45° Convegno Nazionale di Studi di Medicina Trasfusionale

Rimini | 29-31 maggio 2024

SIMTI

Stato dell'arte sui trapianti di CSE

Fabio Ciceri

IRCCS H San Raffaele Milano

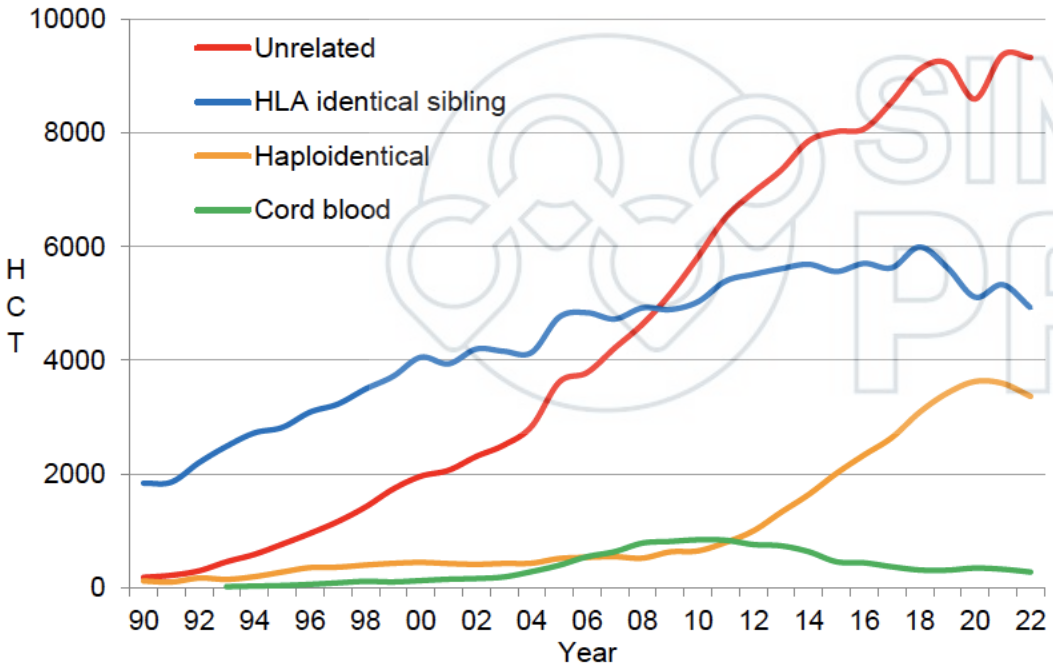
Il sottoscritto, in qualità di Relatore
dichiara che

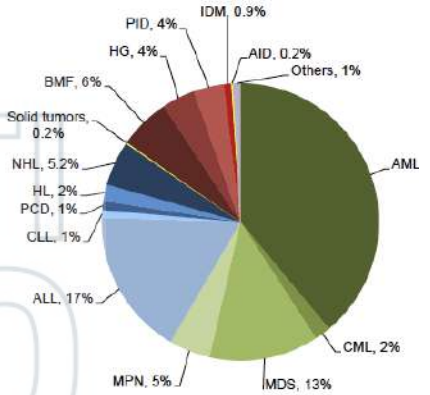
nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.

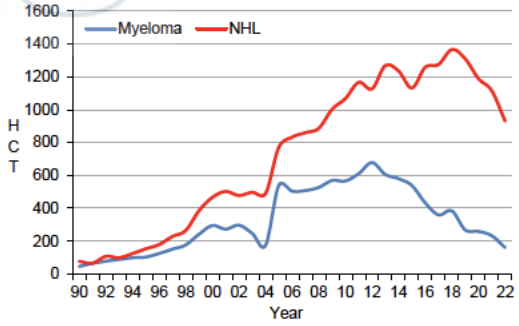
contents

Transplant activity trends

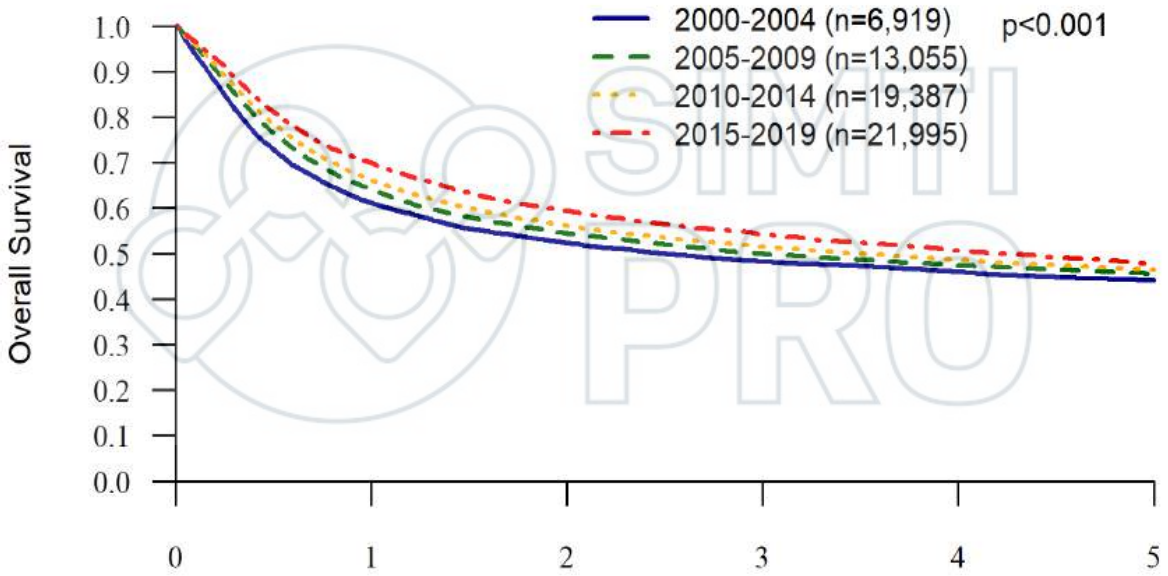
Allogeneic trends





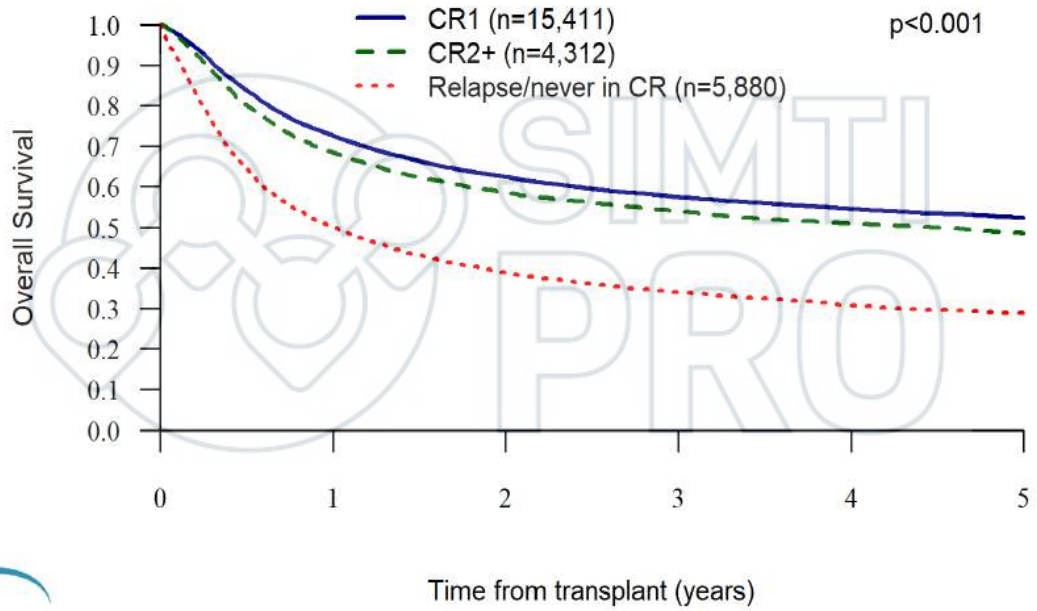


Trends in Survival after Allogeneic HCT for Acute Myelogenous Leukemia (AML), Age >=18y, 2000-2019



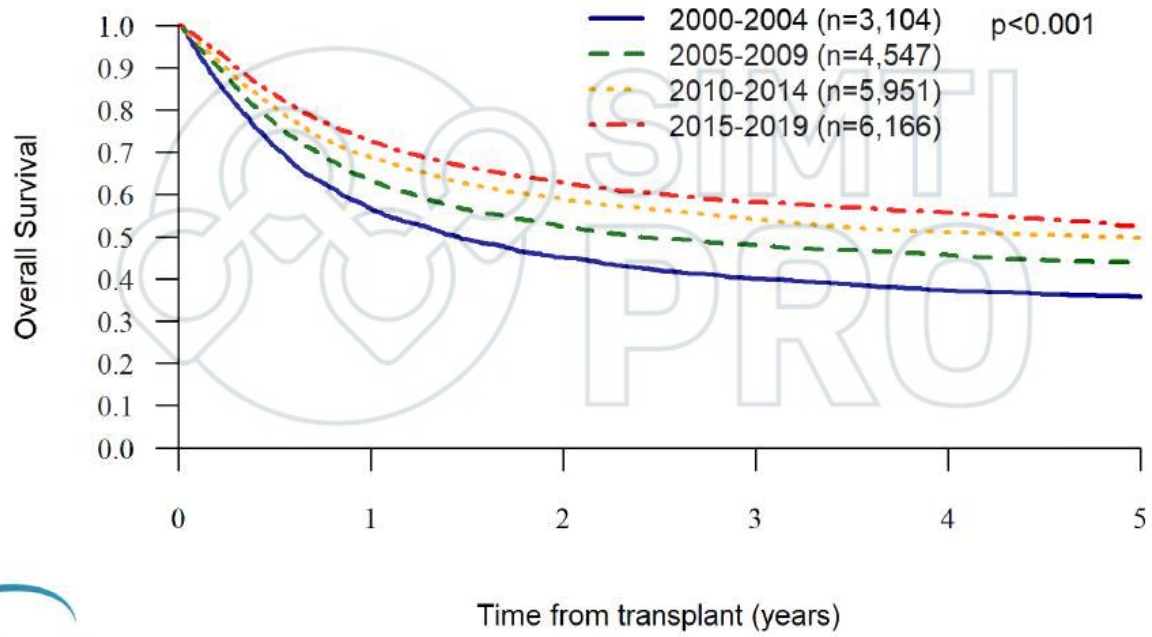
EBMT

Survival after Unrelated Donor HCT for Acute Myelogenous Leukemia (AML), Age >=18y, 2009-2019



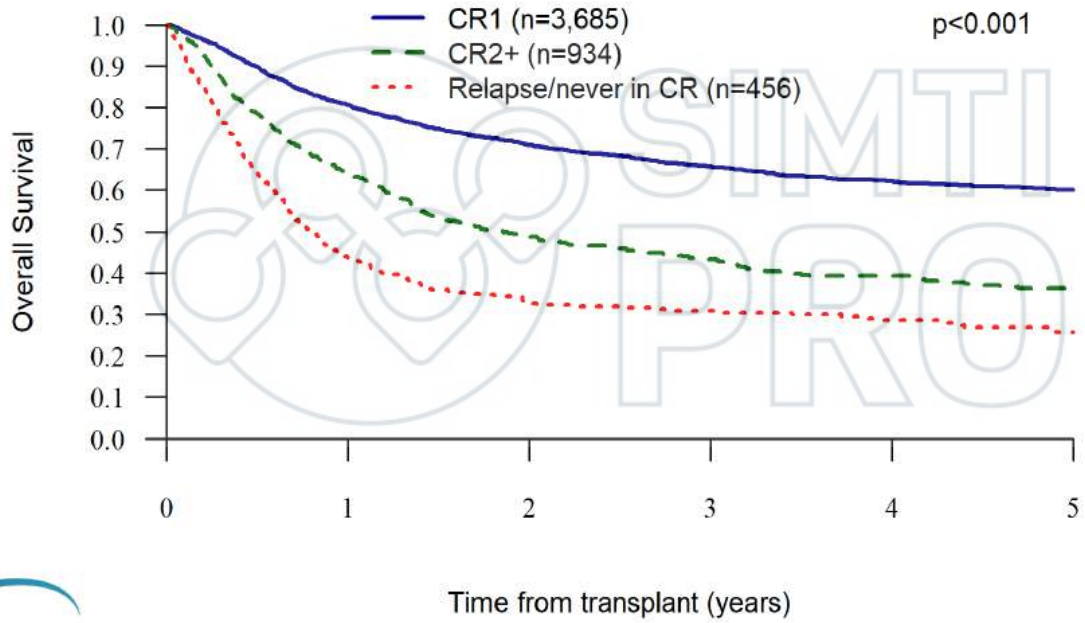
EBMT

Trends in Survival after Allogeneic HCT for Acute Lymphoblastic Leukemia (ALL), Age >=18y, 2000-2019



EBMT

Survival after Matched Related Donor HCT for Acute Lymphoblastic Leukemia (ALL), Age >=18y, 2009-2019



EBMT

EBMT Registry

benchmarking
new opportunities

Benchmarking

R. Saccardi et al.

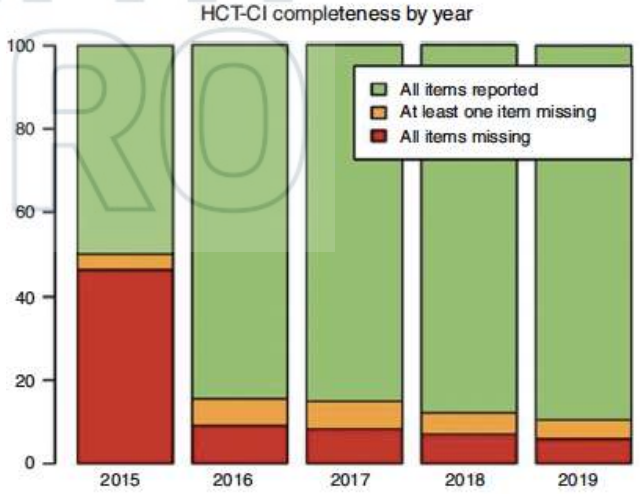
*Adjusted for case mix and centre follow-up

EBMT www.nature.com/bmt

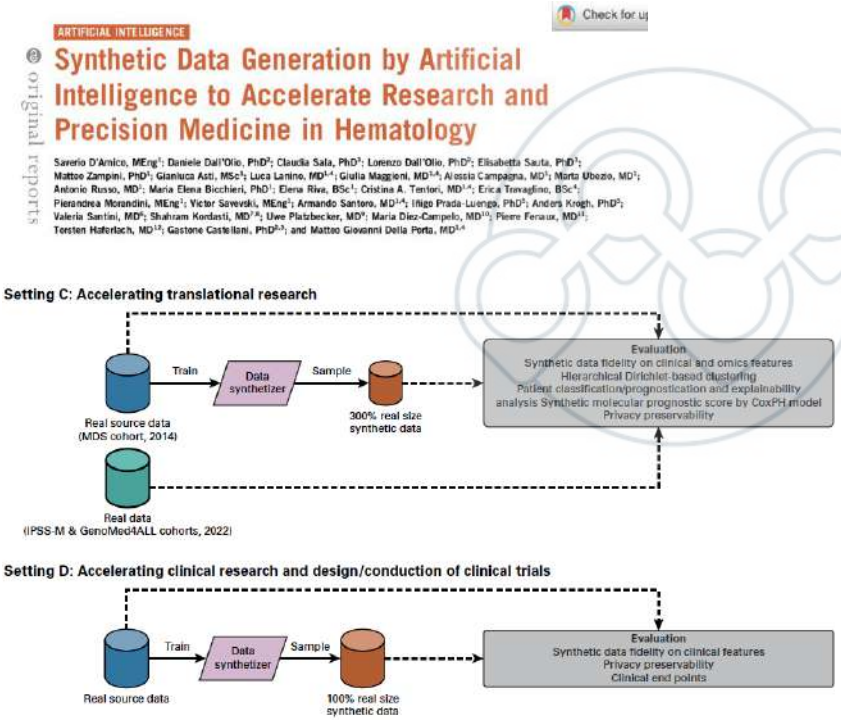
ARTICLE OPEN

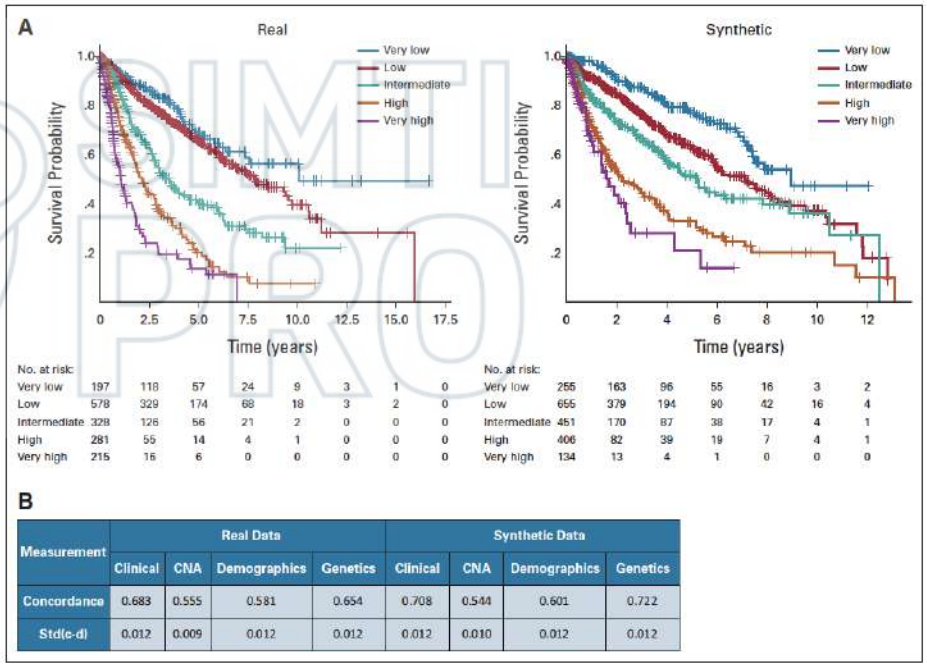
Benchmarking of survival outcomes following Haematopoietic Stem Cell Transplantation (HSCT): an update of the ongoing project of the European Society for Blood and Marrow Transplantation (EBMT) and Joint Accreditation Committee of ISCT and EBMT (JACIE)

Riccardo Saccardi[1,22], Hein Putter[2], Dirk-Jan Eikema[3], Maria Paula Busto[4], Eoin McGrath[5], Bas Middelkoop[4], Gillian Adams[6], Marina Atlija[4], Francis Ayuketang Ayuk[7], Helen Baldomero[8], Yves Beguin[9], Rafael de la Cámara[10], Ángel Cedillo[11], Anna Maria Sureda Balari[12], Christian Chabannon[13], Selim Corbacioglu[14], Harry Dolstra[15], Rafael F. Duarte[16], Rémy Dulery[17], Raffaella Greco[18,19], Andreu Gusi[6], Nada Hamad[20,21,22], Michelle Kenyon[23], Nicolaus Kröger[7], Myriam Labopin[24,23], Julia Lee[25], Per Ljungman[27], Lynn Manson[28], Florence Mensil[29], Noel Milpied[30], Mohamad Mohty[31], Elena Oldani[32], Kim Orchard[33], Jakob Passweg[34], Rachel Pearce[35], Régis Peffault de Latour[35], Hélène A. Poirel[36], Tuula Rintala[37], J. Douglas Rizzo[38], Annalisa Ruggeri[39], Carla Sánchez-Martínez[40], Fermín Sanchez-Guijo[41], Isabel Sánchez-Ortega[4], Marie Trnková[42], David Valcárcel Ferreiras[11,43], Leonie Wilcox[44], Liesbeth C. de Wreede[2] and John A. Snowden[45]



Registry: new opportunities
comparators for prospective studies
EMA: new drugs registration, PASS LTFU studies



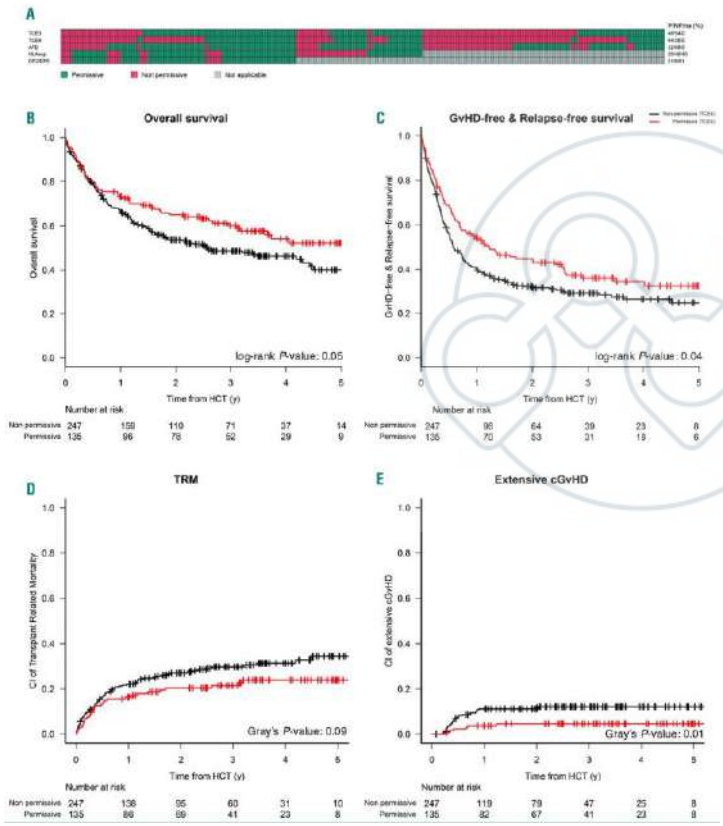


B

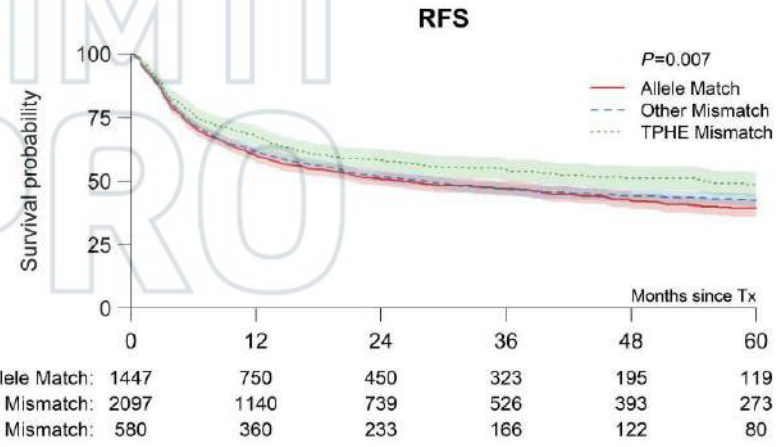
Measurement	Real Data				Synthetic Data			
	Clinical	CNA	Demographics	Genetics	Clinical	CNA	Demographics	Genetics
Concordance	0.683	0.555	0.581	0.654	0.708	0.544	0.601	0.722
Std(c-d)	0.012	0.009	0.012	0.012	0.012	0.010	0.012	0.012

Donor matching

Donor matching: from HLA allele counting to functional testing



Katharina Fleischhauer



haematologica 2020; 105:e189

Lorentino F. et al 2020

Haematologica | 108 February 2023

Ruggeri A. et al 2023

Choice of alternative donors: age effect

blood®

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Younger unrelated donors may be preferable over HLA match in the PTCy era: A study from the ALWP of the EBMT

Tracking no: BLD-2023-023697R2

No impact of 1 allele mismatch

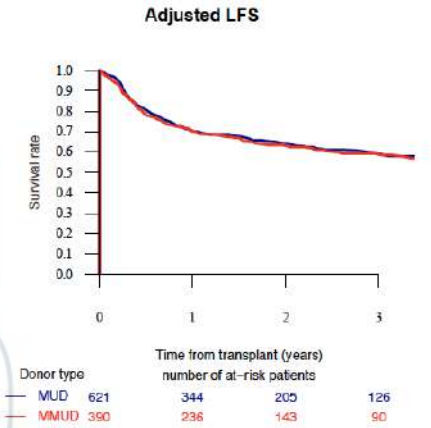
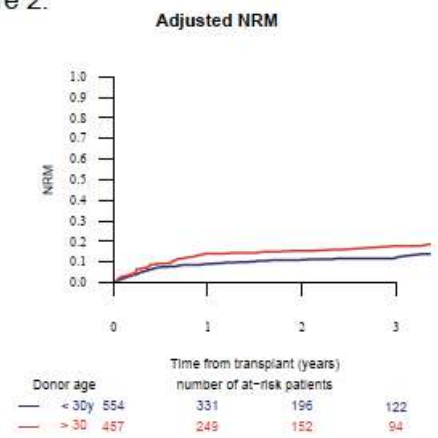
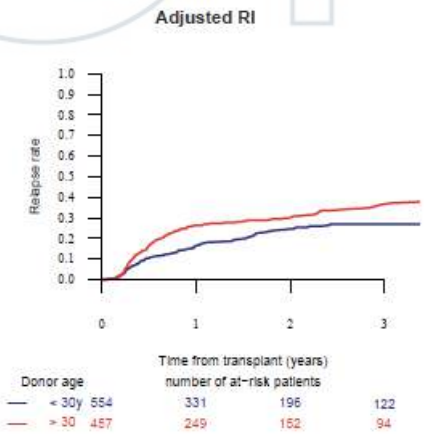
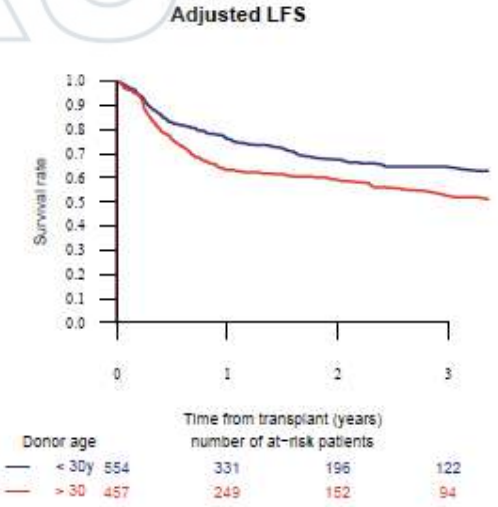


Figure 2.

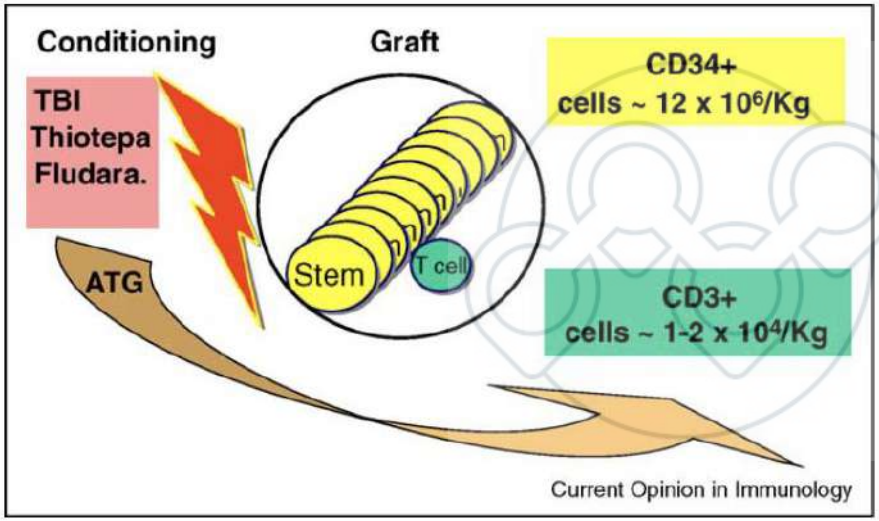


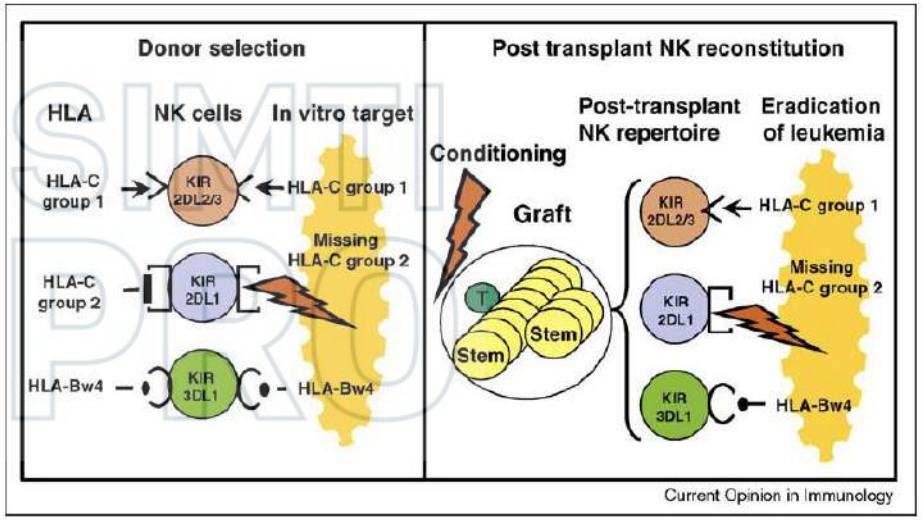




Graft composition

Lessons from ex-vivo T cell depletion
CD34+ selection

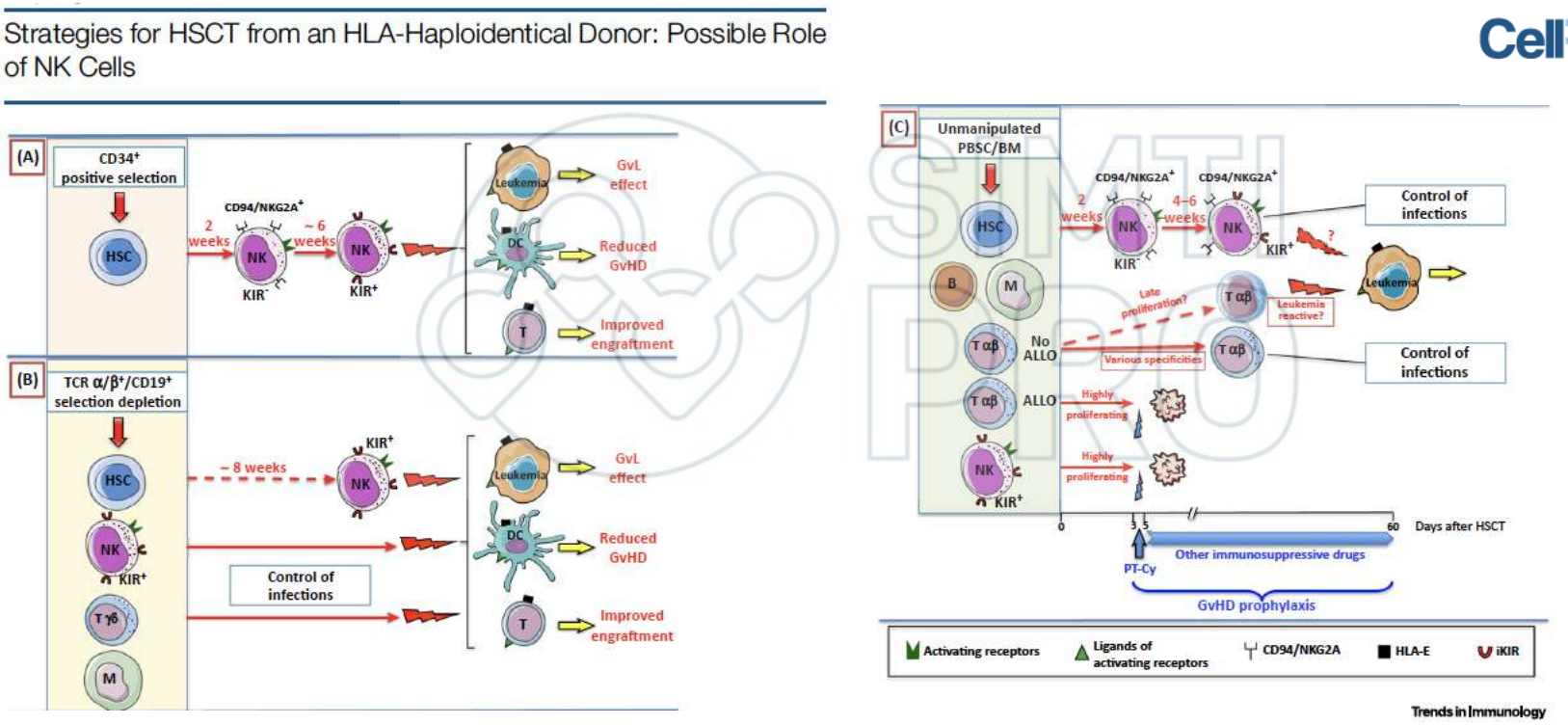




Current Opinion in Immunology 2009, **21**:525–530

Andrea Velardi, Loredana Ruggeri, Franco Aversa, Massimo Martelli

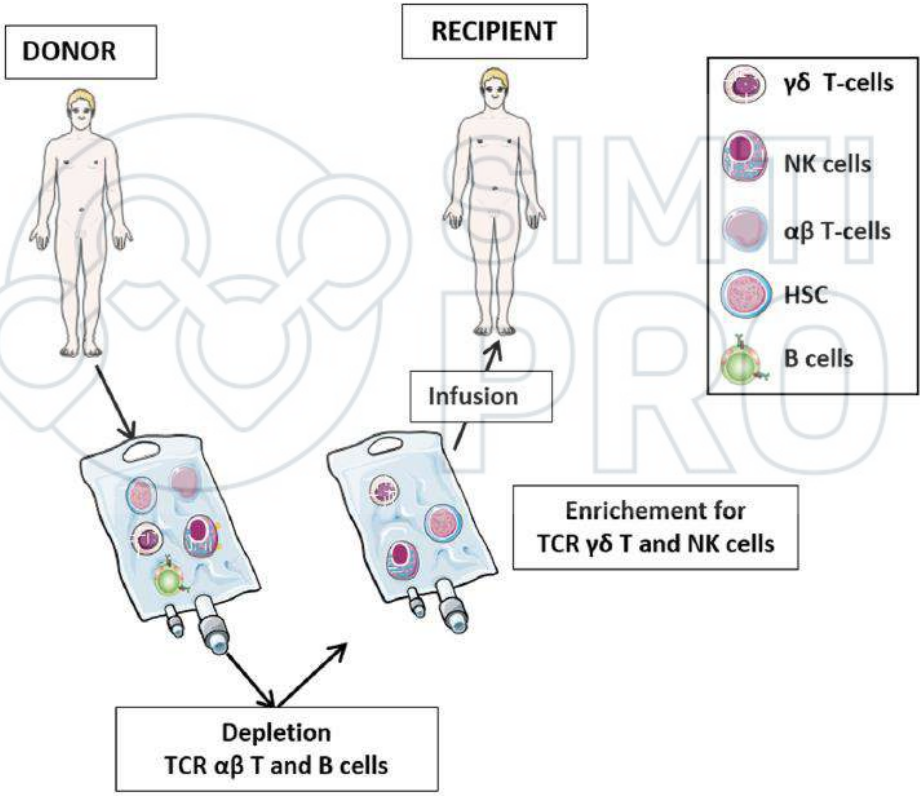
Lessons from ex-vivo T cell depletion
NK cells role in allogeneic transplantation



Franco Locatelli, Daniela Pende, ….Alessandro Moretta, Lorenzo Moretta

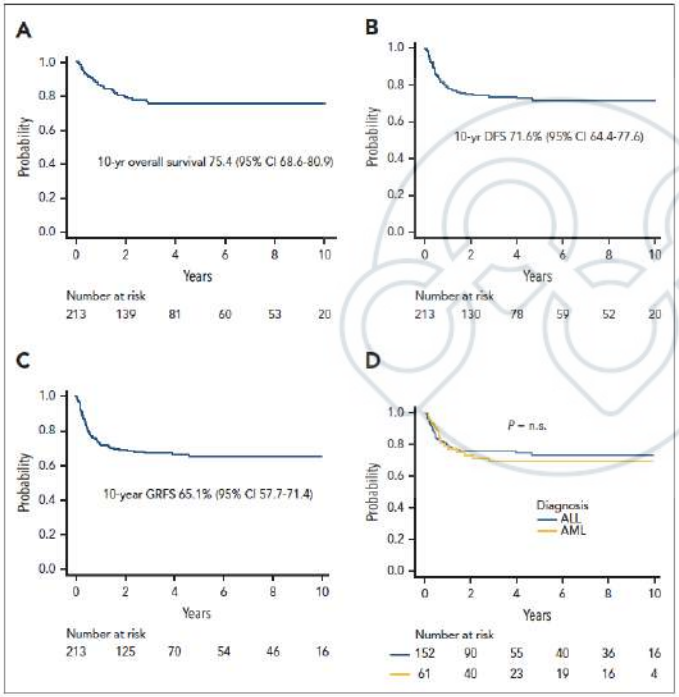
Lessons from ex-vivo T cell depletion

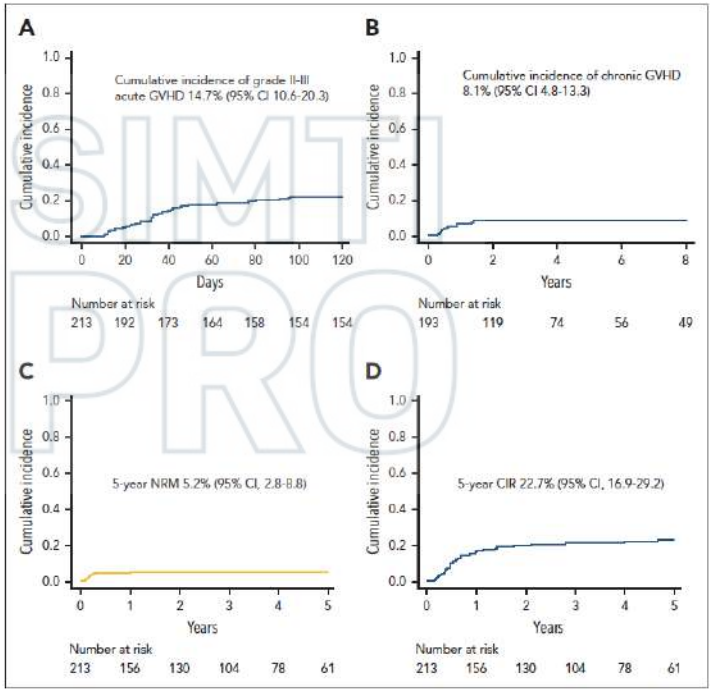
TCRαβ/CD19 cell depletion



Lessons from ex-vivo T cell depletion

TCRαβ/CD19 cell depletion in pediatric acute leukemia





Merli P. et al 2024

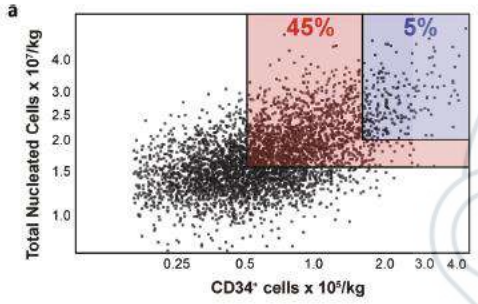
blood® 18 JANUARY 2024 | VOLUME 143, NUMBER 3

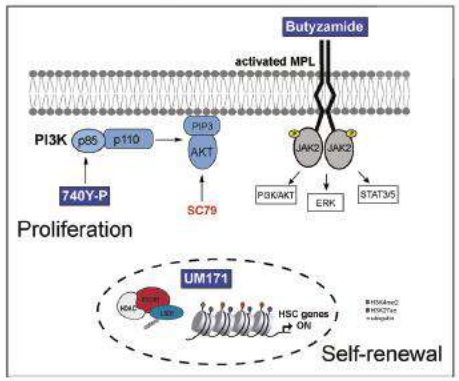
HSC expansion
UM171 in cord blood transplantation

Maria Florencia Tellechea[1], Jalila Chagraoui[1], Sandra Cohen[1] and Guy Sauvageau[1]✉

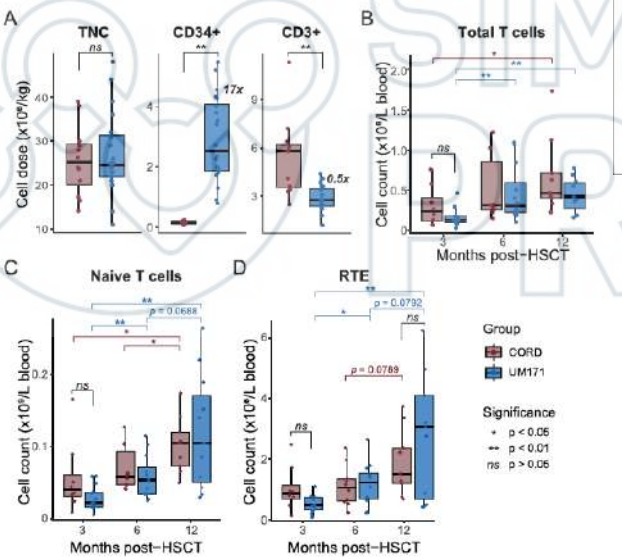
Cell Research (2023) 33:659–660;

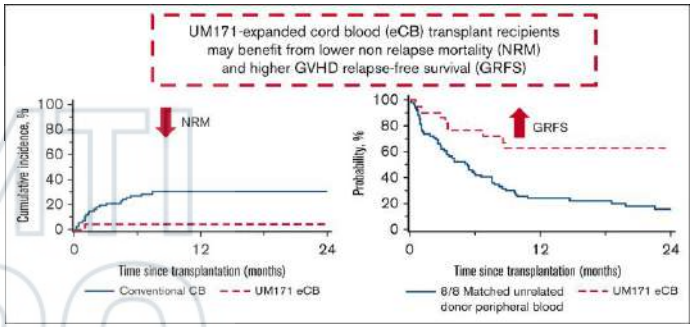
10 OCTOBER 2023 • VOLUME 7, NUMBER 19 blood advances

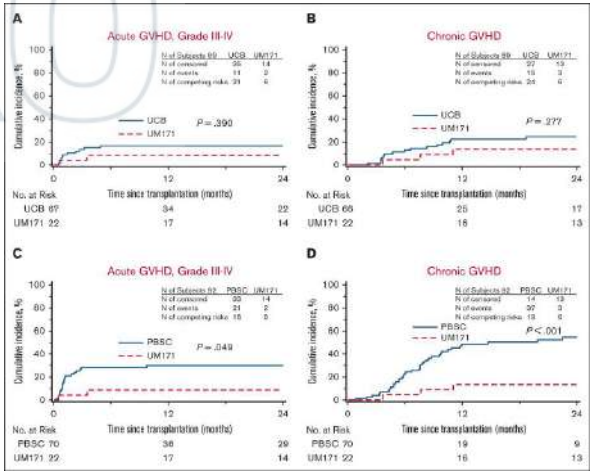




Transplantation and Cellular Therapy 27 (2021) 76.e1–76.e9

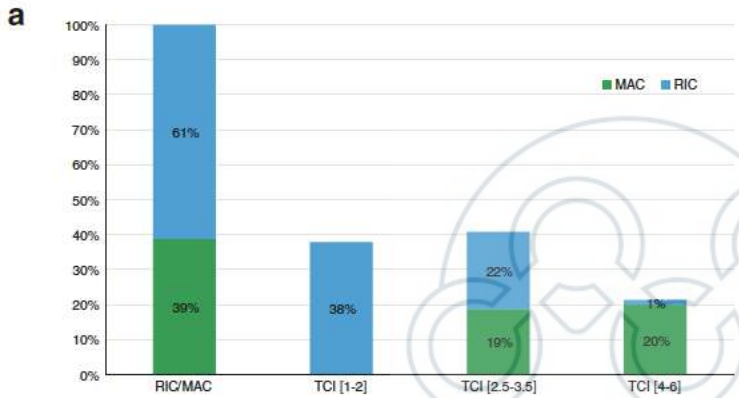


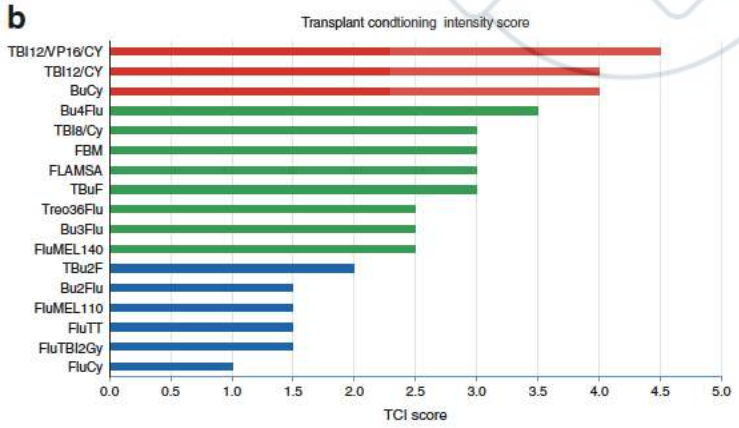




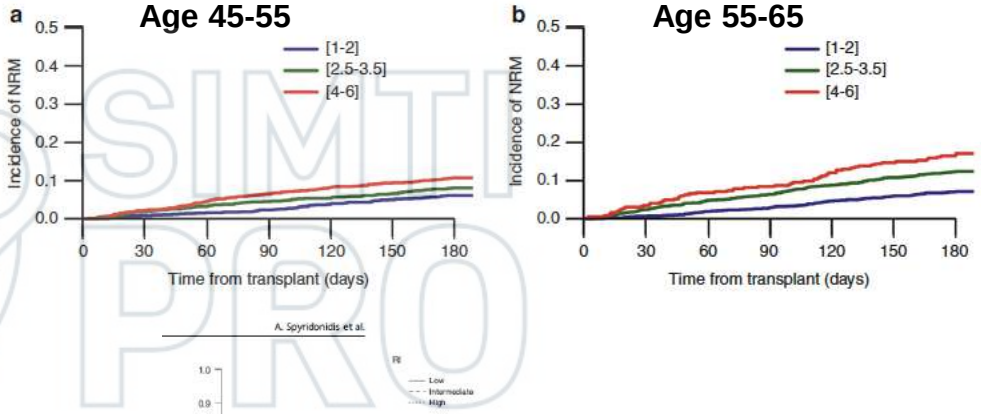
Conditioning

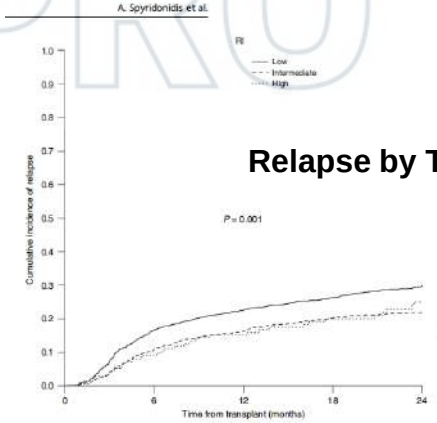
Transplant Conditioning Intensity
A. Spyridonidis ALWP





Bone Marrow Transplantation (2020) 55:1114–1125





Bone Marrow Transplantation (2024) 59:217 – 223

Non toxic conditioning
Antibody based conditioning

Efficient Transplantation via Antibody-Based Clearance of Hematopoietic Stem Cell Niches

Agnieszka Czechowicz, Daniel Kraft, Irving L. Weissman,*† Deepta Bhattacharya†

23 NOVEMBER 2007 VOL 318 SCIENCE www.sciencemag.org

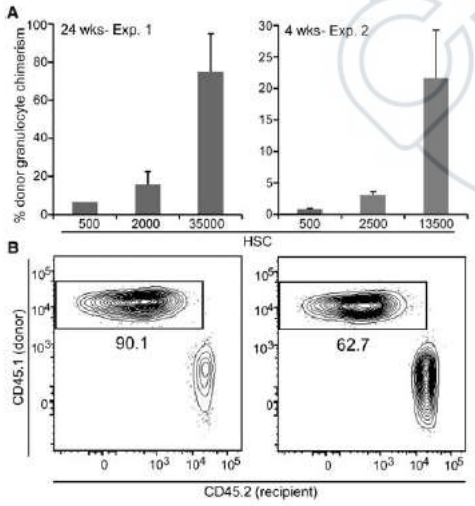


TABLE 1 Antibody-based approaches for hematopoietic stem cell transplantation.

HSC targeting agent	TBI	Immune modulation	Drugs	Donor graft	BM / HSC dose	% Chimerism	Organ graft	Reference
Naked mAb								
Anti-mouse CD45 (Clone 30F11)	-	-	-	Congenic	4×10^7 BM	<2% (day 30)	-	(38)
	5.5Gy	-	-	Congenic	4×10^7 BM	~80% (day 30)	-	
	-	Anti-CD4 +	-	MHC mismatch	4×10^7 BM	<5% (day 30)	-	
	8Gy	Anti-CD8	-	MHC mismatch	4×10^7 BM	>95% (day 30)	-	
30F11	-	-	-	Congenic	4×10^7 BM	<2% (3 months)	-	(41)
	5.5Gy	-	-	Congenic	4×10^7 BM	65% (3 months)	-	
	-	-	-	MHC mismatch	4×10^7 BM	<5% (3 months)	-	
	8Gy	-	-	MHC mismatch	4×10^7 BM	>90% (3 months)	-	
Anti-mouse c-kit (Clone ACK2)	–	–	–	Congenic	35×10^3 HSC	~90% (24 weeks)	–	(48)
ACK2	–	Anti-CD4	–	Minor mismatch	2×10^7 BM	63% (*Fanca*$^{-/-}$) (38 weeks) 93% (*Fancd2*$^{-/-}$) (38 weeks)	–	(50)
ACK2	3Gy	–	–	Haploidentical	1×10^6 BM	~79% (24 weeks)	–	(51)
Naked mAb								
ACK2	-	Anti-CD47	-	Haploidentical	3×10^6 Lin-	60% (24 weeks)	-	(53)
ACK2	-	Anti-CD47+ Anti-CD4/8	-	Minor mismatch	BM 15×10^4 LSK HSC	~20% (24 weeks)	-	
ACK2	-	Anti-CD47+	-	Haploidentical	3×10^6 BM	~20% (16 weeks)	Accept	(55)
	-	Anti-CD122 + Anti-CD40L	-	Haploidentical	9×10^3 LSK	~30% (16 weeks)	-	
	-	Anti-CD47+ Anti-CD122 + Anti-CD40L + Anti-CD4/8	-	MHC mismatch	9×10^3 LSK	>50% (8 weeks)		
		Anti-CD47+ Anti-CD122 + Anti-CD40L + Anti-CD4/8						

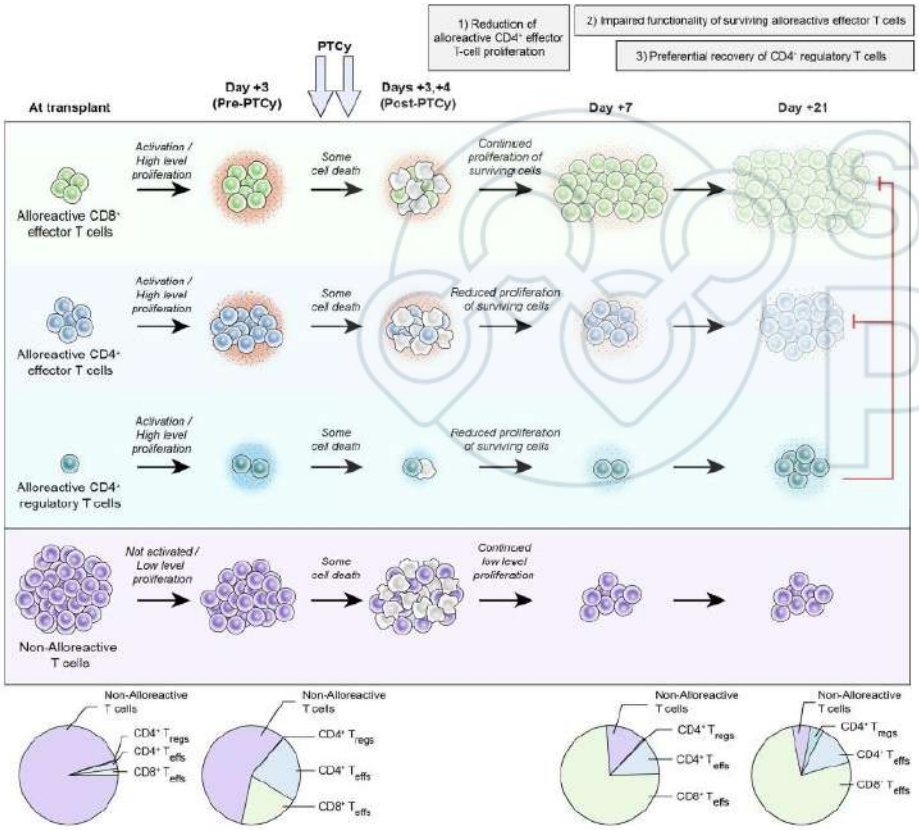
Asim Saha[1,2] and Bruce R. Blazar[1,2]*

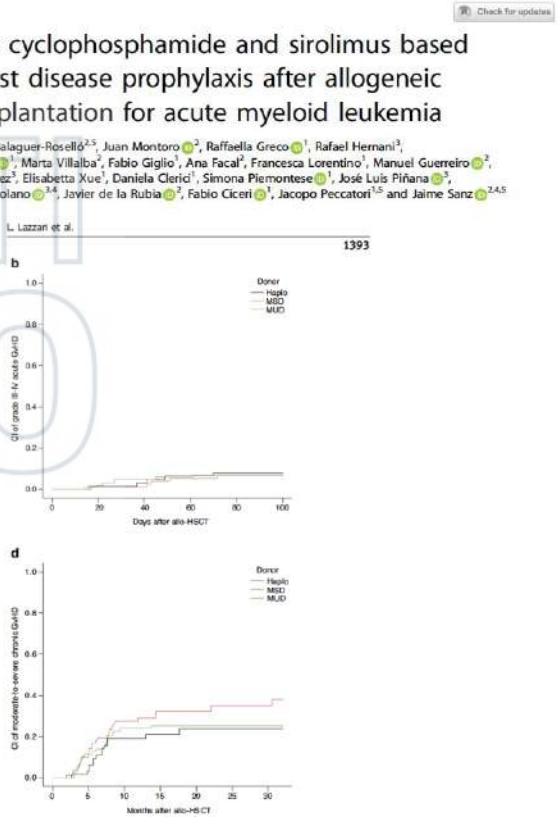
frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 20 October 2022
DOI 10.3389/fimmu.2022.1031334

GvHD prophylaxis

PTCy mediated GvHD prevention
a role for Tregs expansion





ARTICLE OPEN

Post-transplant cyclophosphamide and sirolimus based graft-versus-host disease prophylaxis after allogeneic stem cell transplantation for acute myeloid leukemia

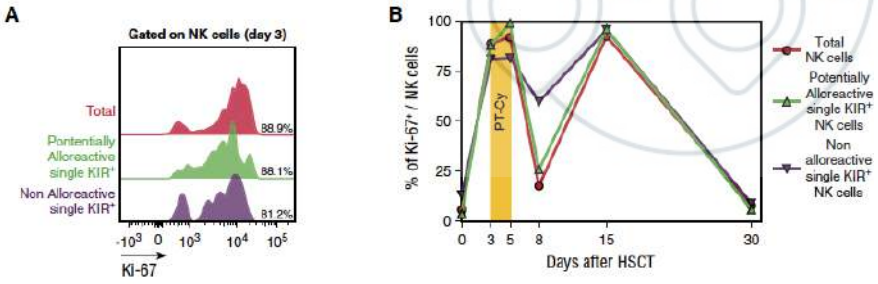
Lorenzo Lazzari[1,5✉], Aitana Balaguer-Roselló[2,5], Juan Montoro[2], Raffaella Greco[1], Rafael Hernani[3], María Teresa Lupo-Stanghellini[1], Marta Villalba[2], Fabio Giglio[1], Ana Facal[2], Francesca Lorentino[1], Manuel Guerreiro[2], Alessandro Bruno[1], Ariadna Pérez[3], Elisabetta Xue[1], Daniela Clerici[1], Simona Piemontese[1], José Luis Piñana[3], Miguel Ángel Sanz[2], Carlos Solano[3,4], Javier de la Rubia[2], Fabio Ciceri[1], Jacopo Peccatori[1,5] and Jaime Sanz[2,4,5]

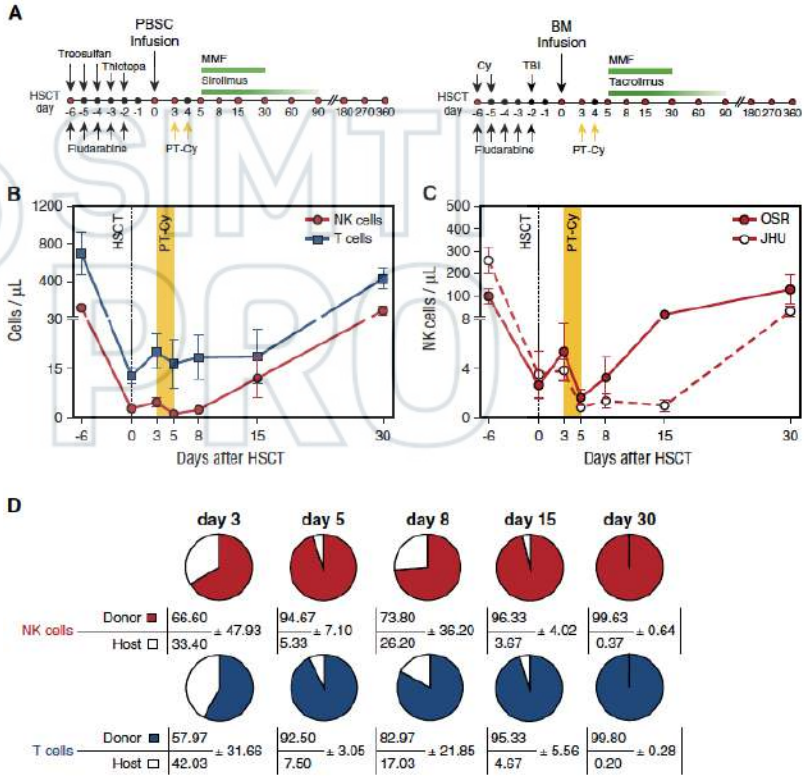
PTCy impact on NK cell recovery

TRANSPLANTATION

NK cell recovery after haploidentical HSCT with posttransplant cyclophosphamide: dynamics and clinical implications

Antonio Russo,[1,2,*] Giacomo Oliveira,[1,3,*] Sofia Berglund,[4] Raffaella Greco,[2] Valentina Gambacorta,[1] Nicoletta Cieri,[3] Cristina Toffalori,[1] Laura Zito,[1] Francesca Lorentino,[2] Simona Piemontese,[2] Mara Morelli,[2] Fabio Giglio,[2] Andrea Assanelli,[2] Maria Teresa Lupo Stanghellini,[2] Chiara Bonini,[3,5] Jacopo Peccatori,[2] Fabio Ciceri,[2,5] Leo Luznik,[4,†] and Luca Vago[1,2,†]





Dynamic biomarkers of GvHD

towards an on-time personalized prevention / pre-emptive

Interleukin-6 as Biomarker for Acute GvHD and Survival After Allogeneic Transplant With Post-transplant Cyclophosphamide

Raffaella Greco[1†], Francesca Lorentino[1†], Rosamaria Milli[1,2], Maria Teresa Lupo Stanghellini[1], Fabio Giglio[1], Daniela Clerici[1], Elisabetta Xua[1], Lorenzo Lazzari[1], Simona Piemontese[1], Sara Mastaglio[1], Andrea Assanelli[1], Sarah Markdel[1], Consuelo Corti[1], Massimo Bernardi[1], Fabio Ciceri[1,3*] and Jacopo Peccatori[1*]

frontiers in Immunology

October 2019 | Volume 10 | Article 2319

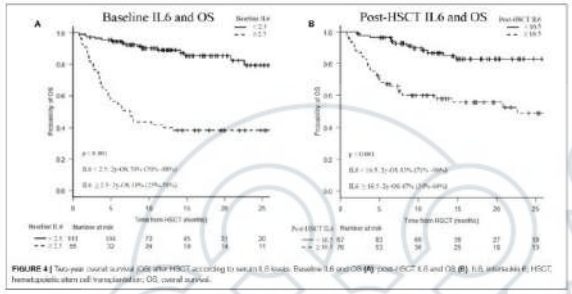


FIGURE 4 | Two-year overall survival (OS) after HSCT according to serum IL6 levels. Baseline IL6 and OS (A); post-HSCT IL6 and OS (B). IL6, interleukin 6; HSCT, hematopoietic stem cell transplantation; OS, overall survival.

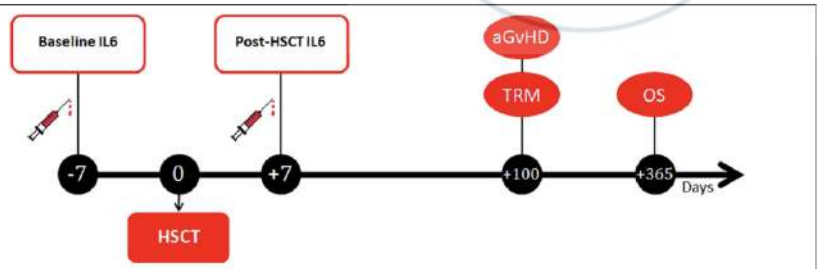


FIGURE 1 | Timepoints of blood samples collection and clinical outcomes assessment. IL6, Interleukin 6; HSCT, hematopoietic stem cell transplantation; aGvHD, acute graft-vs.-host disease; TRM, transplant-related mortality; OS, overall survival.

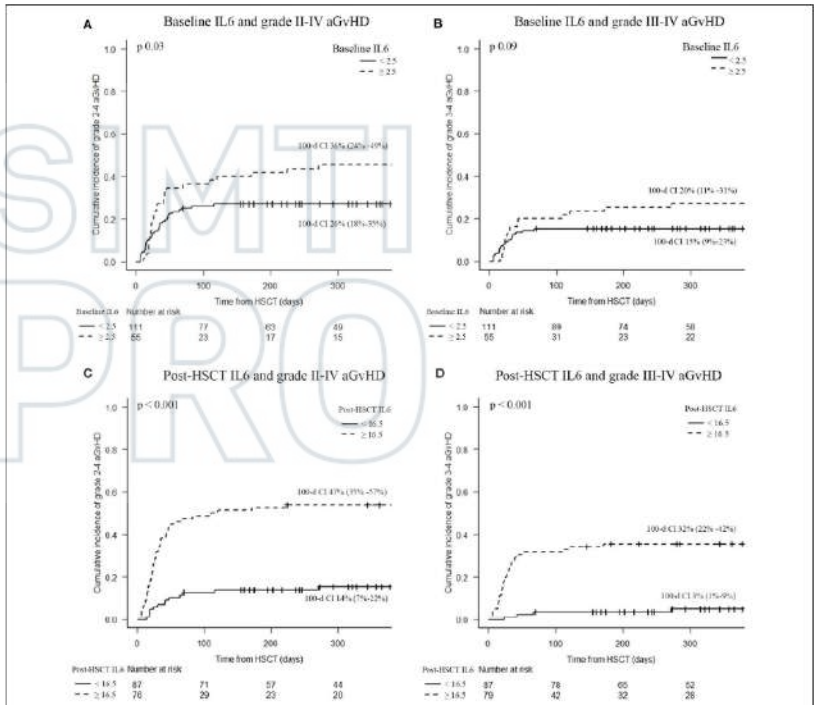
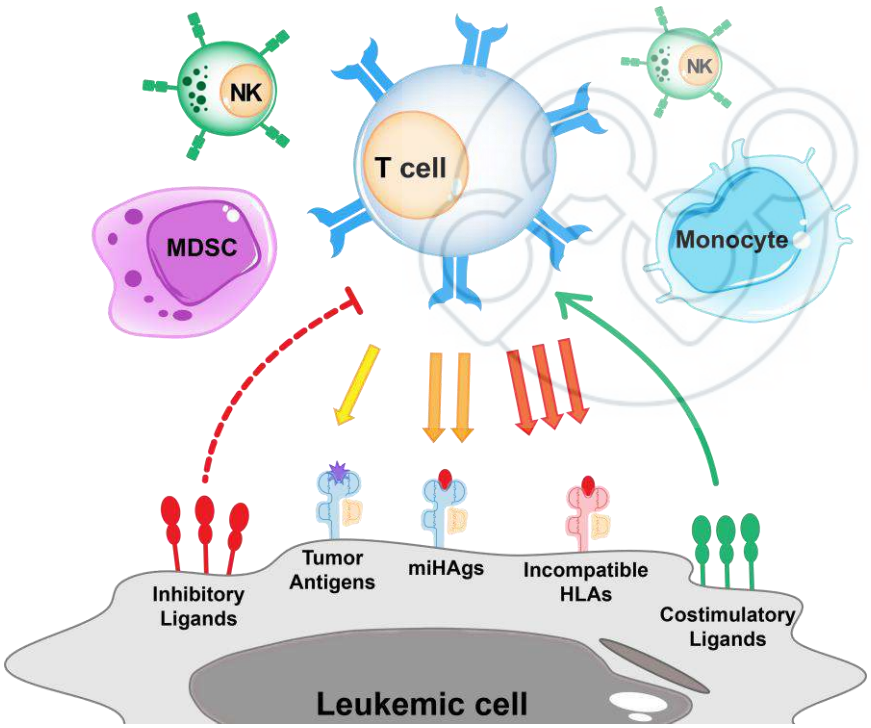


FIGURE 3 | Acute GvHD incidence according to serum IL6 levels. Baseline IL6 and grade II–IV aGvHD **(A)**, baseline IL6 and grade III–IV aGvHD **(B)**, post-HSCT IL6 and grade II–IV aGvHD **(C)**, post-HSCT IL8 and grade III–IV aGvHD **(D)**. CI of acute GvHD were calculated 100 days after HSCT. IL6, Interleukin 6; HSCT, hematopoietic stem cell transplantation; aGvHD, acute graft-vs.-host disease.

Relapse
prevention and treatment

Allo-HCT and the Graft-versus-Tumor Effect

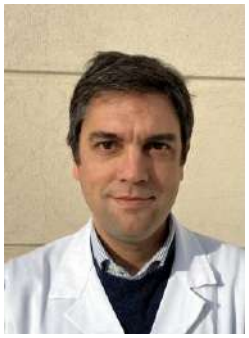
Allo-HCT represents one of the first and possibly the most comprehensive form of **adoptive immunotherapy of cancer**



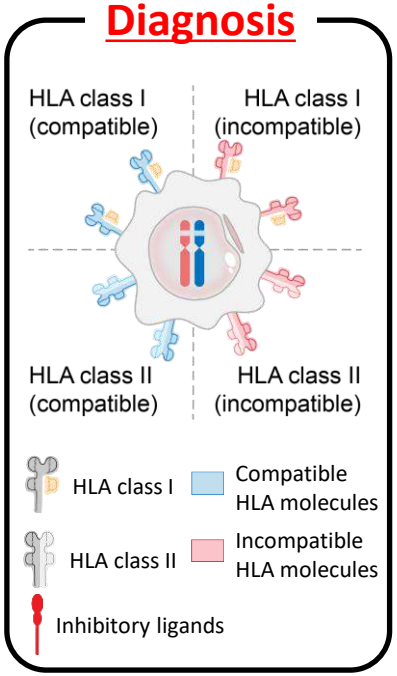
The Graft-versus-Tumor effect of Allo-HCT is:

- mediated by **multiple cell types**, in different maturation states and directed against multiple targets
- T cell play a major role, and are largely directed against minor and major **histocompatibility antigens** mismatched between donor and recipient
- highly dependent on the **balance of signals** received by T cells from tumor cells and the bone marrow immune microenvironment

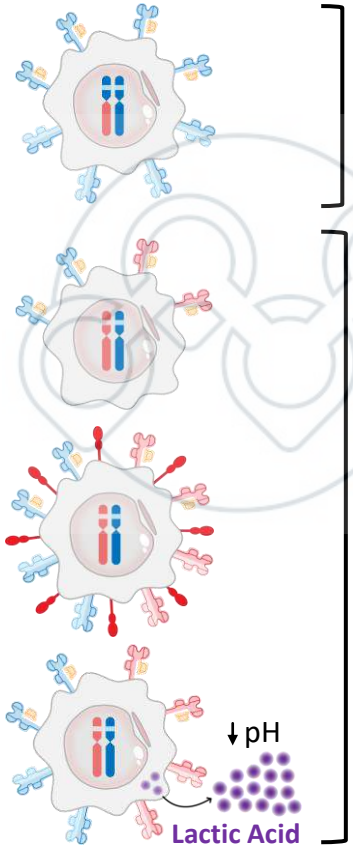
Mechanisms of Post-Transplantation Immune Escape



Diagnosis



Relapse



Genomic

HLA haplotype loss

Vago, NEJM, 2009; Crucitti, Leukemia, 2015; Ahci and Toffalori, Blood, 2017

Non-Genomic

Downregulation of HLA Class II molecules

Christopher, NEJM, 2018; Toffalori, Nat Med, 2019

Upregulation of T cell inhibitory ligands

Toffalori, Nat Med, 2019; Noviello and Manfredi, Nat Comm, 2019

Impairment of T cell metabolic fitness

Uhl, Sci Transl Med, 2020

Treatment Strategies Specific for Each Relapse Modality

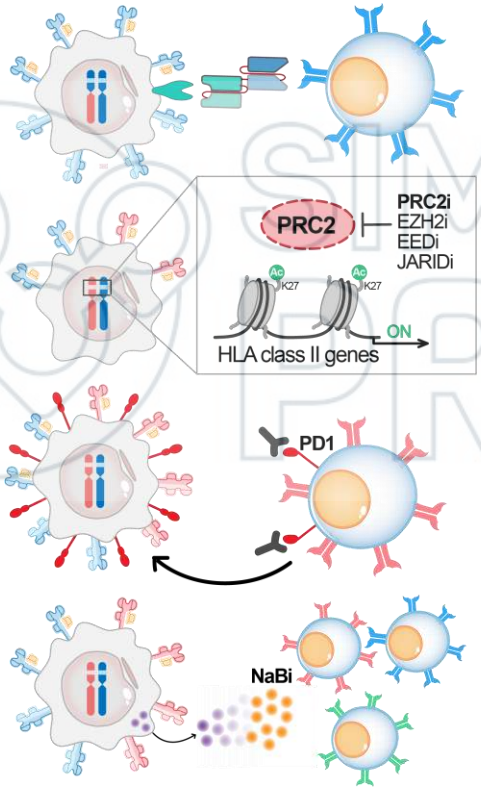
Mechanism

HLA haplotype loss

Downregulation of HLA Class II molecules

Upregulation of T cell inhibitory ligands

Impairment of T cell metabolic fitness



Approach

Second allo-HCT, Bispecific antibodies

Vago and Ciceri, BBMT, 2017; Imus, BBMT, 2017; Rovatti, in preparation

Delivery of IFN-γ, Epigenetic drugs (PRC2i)

Rimando, Blood, 2023; Ito, TCT, 2023; Gambacorta, Cancer Discovery, 2022

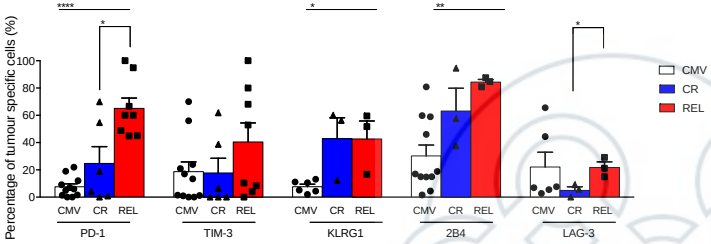
Immune Checkpoint Blockade (+ Hypomethylating agents?)

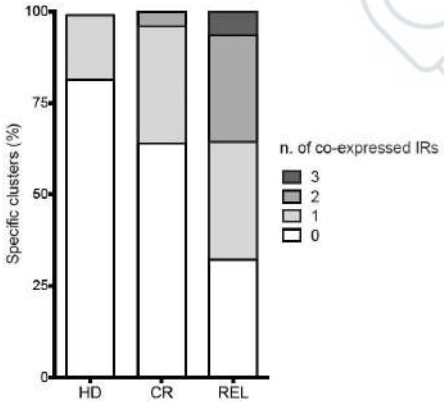
Davids, NEJM, 2016; Penter, Blood, 2023; Apostolova, Br J Hematol, 2023

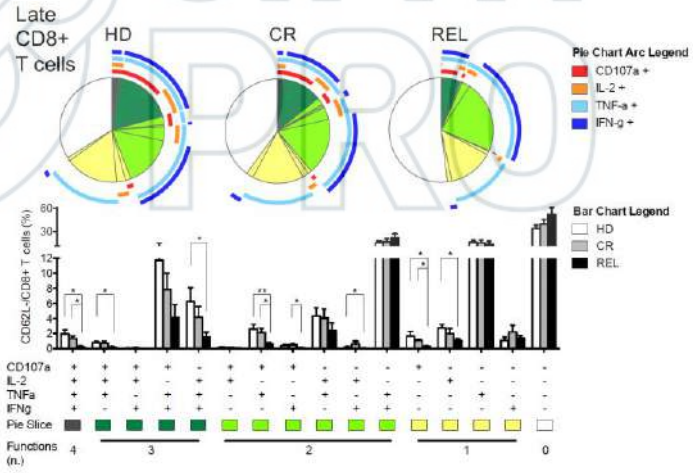
Counterbalancing lactic acid with NaBi

Uhl, Sci Transl Med, 2020

TAA specific T cells are profoundly exhausted in AML patients prone to relapse after allo-HSCT







Maddalena Noviello

Noviello, Manfredi et al., *Nat Comm* 2019

Alois Gratwohl, EBMT President from 1994-1997.

"You choose to be a transplanter
…. if you want to do it together"

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Building capacities

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Thanks!

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

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Gruppo San Donato

grazie