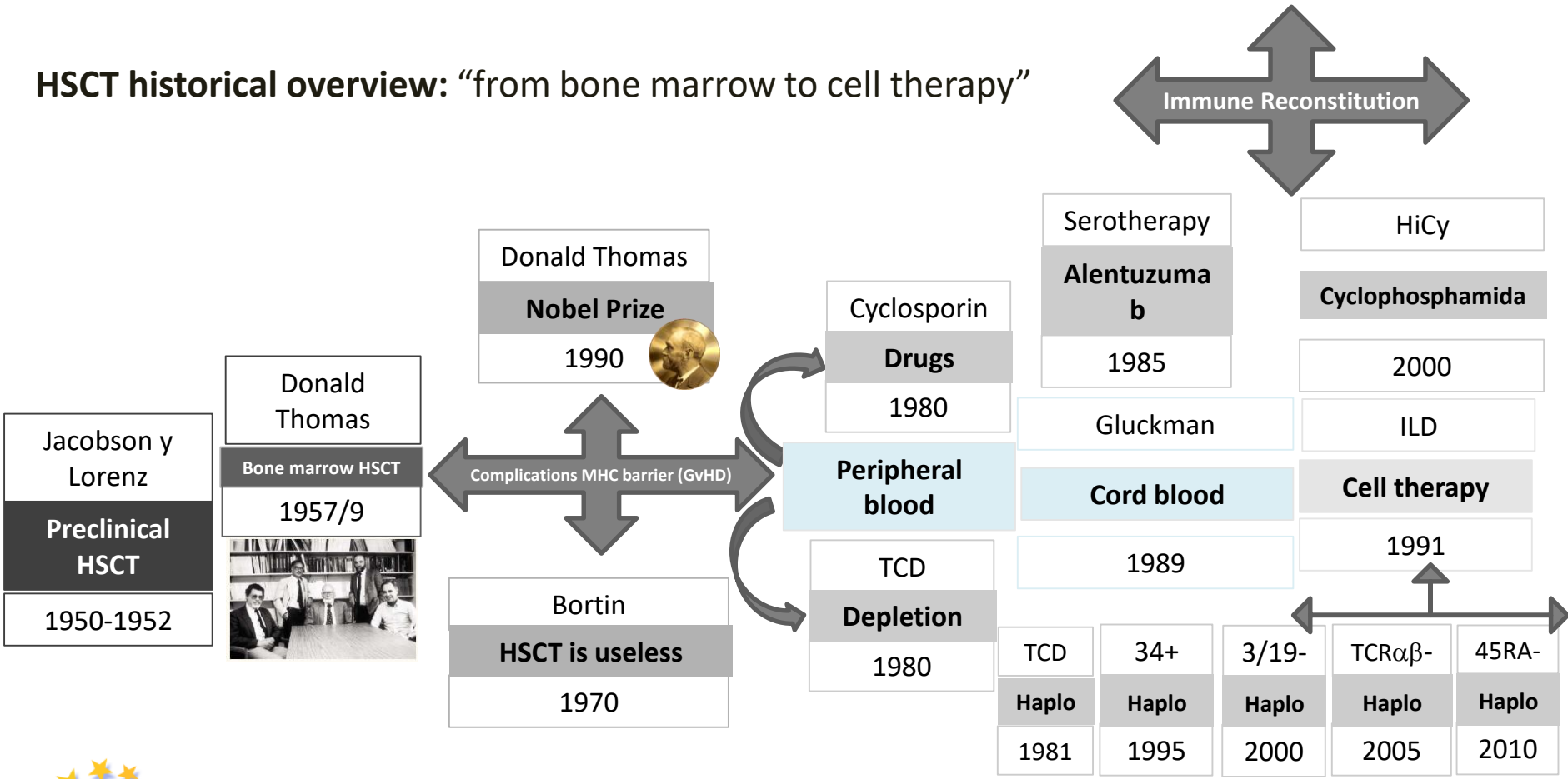
HSCT outcome: "from chemo to immune THERAPY"

HSCT historical overview: "from bone marrow to cell therapy"



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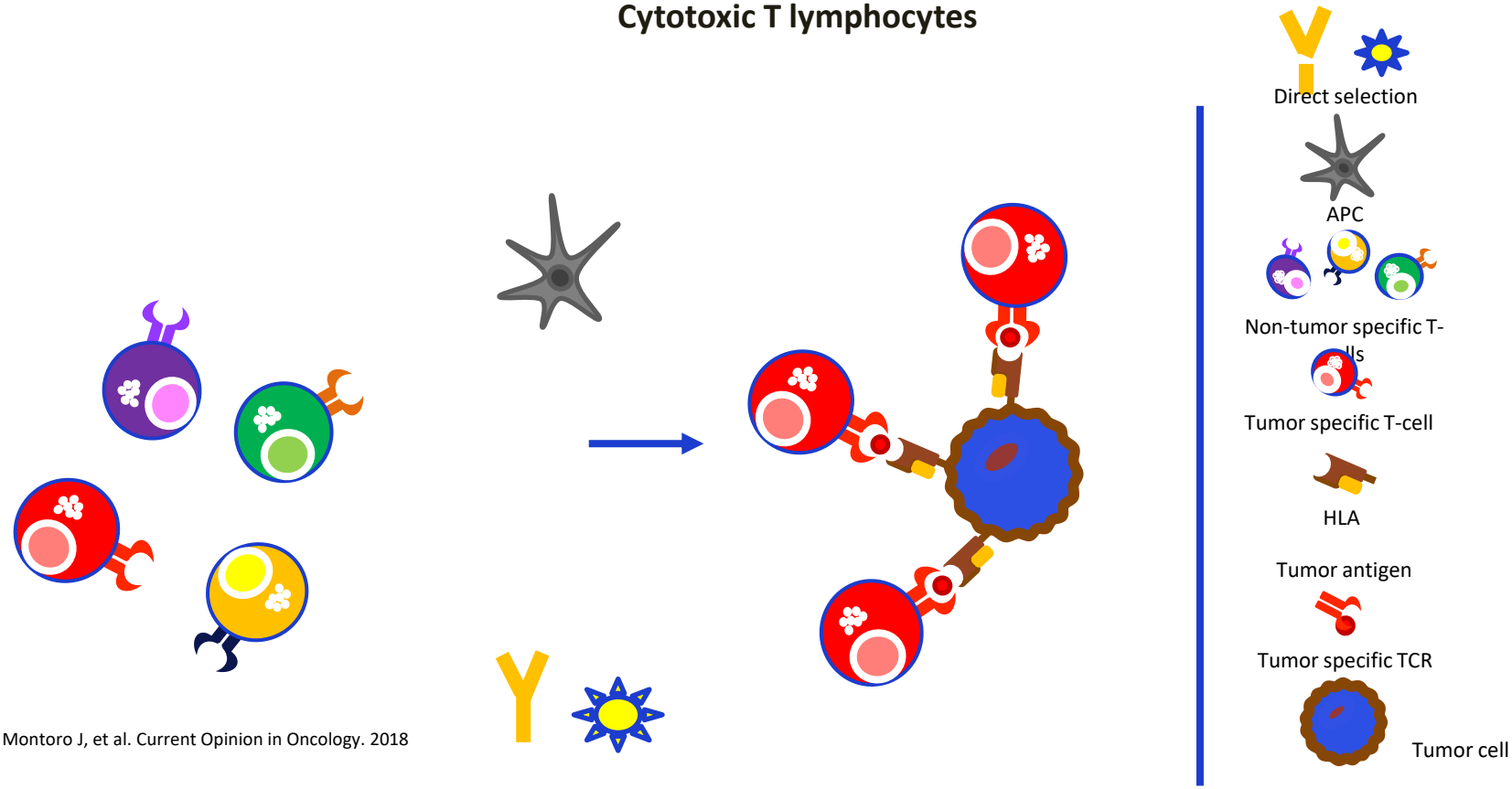
Cytotoxic T lymphocytes



Montoro J, et al. Current Opinion in Oncology. 2018

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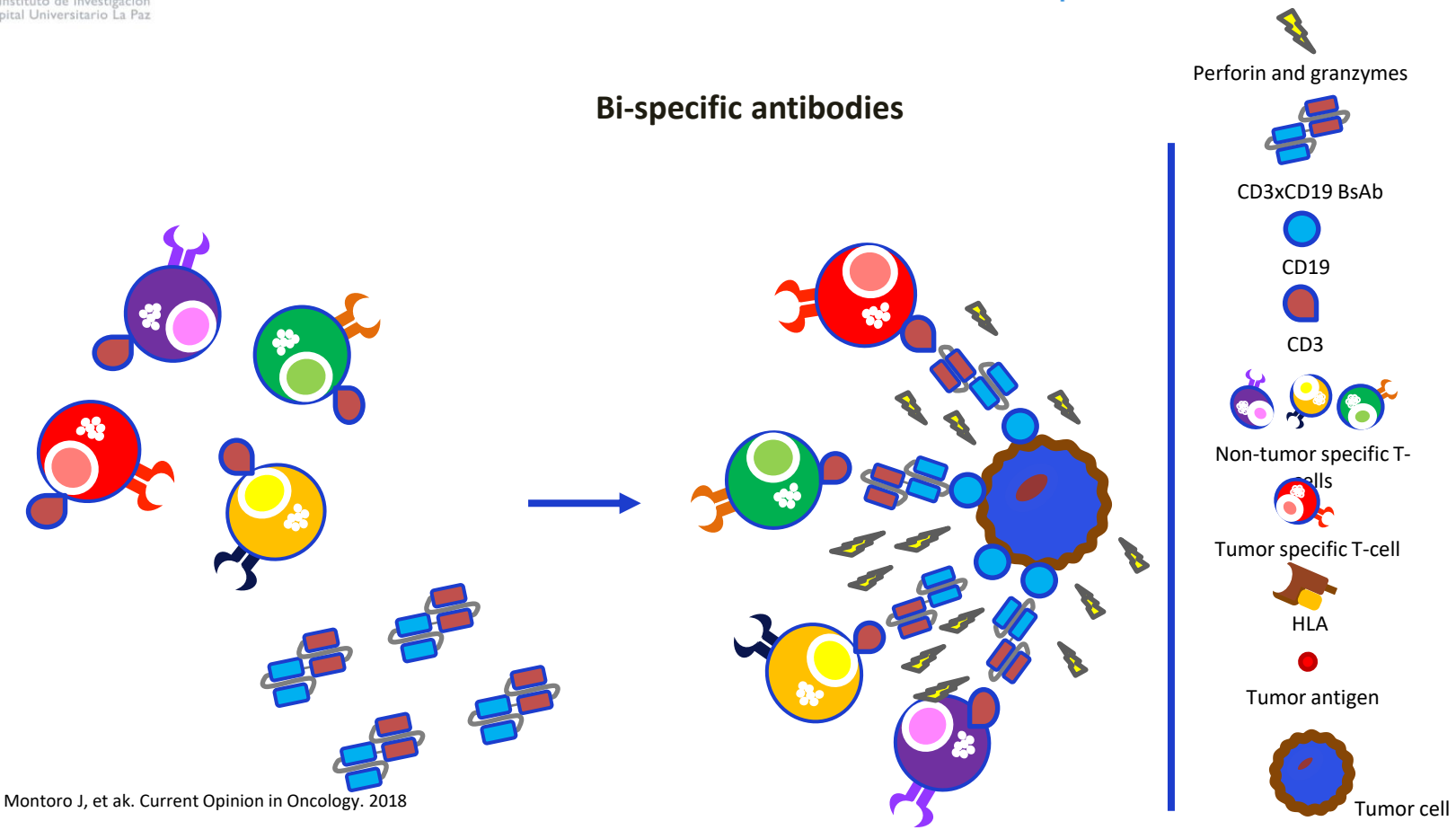
Bi-specific antibodies



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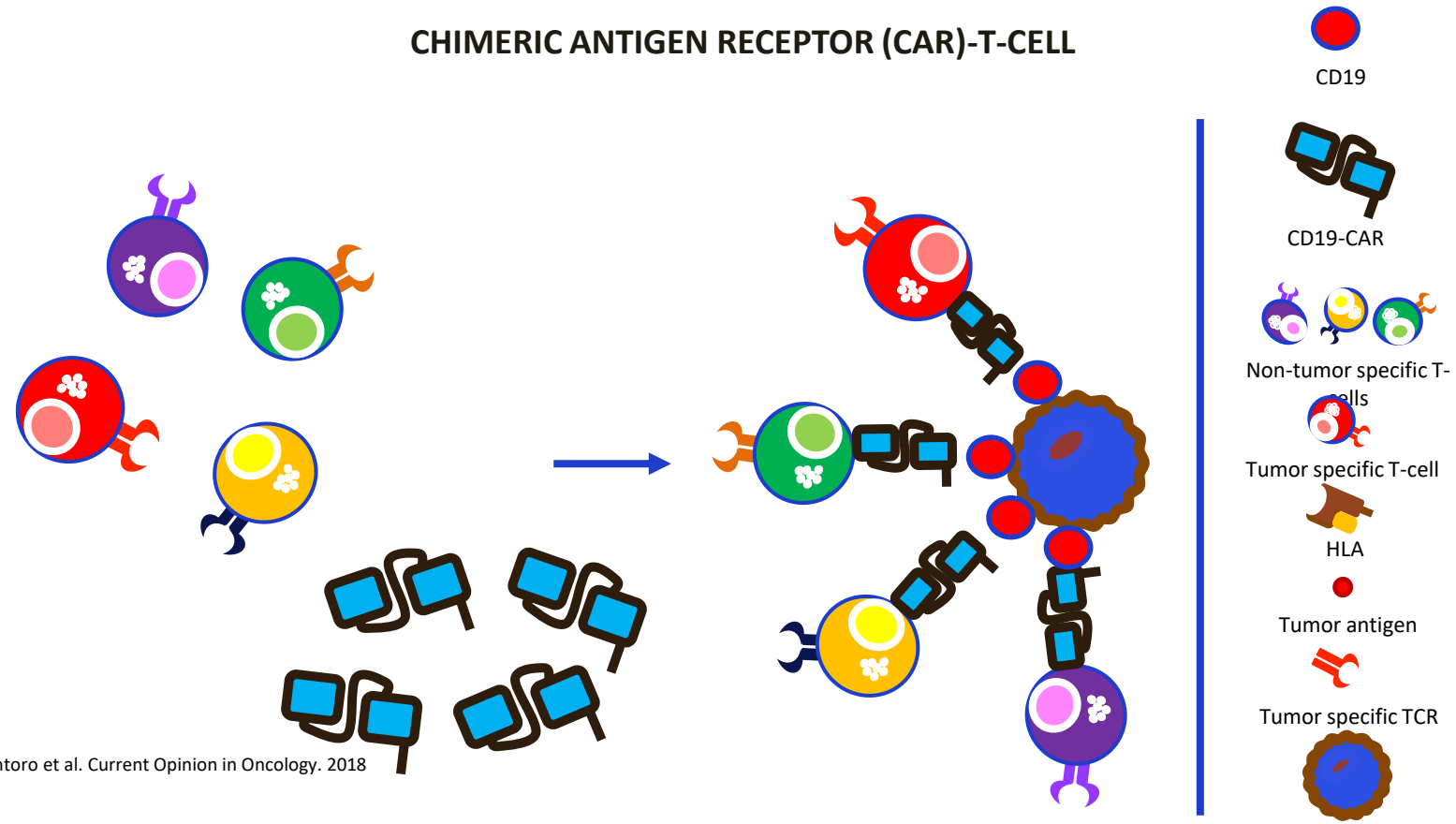
CHIMERIC ANTIGEN RECEPTOR (CAR)-T-CELL



Montoro et al. Current Opinion in Oncology. 2018

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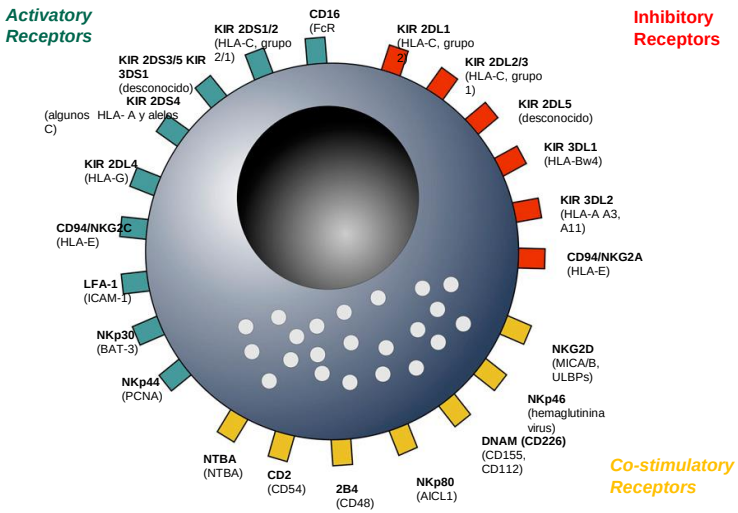
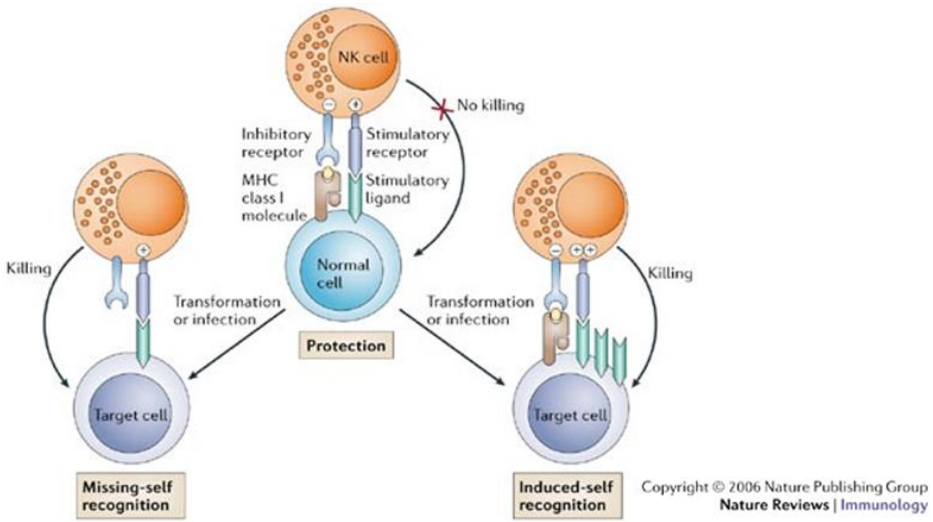
Natural Killer cells for cancer cell therapy





- ✓ These functions are performed in the context of a learning process ("licensing") regulated mainly by inhibitory KIR receptors and their ligands (HLA class I molecules, in humans).
- ✓ In a basal situation the cells of the different tissues express their own ligands (self), HLA class I, so they are protected.

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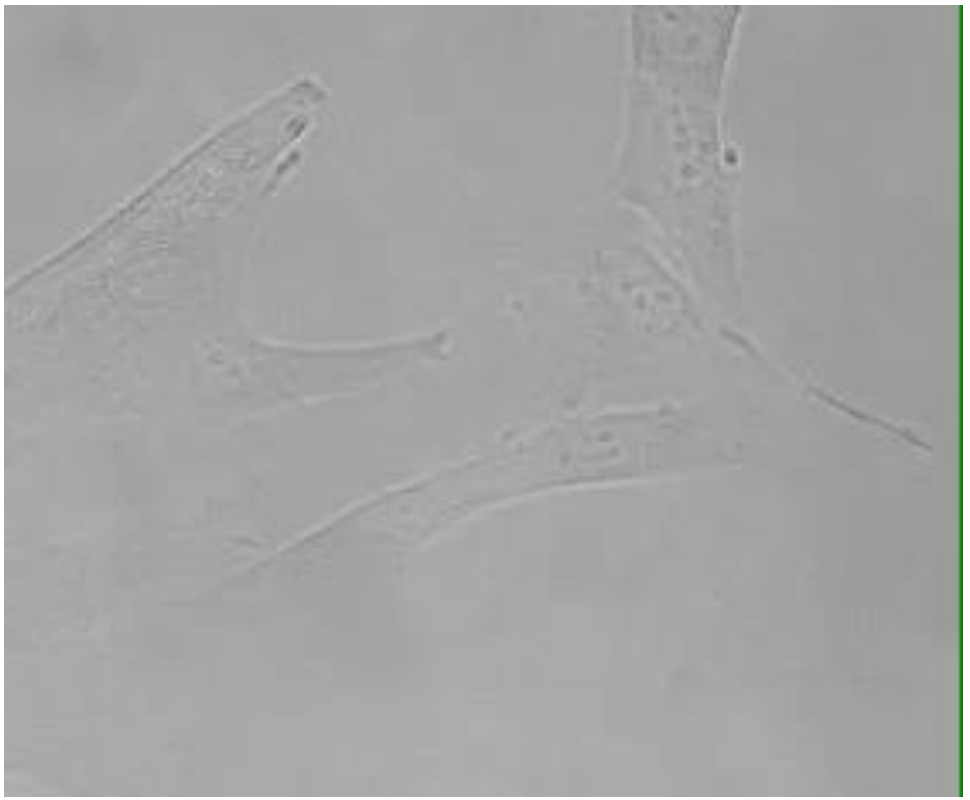
Natural Killer cells for cancer cell therapy



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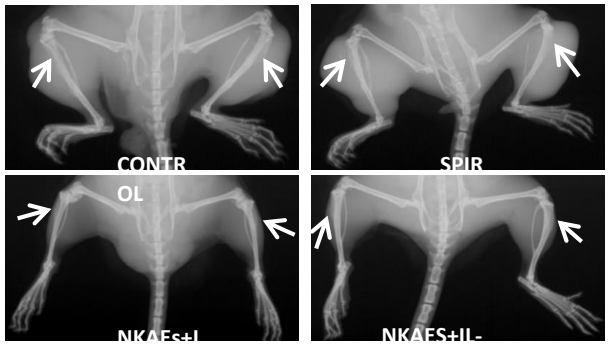
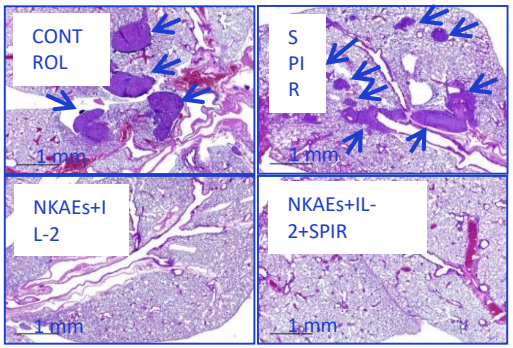
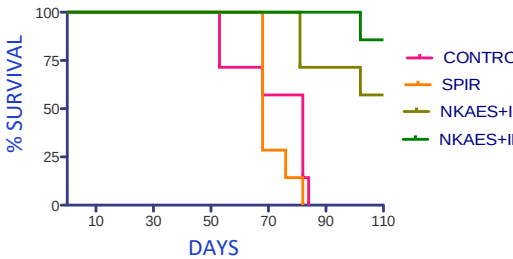
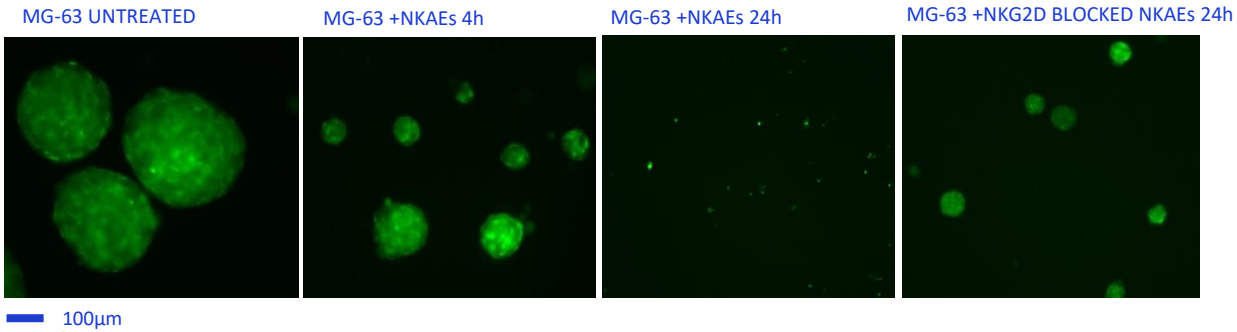
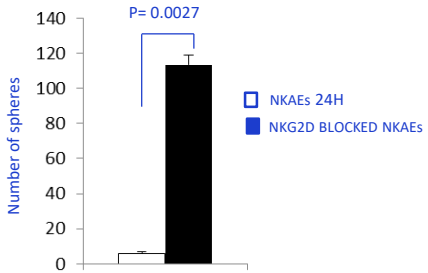






Fernández L et al. Cancer Letter 2016.



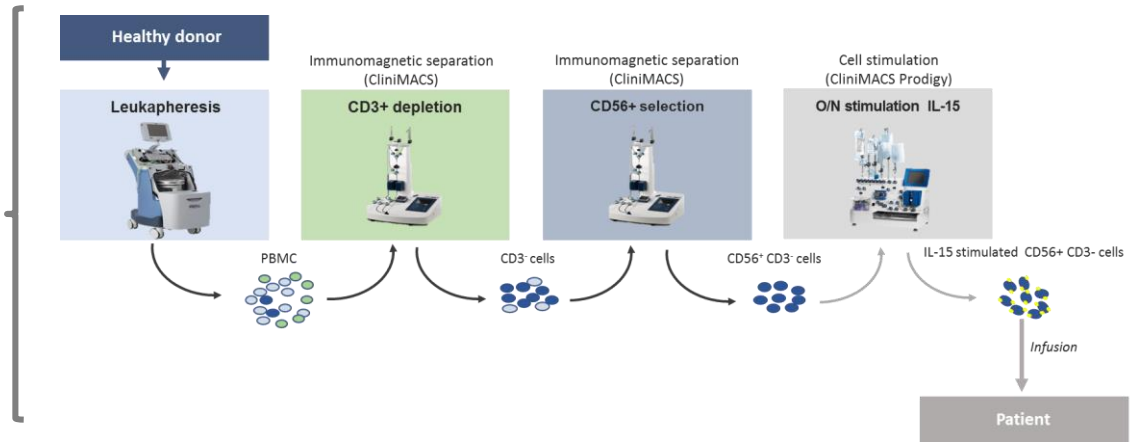


Fernández L et al. Cancer Letter 2016.

Natural Killer cells for cancer cell therapy

Activation and expansion protocols:

- **Overnight stimulation with IL-15**



- **15-21 days co-culture with K562-mb15-4.1bbl**

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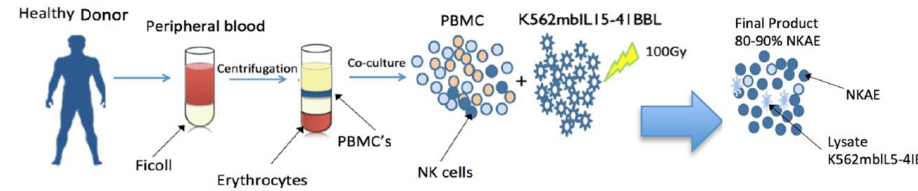

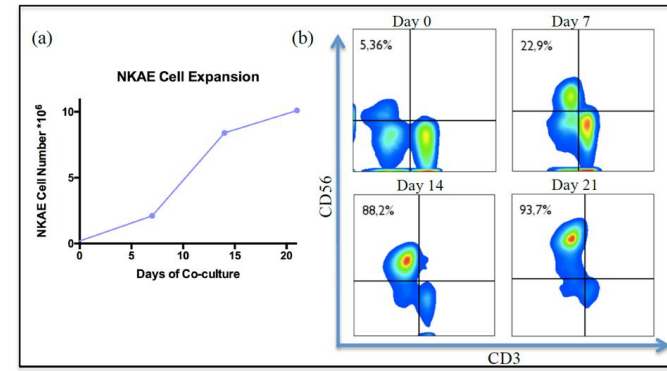

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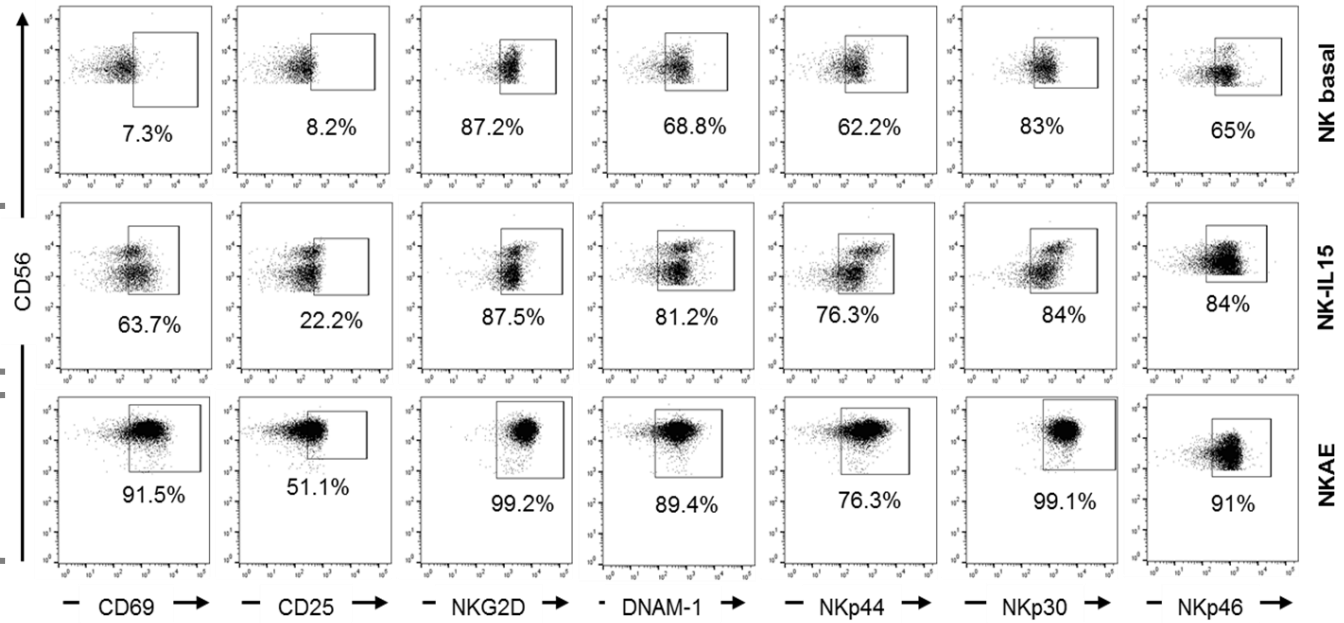

Fernández F, et al. Transfusion 2018. How do we manufacture clinical-grade interleukin-15-stimulated natural killer cell products for cancer treatment?

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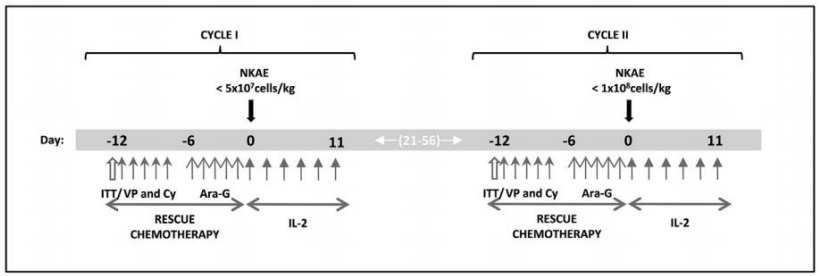
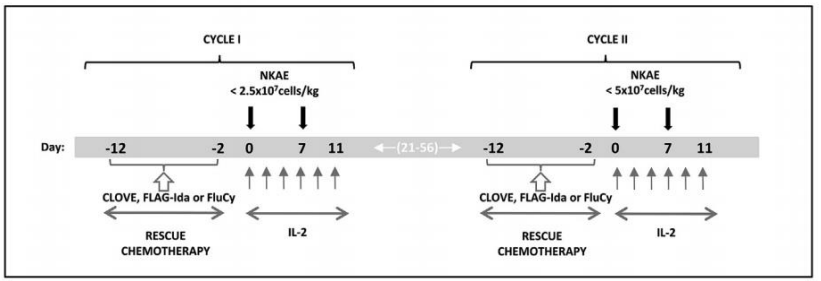
Natural Killer cells for cancer cell therapy

❖ HNJ-NKAES-2012



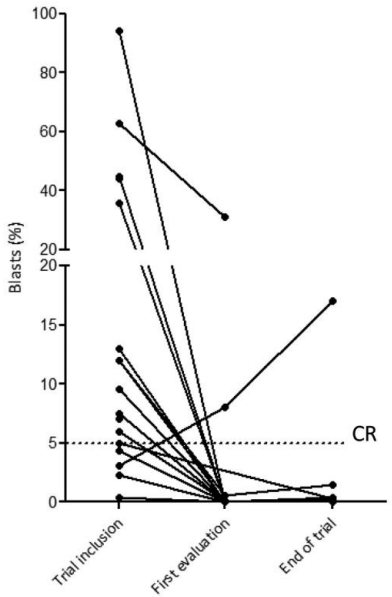
❖ LYDIA



- In both cases, two cycles of rescue chemotherapy followed by NKAE and IL-2 infusions were administered

Vela M, et al. Cancer Lett. 2018. Haploidentical IL-15/41BBL activated and expanded natural killer cell infusion therapy after salvage chemotherapy in children with relapsed and refractory leukemia.

Natural Killer cells for cancer cell therapy



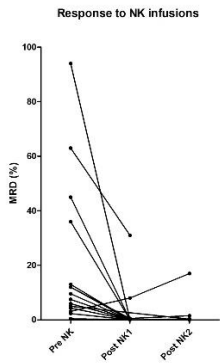
- **Bone marrow response to treatment.**

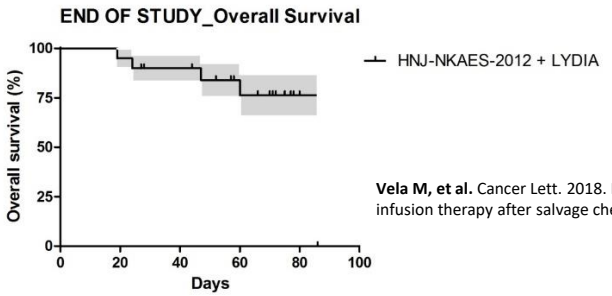
  Percentage of blasts of each patient at trial inclusion, after first treatment cycle and at he end of the study are indicated.

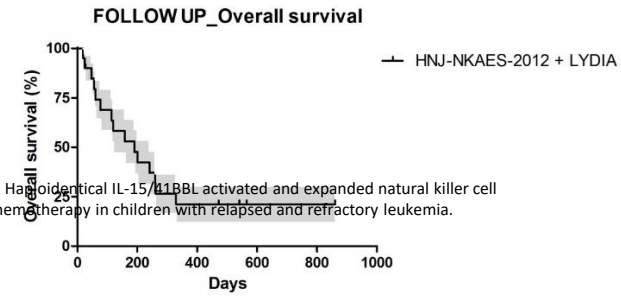
Vela M, et al. Cancer Lett. 2018. Haploidentical IL-15/41BBL activated and expanded natural killer cell infusion therapy after salvage chemotherapy in children with relapsed and refractory leukemia.

Natural Killer cells for cancer cell therapy

	NCT01944982	NCT02074657	
	HNJ-NKAEs (EudraCT: 2012-005146-38)	LANK-2/LYDIA (EudraCT: 2012-000054-63)	Total
Characteristic	7	13	20
Response (%)			
Cytological remission	3 (42)	4 (30)	7 (35)
MRD negative	2 (28)	5 (38)	7 (35)
Progression	1(16)	1 (16)	2 (10)
Died because toxicity	1(16)	3 (23)	4 (20)
Get a HSCT (%)	3 (42)	7 (53)	10 (50)
Status			
Alive without disease	1 (14)	5 (38)	6 (30)
[illegible]	150 (27-230)	177 (19-350)	164 (19-350)



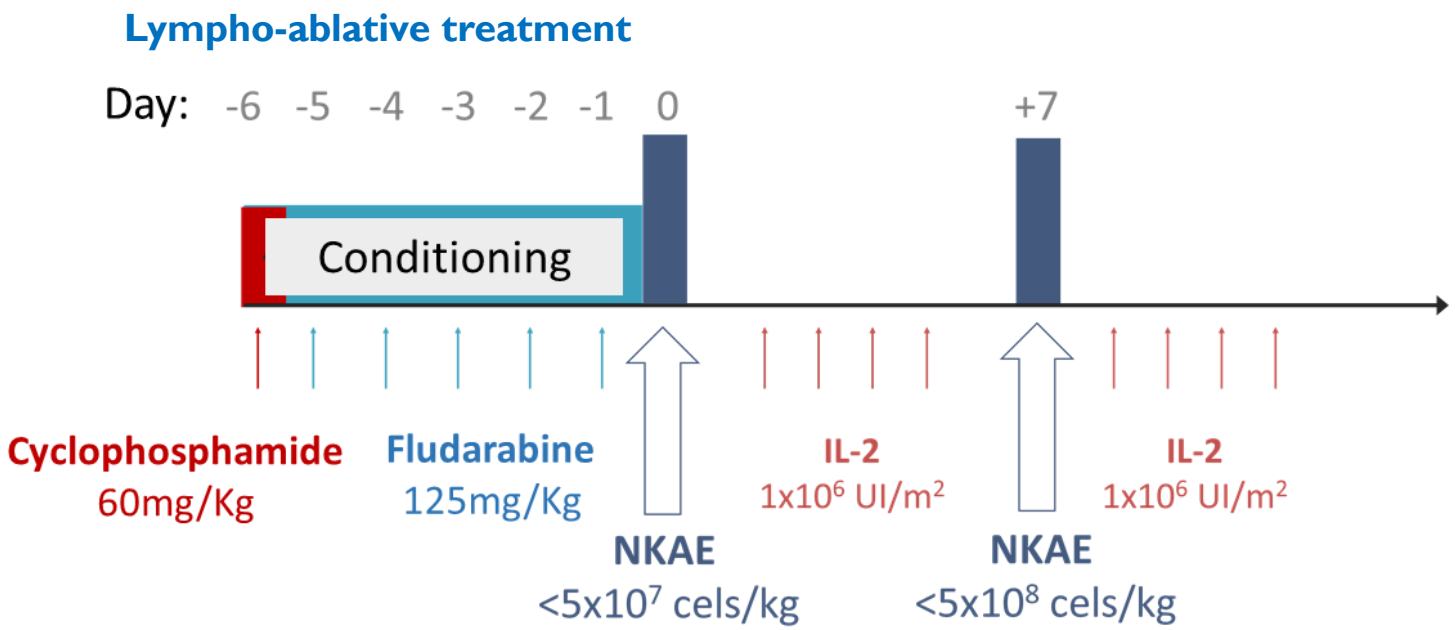




Vela M, et al. Cancer Lett. 2018. Haploidentical IL-15/41BBL activated and expanded natural killer cell infusion therapy after salvage chemotherapy in children with relapsed and refractory leukemia.

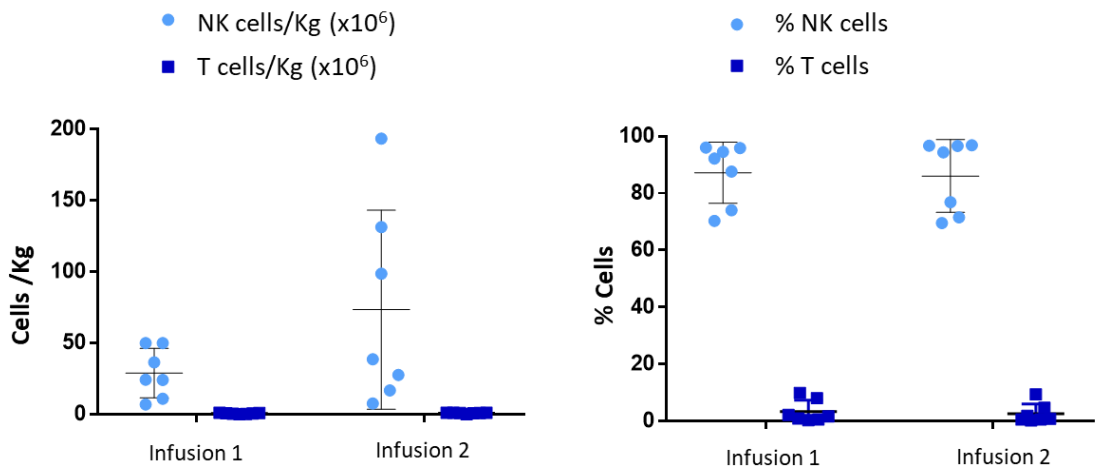
Lydia II trial Protocol

Previous treatment: Spanish protocol (SEHOP 2002) including 2 inductions + 2 consolidation cycles



Sissini L, et al. EBMT Cell Therapy oral communication 2019.

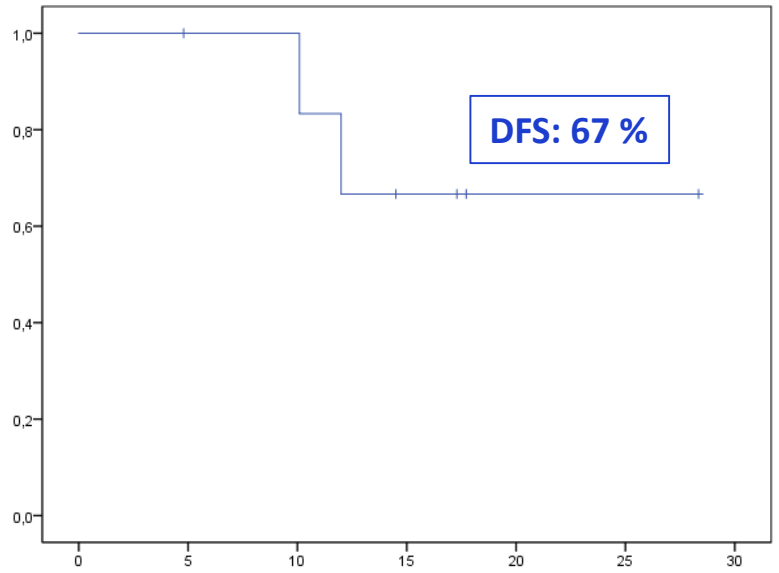
Characteristics of NKAE products infused



13 products in 7 patients	cells/kg ($x10^6$)	%
NK cells	**51.14** ± 53.99	**86.64** ± 11.36
T lymphocytes	0.69 ± 0.35	2.94 ± 3.55

Sissini L, et al. EBMT Cell Therapy oral communication 2019.

Results



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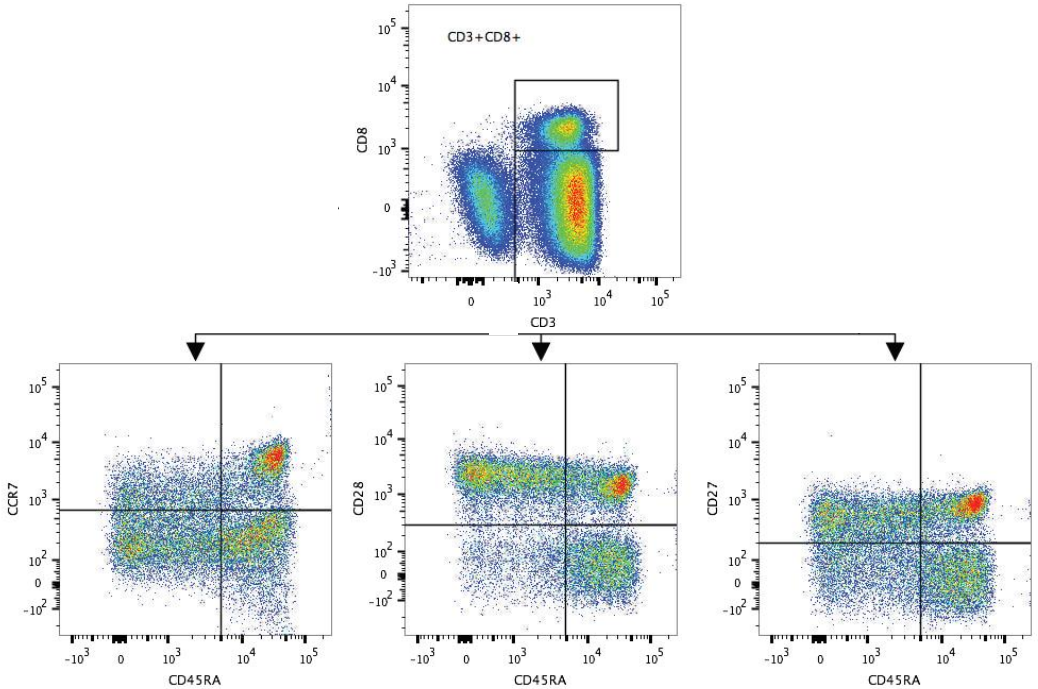
Why memo T cell as adoptive immunotherapy?



These subsets:

1. **Baive (CD45RA+CD27+),**
2. **Central memory (CM; CD45RA-CD27+),**
3. **EM (CD45RA-CD27-),**
4. **EMRA (CD45RA+CD27-)**

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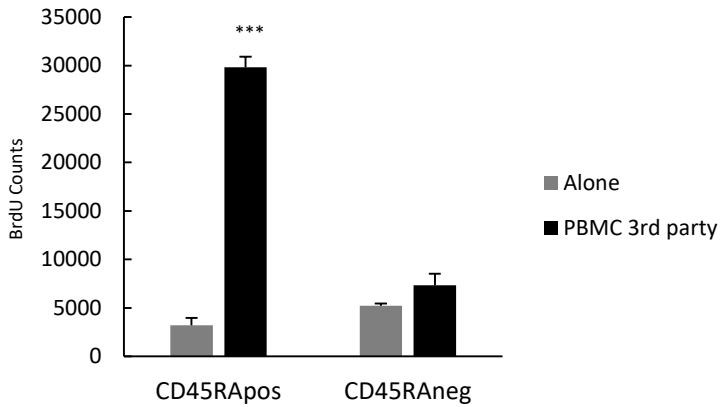

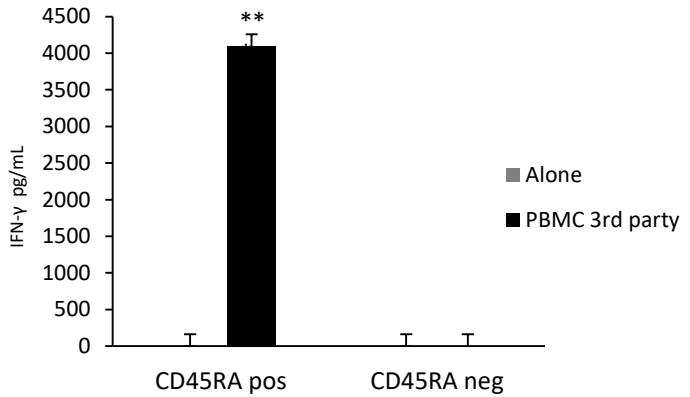

Fernandez L et al. Clin Can Research 2017

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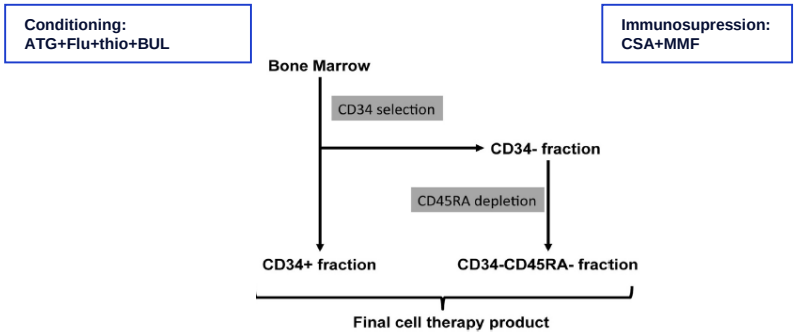


n=5	CD34+	CD3+	T naive	NK	CD14	B cells
X10e6/kg (CD45RA)	11	89	<0.003	0.16	1.21	0

- **Bone marrow mismatch related Graft**.
- Myeloablative conditioning.
- 4/5 engraftment.
- 1/5 aGvHD grade I.
- No viral disease
- 4/5 alive
- Clinical grade depletion of CD45RA naïve T cells from an allograft might be a treatment option for patients with combined immunodeficiency at high risk of GvHD, infection, or both in an HLA mismatch setting.

Touzot et al. J Allergy Clin Immunol. 2015

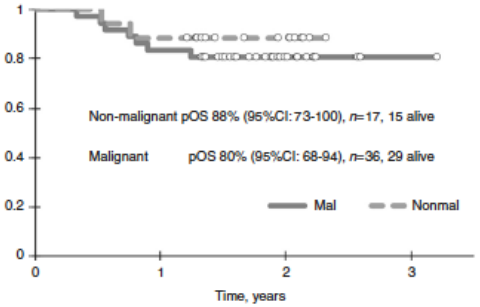
Why memo T cell as adoptive immunotherapy?

Bone Marrow Transplantation (2018) 53:264–273
https://doi.org/10.1038/s41409-017-0035-y

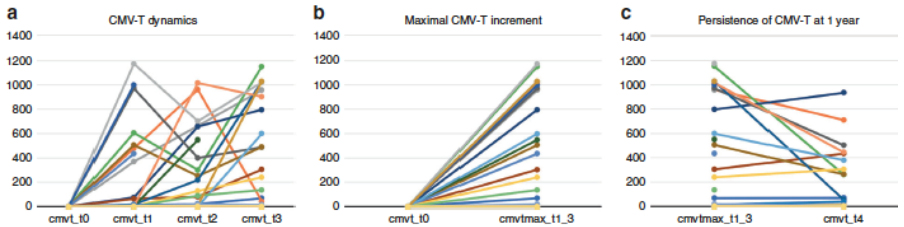
ARTICLE

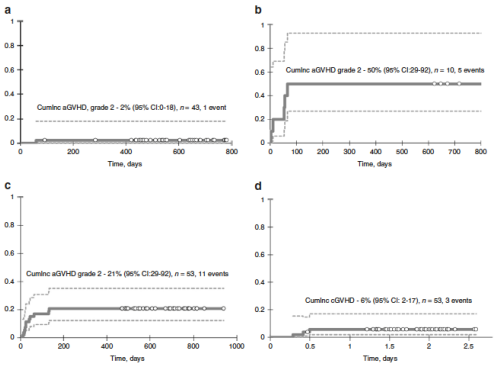
Low-dose donor memory T-cell infusion after TCR alpha/beta depleted unrelated and haploidentical transplantation: results of a pilot trial

Michael Maschan[1] · Sergey Blagov[1] · Larisa Shelikhova[1] · Zhanna Shekhovtsova[1] · Dmitriy Balashov[1] · Julia Starichkova[2] · Elena Kurnikova[3] · Elena Boyakova[4] · Yakov Muzalevskii[3] · Alexei Kazachenok[3] · Pavel Trakhtman[3] · Elena Osipova[5] · Natalia Khripkova[5] · Vladimir Zhogov[5] · Galina Novichkova[6] · Alexei Maschan[1]



MemoryT-cell DLI after αβT-depleted haplo and MUD HSCT





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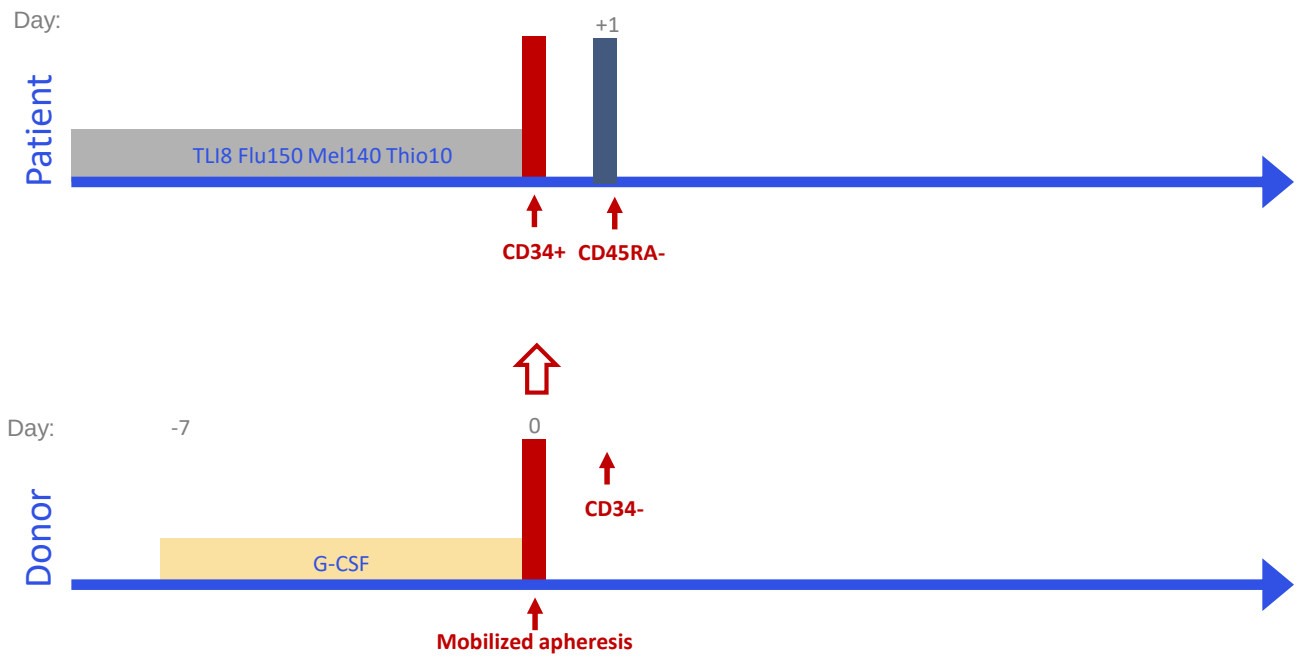
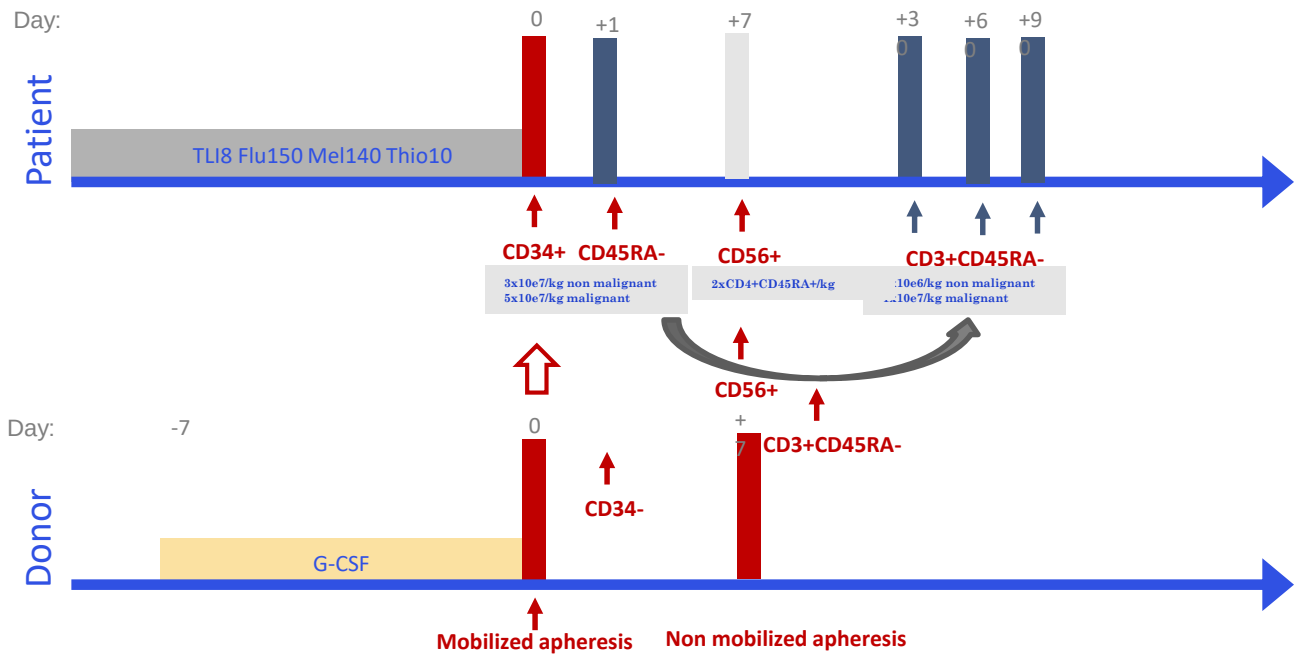
NK cell and memo T cell as adoptive immunotherapy



Gassior M et al. In preparation

NK cell and memo T cell as adoptive immunotherapy

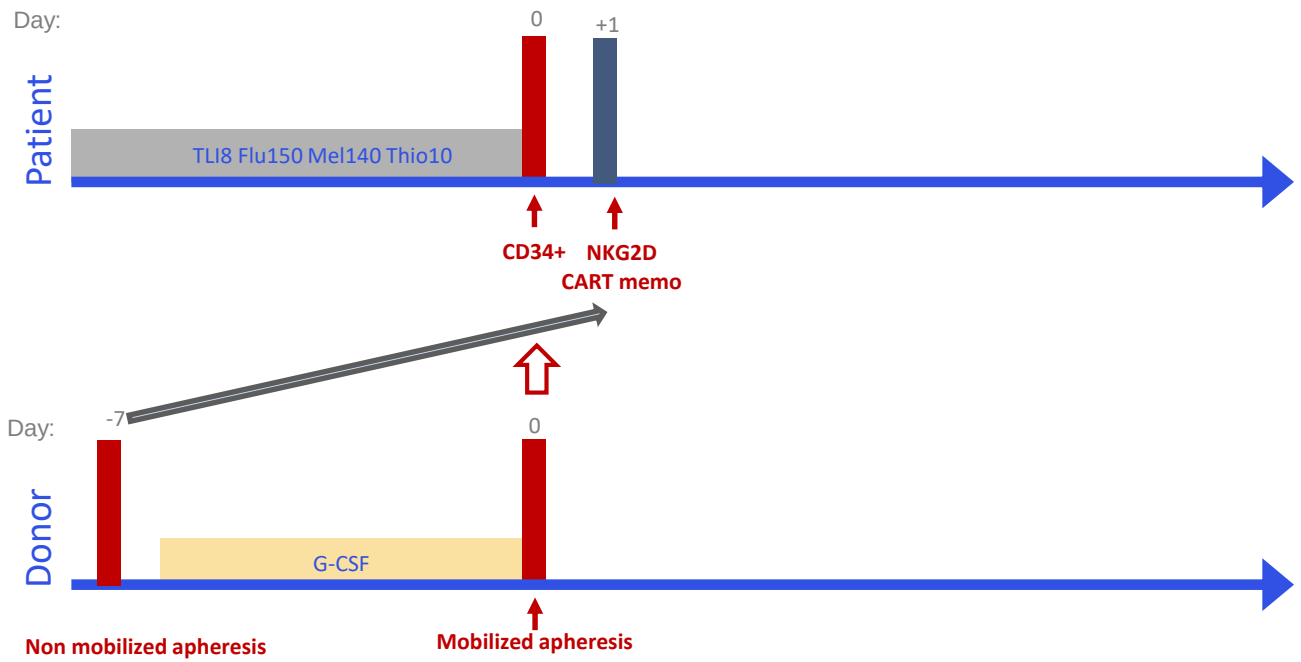
HIGH DOSE OF MEMORY (hm) T and NK cells DLI TO IMPROVE:



Gassior M et al. In preparation

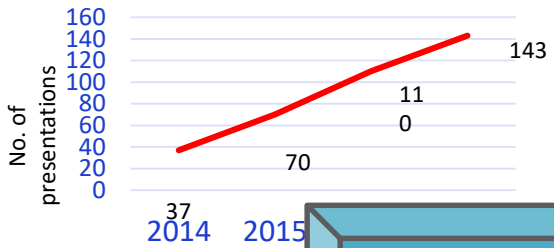
NKG2D CAR T memo cells as adoptive immunotherapy

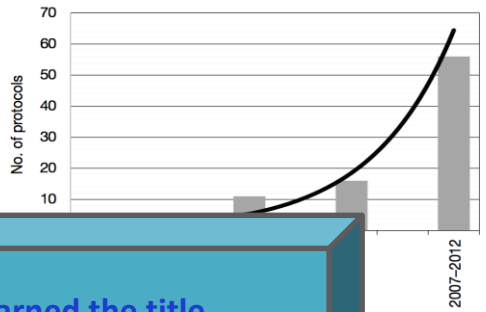
NKG2D CART memo as DLI :



Gassior M et al. In preparation

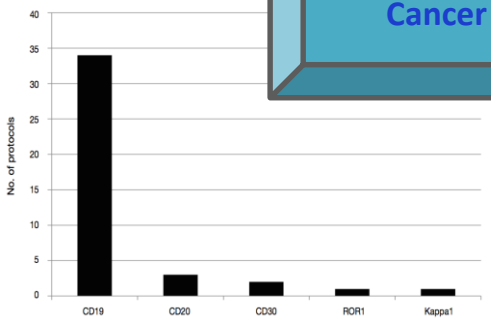
CARs: State of the science



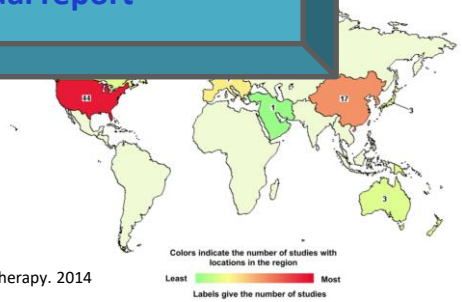


CAR T-cell immunotherapy earned the title "Advance of the Year" in the ASCO Clinical Cancer Advances 2018 annual report

atol Malig Rep.



Corrigan-Curay J., et al. Molecular Therapy. 2014



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First two CAR-T cell medicines recommended for approval in EU

NOVARTIS

Novartis LAL <25 y: 475,000 $ / patient response) 408 m€
Soon in April that LAL in Adults and later NHL

NICE = £282,000 per patient (Sep 5, 2018)
317 m€

Kite
A GILEAD Company

Kite NHL DLBCL: 373,000 $ / patient

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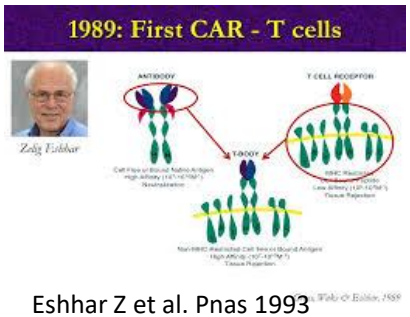
CAR-T cells : “from the T-cell body approach to first class FDA approval”

The T-body approach



Eshhar Z et al. Pnas 1993

M. Sadelain

D. Campana

T-Body 1993

HER2-CAR 1994

GD2-CAR 2001

CD19-CAR 2003

CD28 CAR 2002

41BB CAR 2004

Kymriah, Novartis Pharmaceuticals **(Tisagenlecleucel)**

FDA approval 8/30/2017

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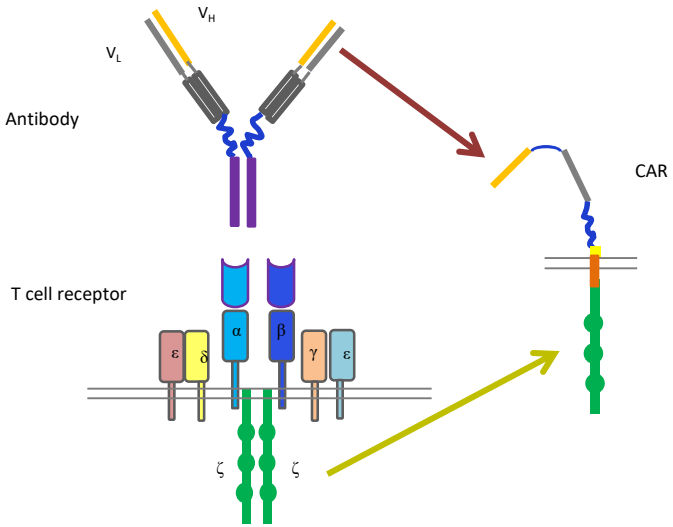
CAR-T cells : "from the T-cell body approach to first class FDA approval"

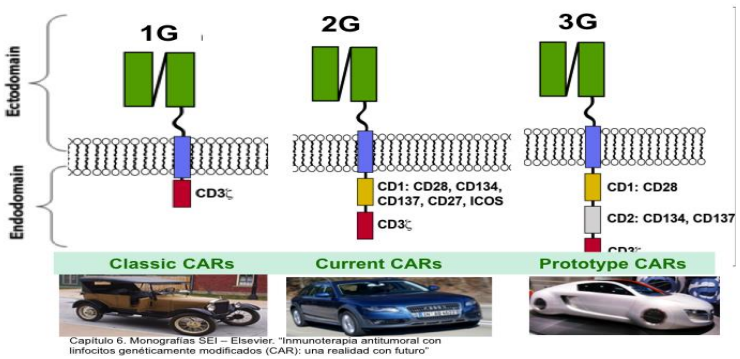
STRUCTURE AND FUNCTION

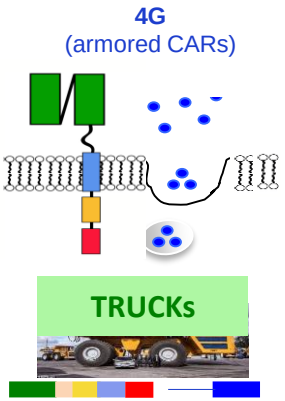
- Engineered receptor → redirect immune cells

  Phusion protein: Recognition Domain + Cytotoxic domain (CD3ζ) [+ costimulation (CD28/4-1BB)]



Adapted from:
B. Savoldo, G. Dotti / Immunology Letters 155 (2013) 40–42





T cells Redirected for Universal Cytokine Killing

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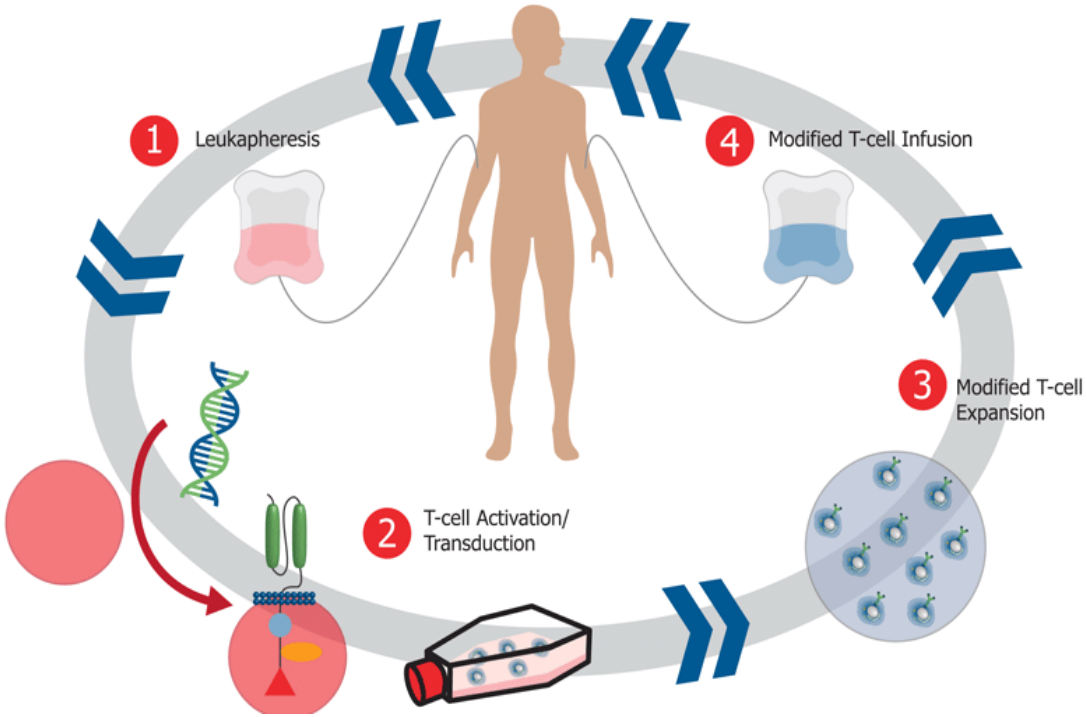
CAR-T cell therapy



Rockland Immunochemicals®

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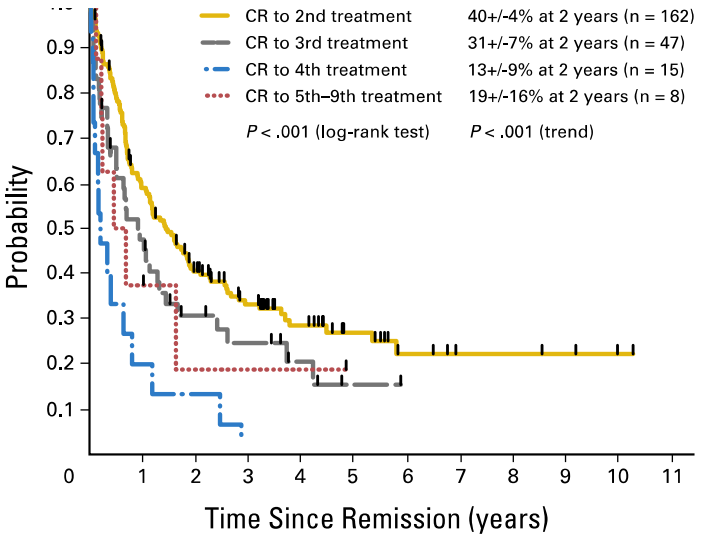
Childhood leukemia

- By contrast with the steadily improved outcome of patients with newly diagnosed ALL, little progress has been made in the treatment of relapsed ALL

- r/r ALL: clofarabine+cy+etoposide. Toxic-related mortality 24%

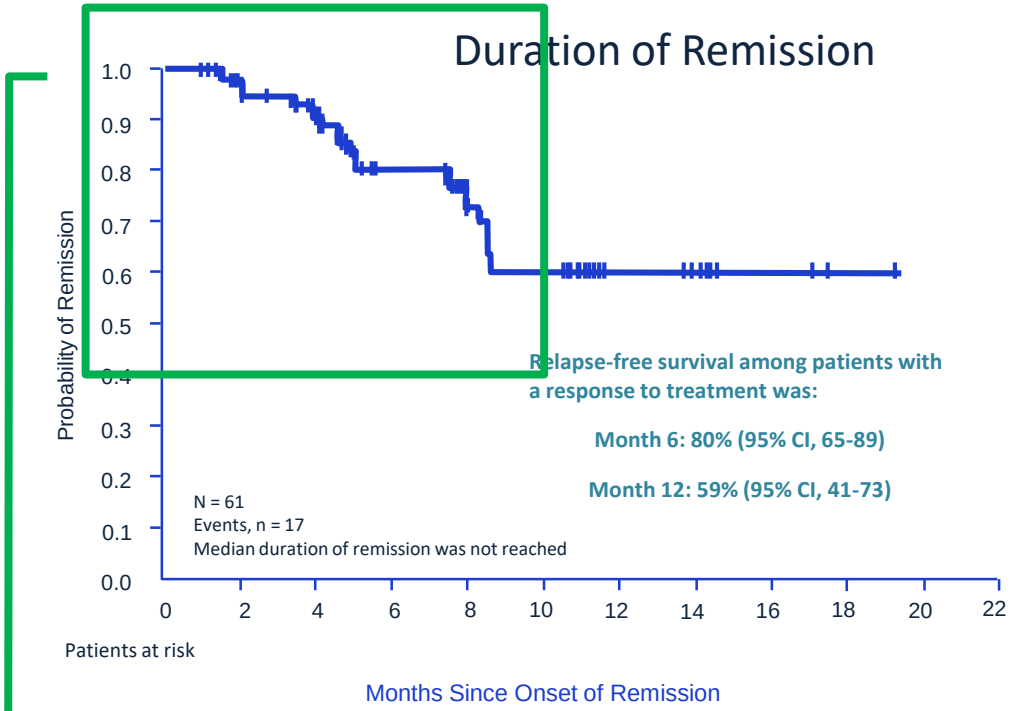


Ko et al. J Clin Oncol 2010

CART19 Efficacy

75 patients who received a tisagenlecleucel infusion and had at least 3 months of follow-up:

- Overall remission rate was 81% (95% CI, 71 to 89)
  - 45 patients (60%) had complete remission
  - 16 (21%) had complete remission with incomplete hematologic recovery.
  - All of them were negative for minimal residual disease



1 CD19+
15 CD19-
No CNS relapse

N Engl J Med 2018;378:439-48.

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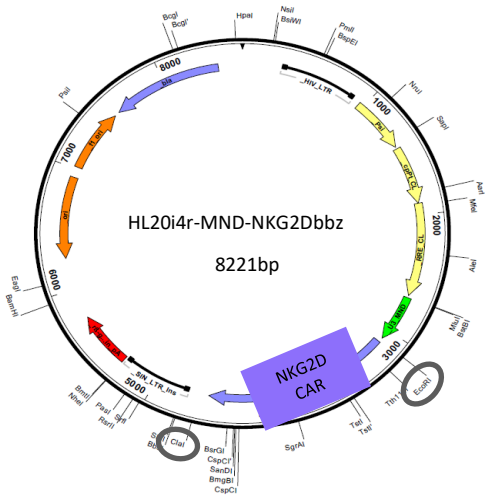
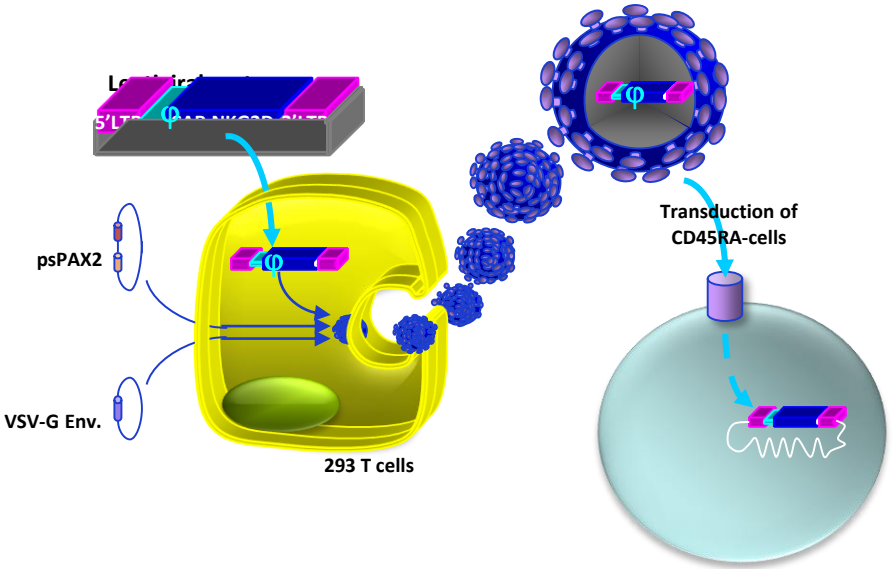
The T-NK approach: opportunity and innovation

The T-NK approach





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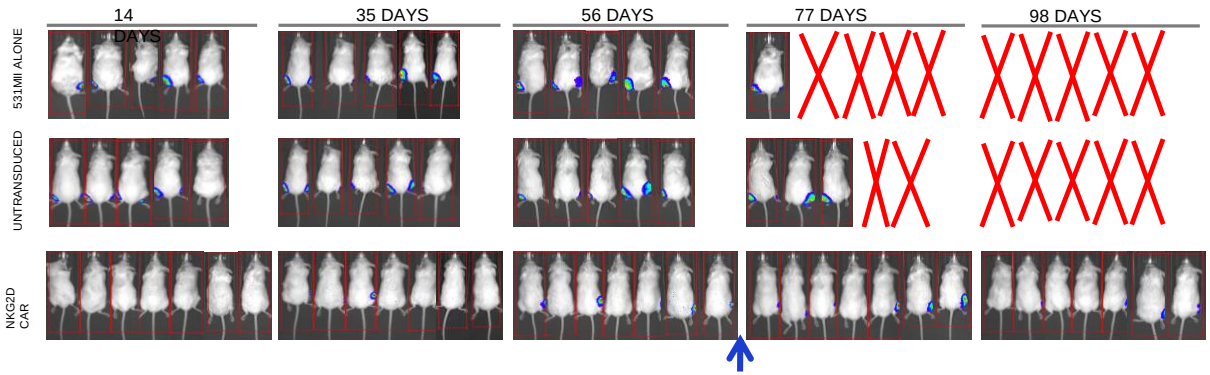
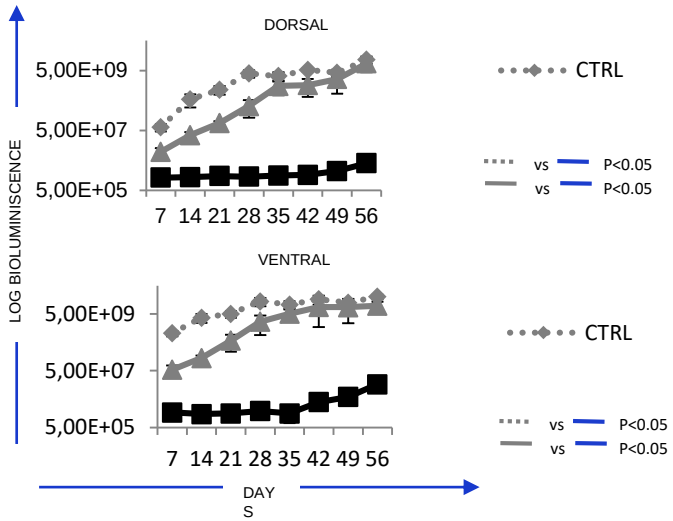
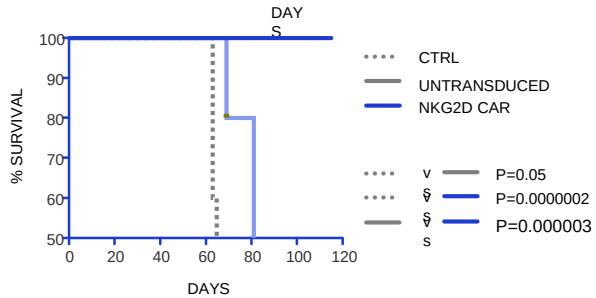
The T-NK approach: opportunity and innovation

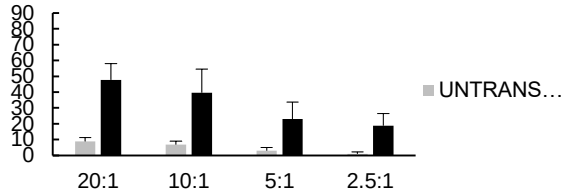


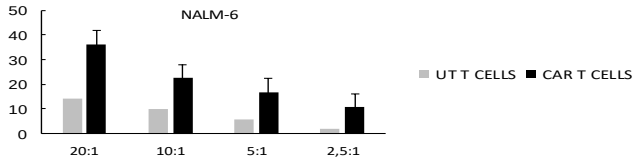


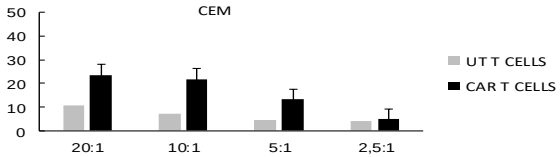


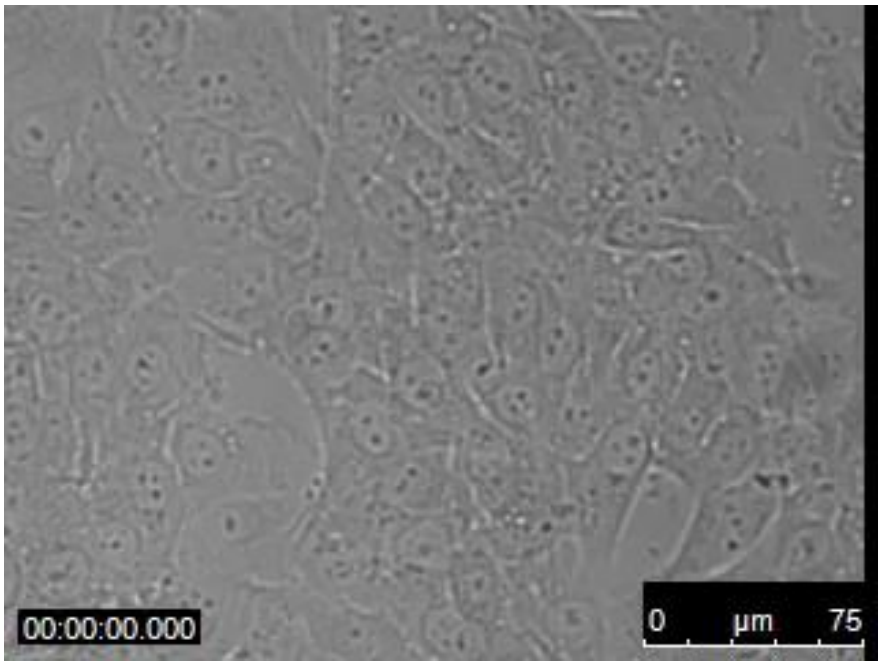
Fernandez et al. *Clin Can Res* 2016

The T-NK approach against solid tumours









Pérez Martínez et al. *GECAR* 2019

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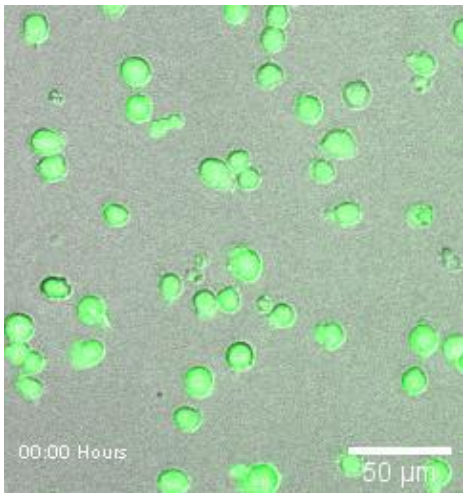
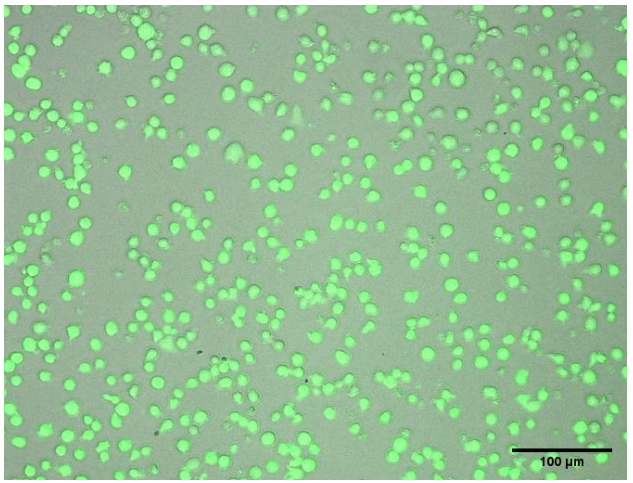
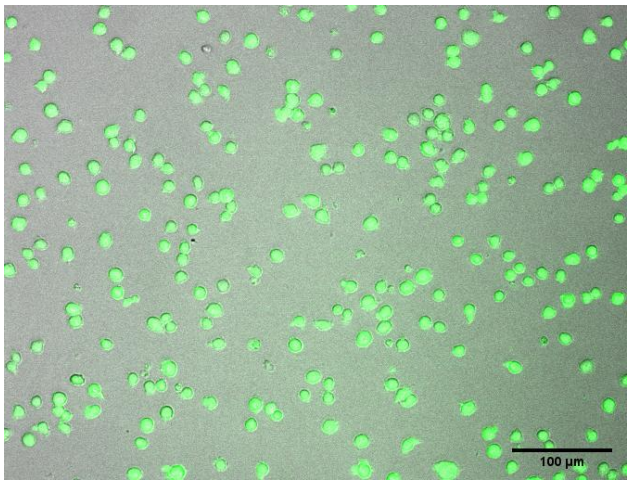
The T-NK approach against non B acute Leukemia







Pérez Martínez et al. *GECAR* 2019

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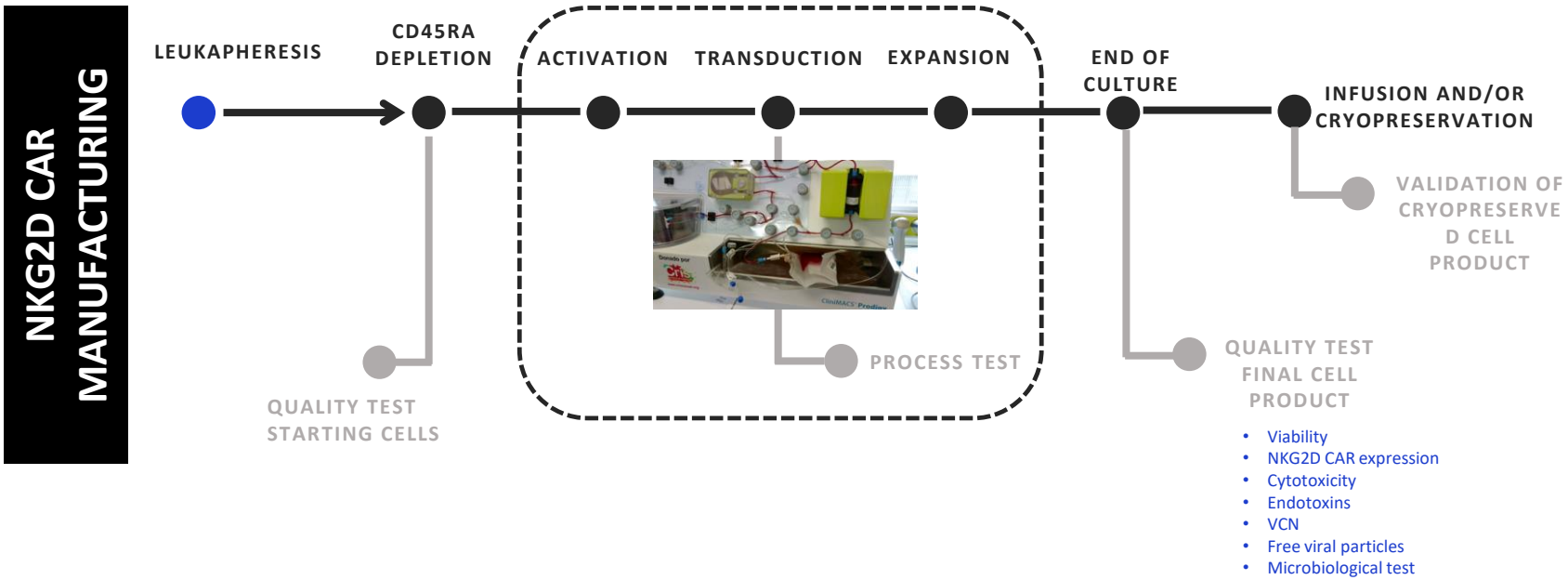
Clinical grade automated production of NKG2D-CAR T cells



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Characteristics of manufactured NKG2D-CAR T cells

Test	Specification	1-565-2	1-518-3	1-595
Number of cells ($x10^6$)	N/A	2740	2140	1350
Cell viability	≥60%	65%	81.4%	82%
NKG2D expression	≥50%	55%	87.4%	91%
Potency	vs. Jurkat: ≥20% vs. 531MII: ≥20%	vs. Jurkat: 100% vs. 531MII: 20%	vs. Jurkat: 80% vs. 531MII: 42%	vs. Jurkat: N/A vs. 531MII: N/A
Mycoplasma/Sterility	Negative	Negative	Negative	Negative
Endotoxins	< 0.25 EU/ml	0.019 EU/ml	0.0035 EU/ml	0.01 EU/ml
Genome integrated copy/cell	≤ 5 copies/cell	3.62	12.32	2.43
Oncogenic gene expression (myc, tert)	No overexpression	No overexpression	No overexpression	Myc overexpression
Genetic stability	Normal CGH	Normal CGH	Normal CGH	Normal CGH

CliniMACS Prodigy (Miltenyi Biotec)

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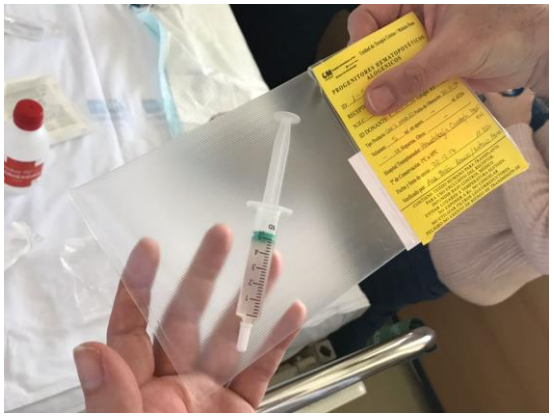
CART cells can be produced “in house”



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Cell and advanced therapies for children with cancer

1. A dream comes true: "Immunotherapy as reality"

2. Immune effector cells as old new drugs for childhood cancer
   a) The killer cells
   b) The memory cells
   c) The cell engineering

3. Hospital needs transformation: Research University Hospital

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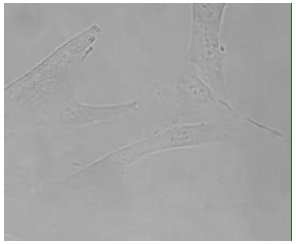
Cris Unit for Translational Research and Advanced Therapies



Instituto de Investigación Hospital Universitario La paz (IdiPAZ)

Centro Nacional de Investigaciones Oncológicas (CNIO)

Experimentación preclínica

Actividad anti tumoral de los linfocitos T de memoria CAR-NKG2D

Comunidad científica

Publicaciones

Fernández et al. Clin. Cancer Res. 2017 (D1)

Ud. Terapias Avanzadas (Hospital La Paz)

Producción celular

Células T memoria CAR-NKG2D a escala clínica

UNIDAD DE HEMATO-ONCOLOGÍA PEDIÁTRICA

TRATAMIENTOS PERSONALIZADOS

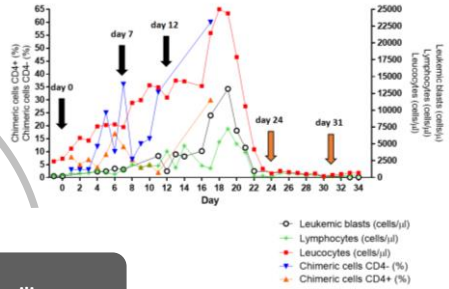
Pacientes

Leucemia refractaria tratamientos convencionales

Ud. Calidad Terapias avanzadas (Hospital La Paz)

Agencias reguladoras

IMPD, Guía de producción



Familias

Donantes sanos

Selección donante óptimo

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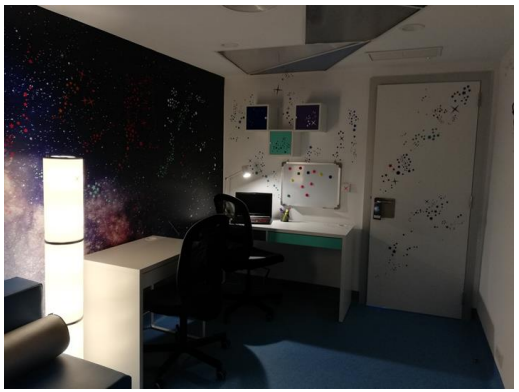
Hospital Universitario La Paz

Hospital Universitario La Paz SaludMadrid

Cris contra el cáncer

Cris Unit for Translational Research and Advanced Therapies



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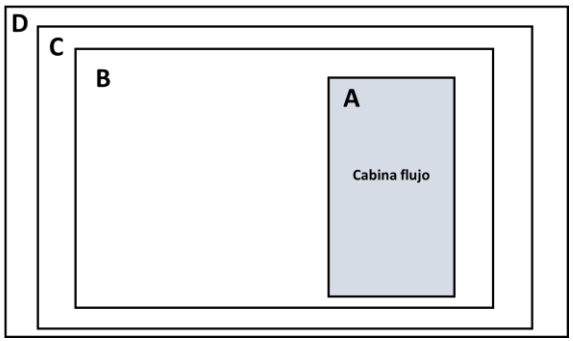
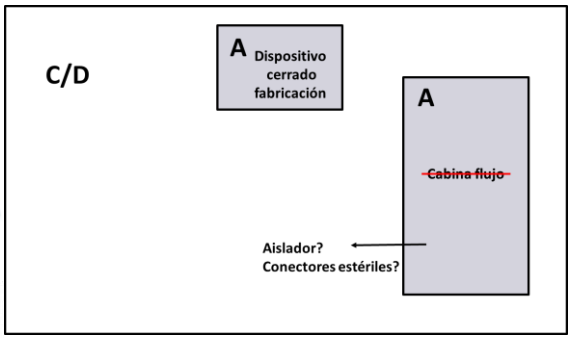
Cris Unit for Translational Research and Advanced Therapies

Qualification

- **GMP facilities**



- **GMP facilities**



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Inmunoterapy

Tumor recognition
Especific antigens

Multiple targets
Multiple cells

Tumor burden
Dinamic process

Response biomarkers

Multidisciplinary team

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Cris Unit for Translational Research and Advanced Therapies

Pediatric Hemato-Oncology, Stem Cell Transplantation and Cell Therapy Group

Departamento de Inmunidad Innata, Instituto de Investigación del Hospital Universiatrio La Paz (IdiPAZ)

Composición:

- Dr. Antonio Pérez Martínez (IP y facultativo hematooncología infantil)
- Dra. María Vela
- Jaime Valentín
- Pablo González
- Ariadna Brito

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Hospital Universitario La Paz

Hospital Universitario La Paz SaludMadrid

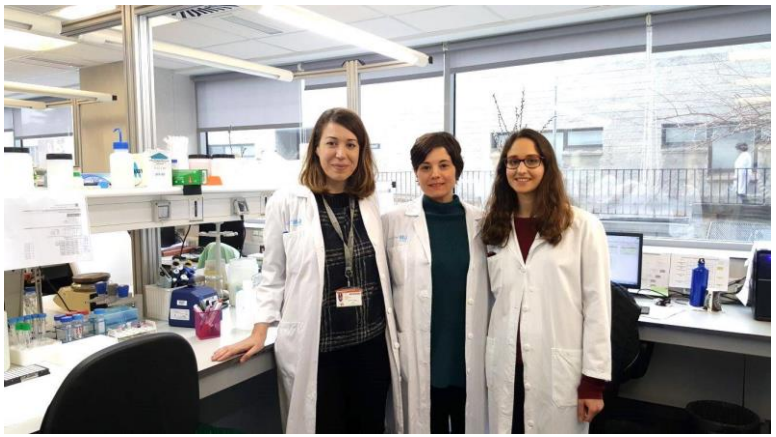
Cris Unit for Translational Research and Advanced Therapies

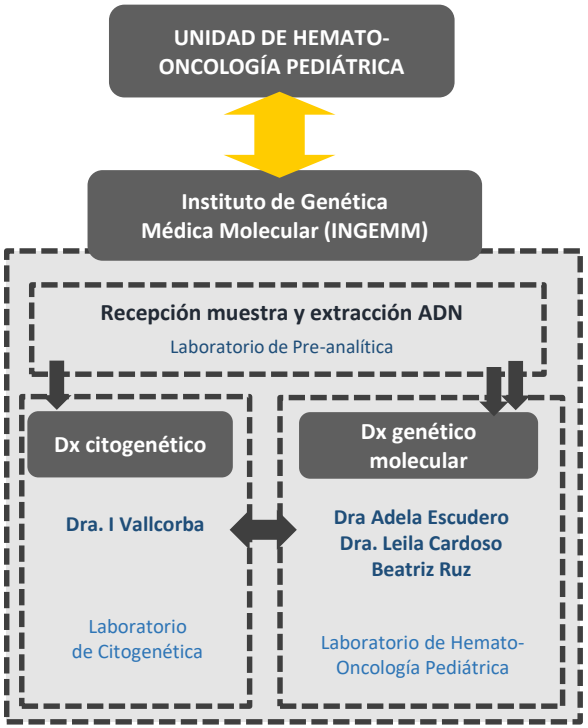
Molecular Pediatric Hemato-Oncology Group

Sección 12, Instituto de Genética Médica y Molecular (INGEMM)

Composición:

- Dr. Antonio Pérez Martínez (IP y facultativo hemaotoncología infantil)
- Dra. Adela Escudero (Genetista)
- Dra. Leila Cardoso (Genetista/técnico)
- Beatriz Ruz (bioinformática)





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Cris contra el cáncer

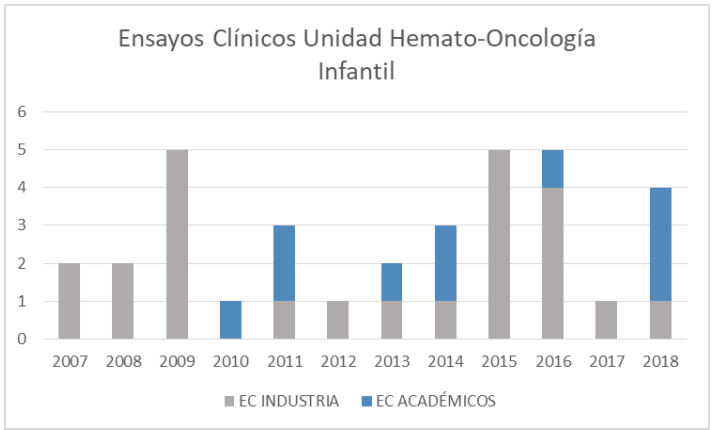
Cris Unit for Translational Research and Advanced Therapies

Pediatric Hemato-Oncology, Stem Cell Transplantation and Cell Therapy Early Phase Clinical Trial Unit

- 37 Ensayos Clínicos en total desde el año 2007 (industria y académicos)
- 15 Ensayos clínicos desde el 2015 en 10 de los cuales el investigador principal es el candidato (industria y académicos)

Composición:

- Dr. Antonio Pérez Martínez (IP y facultativo hemaotoncología infantil)
- Mario Muñoz
- Dra. Isabel Mirones Aguilar



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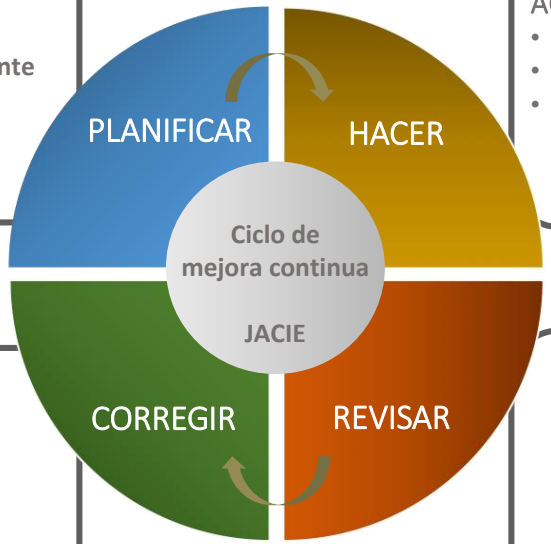
International Standars and Quality Certification (JACIE) in Stem Cell Transplantation and Cell Therapies

PLANIFICACIÓN
- Manual de calidad
- Organigrama programa trasplante
- Procedimientos generales
- Procedimientos normalizados

ACCIÓN
- Instalaciones y personal adecuado
- Formación inicial continuada
- Delimitación de las tareas del personal de su área especializada



CORRECCIÓN
- Medidas correctoras
- Indicadores de Calidad
- Procedimientos
- Acuerdos con terceros

REVISIÓN (registros)
- Análisis resultados clínicos
- Auditorias internas
- Registro incidencias
- Indicadores de calidad

Composición:
- Dr. Antonio Pérez Mart
- Alba Fernández-Arroyo
- Dra. Isabel Mirones Ag

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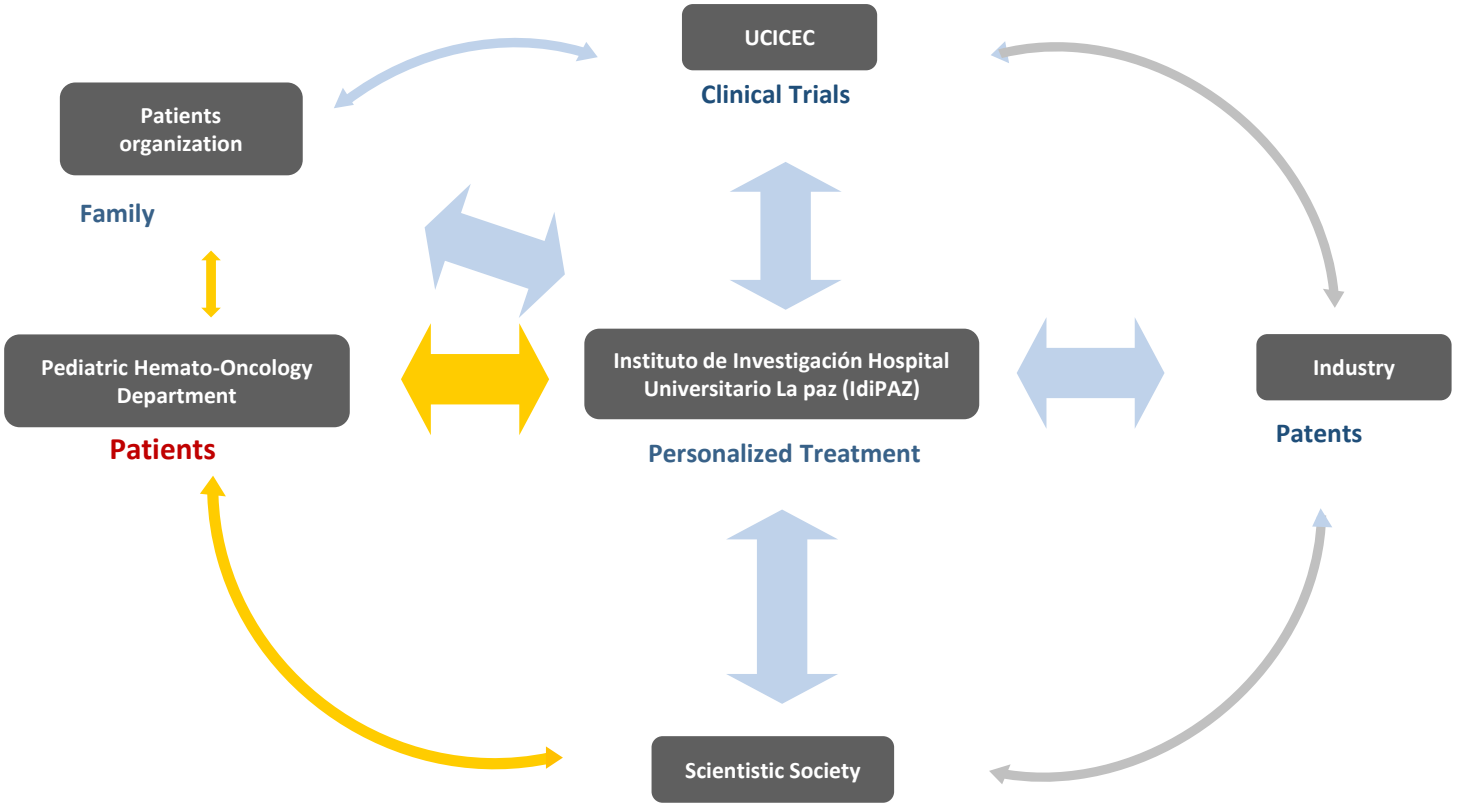
Cris Unit for Translational Research and Advanced Therapies



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UCICEC

Clinical Trials
EC SANKOMA
EudraCT 2016-003578- 42

PROTOCOLO DE ENSAYO CLÍNICO

Ensayo Clínico Fase I/II, multicéntrico, abi... de infusión de células NK activadas para el tratamiento de niños, adolescen... adultos jóvenes con sarcomas

Promotor: ANTONIO PÉREZ-MARTÍNEZ

Código de Protocolo: SANKOMA_2016

Código EudraCT: 2016-003578-42

Versión protocolo: versión 2 de 10 de julio de 2(

agencia española de medicamentos y productos sanitarios

Patients Organization

Family
La Sonrisa de Álex, FMPJ

Pediatric Hemato-Oncology Department

Pacientes
Sarcoma metastásico/refractario

Instituto de Investigación Hospital Universitario La paz (IdiPAZ)

Personalized treatment
Combining NK cell therapy and humoral therapy αCXCR4

Industry

Bristol-Myers Squibb

Patents
Bristol Myers Squibb and FIHULP:
U.S. Application No. 62/642,313

Scientistic Society

Publicaciones: **Vela et al. in preparation (Q1)**
Congresos: **ASCO2018, SIHOP2018, SNI2018, SETGyC2018, SEHOP2018**

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Trial name	Title	Code	EudraCT	NCT
HNJ-NK-2009	TRASPLANTE DE PROGENITORES HEMATOPOYÉTICOS E INFUSIÓN DE CÉLULAS NK IL-15 EN TUMORES SÓLIDOS PEDIÁTRICOS REFRACTARIOS	HNJ-NK-01/2009	2009-010186-23	NCT01337544
HNJ-NKAES-2012	INFUSIÓN DE CÉLULAS NATURAL KILLER EN COMBINACIÓN CON QUIMIOTERAPIA EN PACIENTES PEDIÁTRICOS CON LEUCEMIA/LINFOMA T REFRACTARIA	HJN-NKAES-2012	2012-000054-63	NCT01944982
LYDIA	LANK-2: INMUNOTERAPIA CON CÉLULAS NATURAL KILLER ACTIVADAS Y EXPANDIDAS JUNTO CON QUIMIOTERAPIA DE RESCATE EN NIÑOS, ADOLESCENTES Y ADULTOS JÓVENES CON LEUCEMIA AGUDA EN RECAIDA O REFRACTARIEDAD	LANK-2	2012-005146-38	NCT02074657
LYDIA II	FASE II: INFUSION DE CÉLULAS NATURAL KILLER COMO TRATAMIENTO DE CONSOLIDACION EN NINOS Y ADOLESCENTES CON LEUCEMIA MIELOBLÁSTICA AGUDA	NKCell_LMA_2015	2015-001901-1	NCT02763475
SANKOMA	ENSAYO CLÍNICO FASE I/II, MULTICÉNTRICO, ABIERTO, DE INFUSIÓN DE CÉLULAS NATURAL KILLER ACTIVADAS PARA EL TRATAMIENTO DE NIÑOS, ADOLESCENTES Y ADULTOS JÓVENES CON SARCOMAS	SANKOMA_2016	2016-003578-42	No disponible
GABY	RECEPTOR ANTIGÉNICO QUIMÉRICO NKG2D PARA EL TRATAMIENTO DE PACIENTES PEDIÁTRICOS CON LEUCEMIA AGUDA Y LEUCEMIA MIELOMONOCÍTICA JUVENIL: VALIDACIÓN A ESCALA CLÍNICA Y PRIMER ESTUDIO DE SEGURIDAD EN PACIENTES	No disponible	No disponible	No disponible
PHINK	INFUSIÓN DE CÉLULAS NATURAL KILLER ALOREACTIVAS O ESTIMULADAS TRAS TRASPLANTE HAPLOIDÉNTICO DE PROGENITORES HEMATOPOYÉTICOS EN PACIENTES PEDIÁTRICOS CON NEOPLASIAS HEMATOLOGICAS	No disponible	No disponible	No disponible

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Conclusion

1. Immunotherapy as new treatment reality
2. Immune effector cells as old but new drugs for childhood cancer
3. Hematopoietic Stem Cell Transplantation developing to a Cell Therapy
4. Hospital needs transformation towards a Research University Hospital
5. Industry and Academic Alliance are needed

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" The cure of cancer starts with research"

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Cell and advanced therapies for children with cancer "Cells4kids"

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