

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

ADISCOV
ASSOCIAZIONE DONATRICI ITALIANE
SANGUE CORDONE OMBELICALE

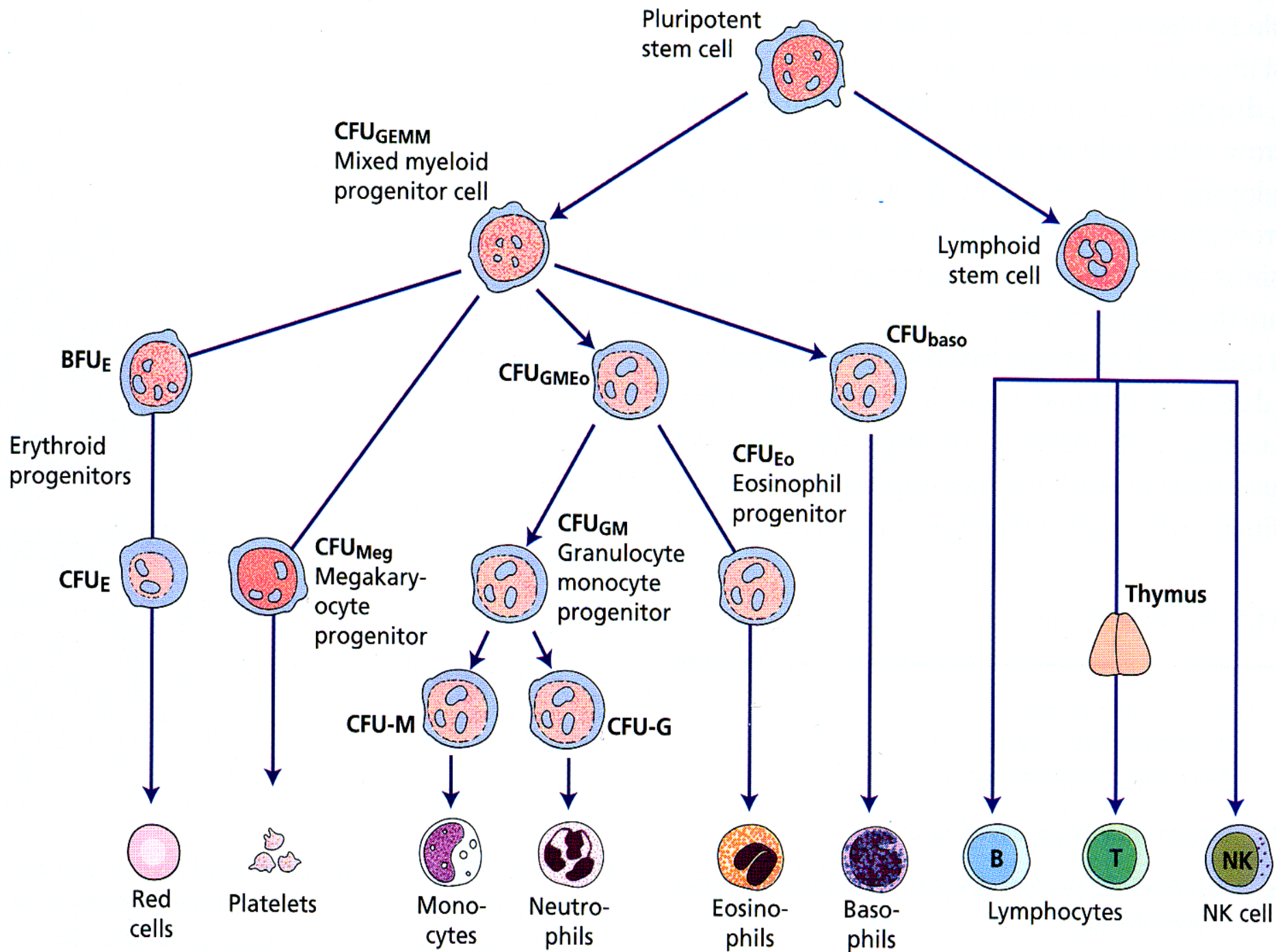
17 ottobre 2013

CONVEGNO
DONAZIONE
SANGUE
CORDONALE

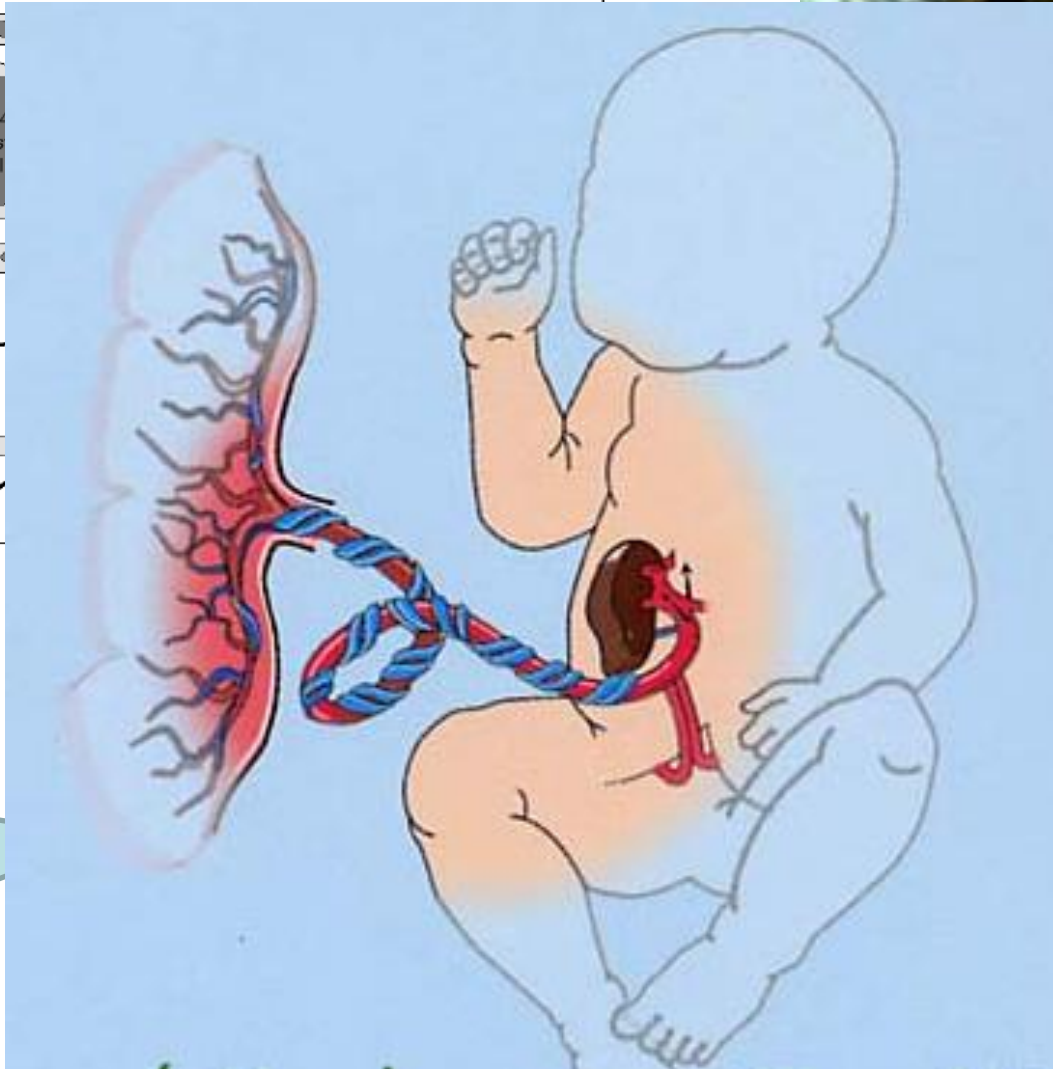
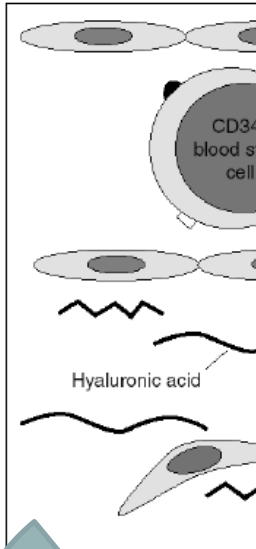


***Biologia, uso clinico
delle cellule staminali
ematopoietiche.
Prospettive future***

Prof. Franco Aversa



Proprieta' migratorie delle *CD34+* umane



Cellulare

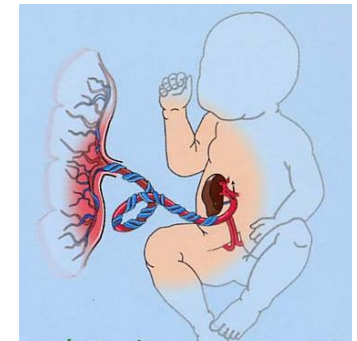
**Prelievo
Midollo
osseo**



**PRELIEVO
CELLULE
STAMINALI
EMATOPOIETICHE
DAL DONATORE**

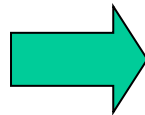


**Raccolta Cellule
Staminali Periferiche**



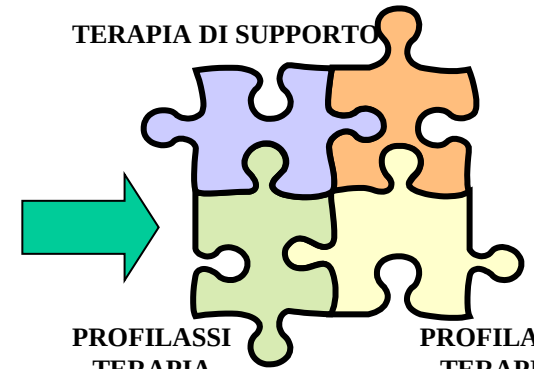
Cordone Ombelicale

**Chemioterapia
Immunosoppressori
+ / - TBI**



INFUSIONE CSE

TERAPIA DI SUPPORTO



**PROFILASSI
TERAPIA
INFEZIONI**

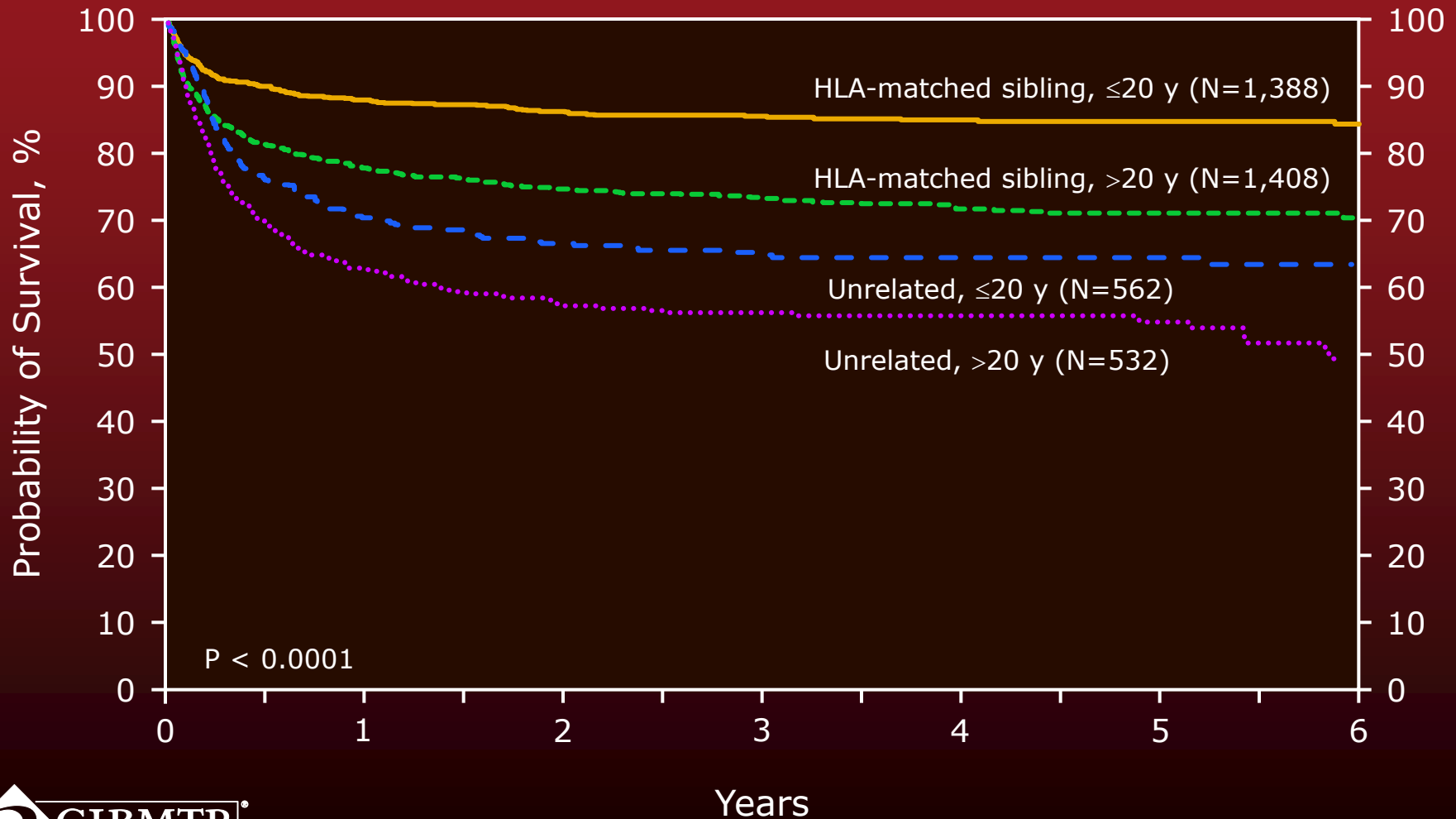
**PROFILASSI
TERAPIA
GVHD**

RICOSTITUZIONE

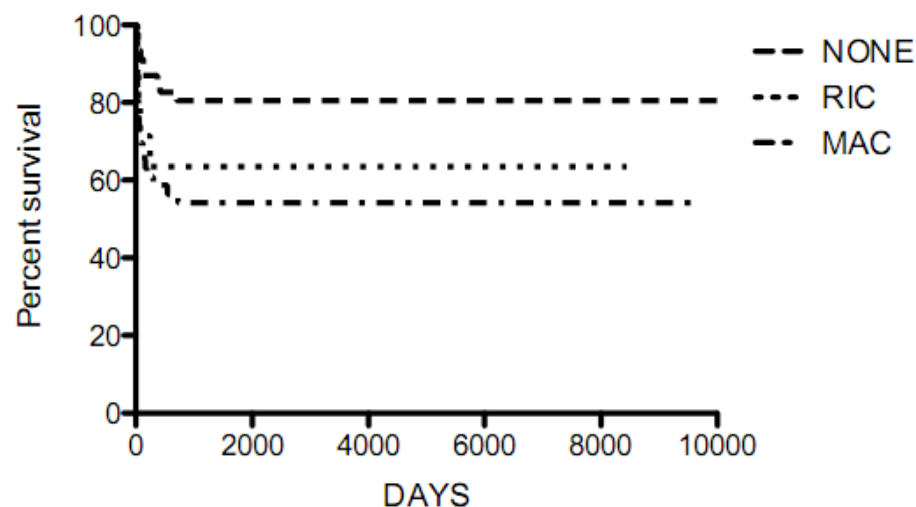
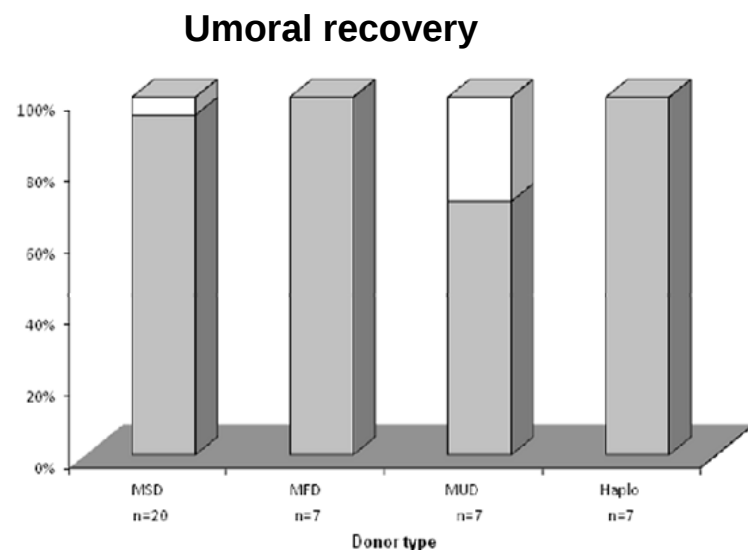
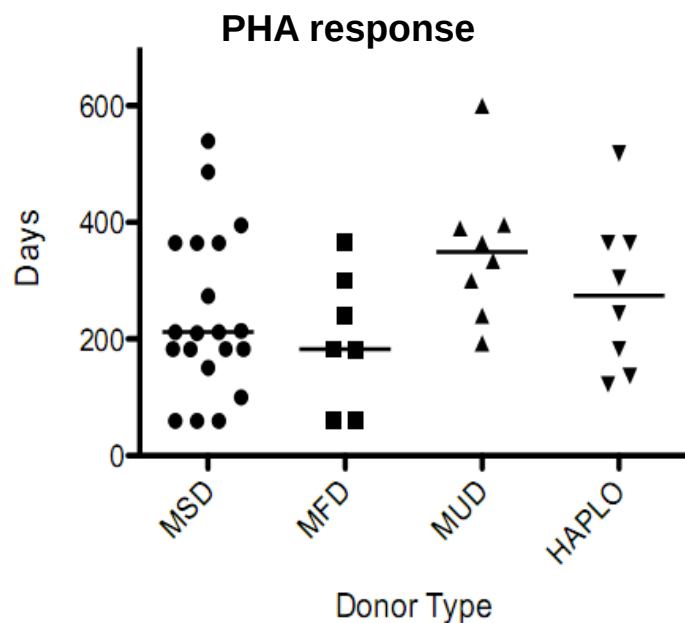
**EMATOLOGICA
IMMUNOLOGICA**

**REGIME di
CONDIZIONAMENTO:
EFFETTO SPAZIO
IMMUNOSOPPRESSIONE
EFFETTO ANTI-LEUCEMICO**

Results in severe aplastic anemia, (1998-2008)



Outcome of hematopoietic stem cell transplantation for adenosine deaminase deficient severe combined immunodeficiency



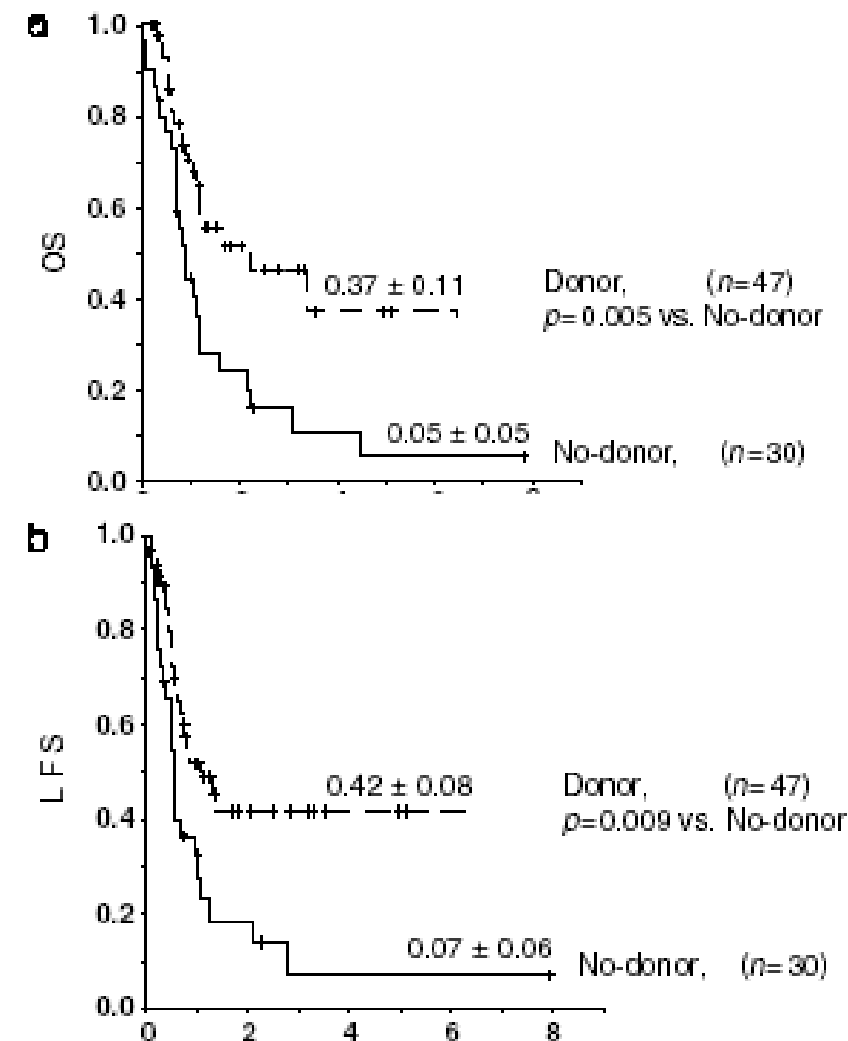
blood

Prepublished online July 12, 2012;
doi:10.1182/blood-2011-12-396879

Early related or unrelated haematopoietic cell transplantation results in higher overall survival and leukaemia-free survival compared with conventional chemotherapy in high-risk acute myeloid leukaemia patients in first complete remission

N Basara¹, A Schulze², U Wedding³, M Mohren⁴, A Gerhardt⁵, C Junghanss⁶, N Peter⁷, G Dölken⁸, C Becker¹, S Heyn¹, C Kliem¹, T Lange¹, R Krah¹, W Pönisch¹, H-J Fricke³, HG Sayer³, H Al-Ali¹, F Kamprad^{9,10} and D Niederwieser¹ for the East German Study Group Hematology and Oncology (OSHO)

Leukemia (2009) 23, 635–640



Trapianto Allogeneico

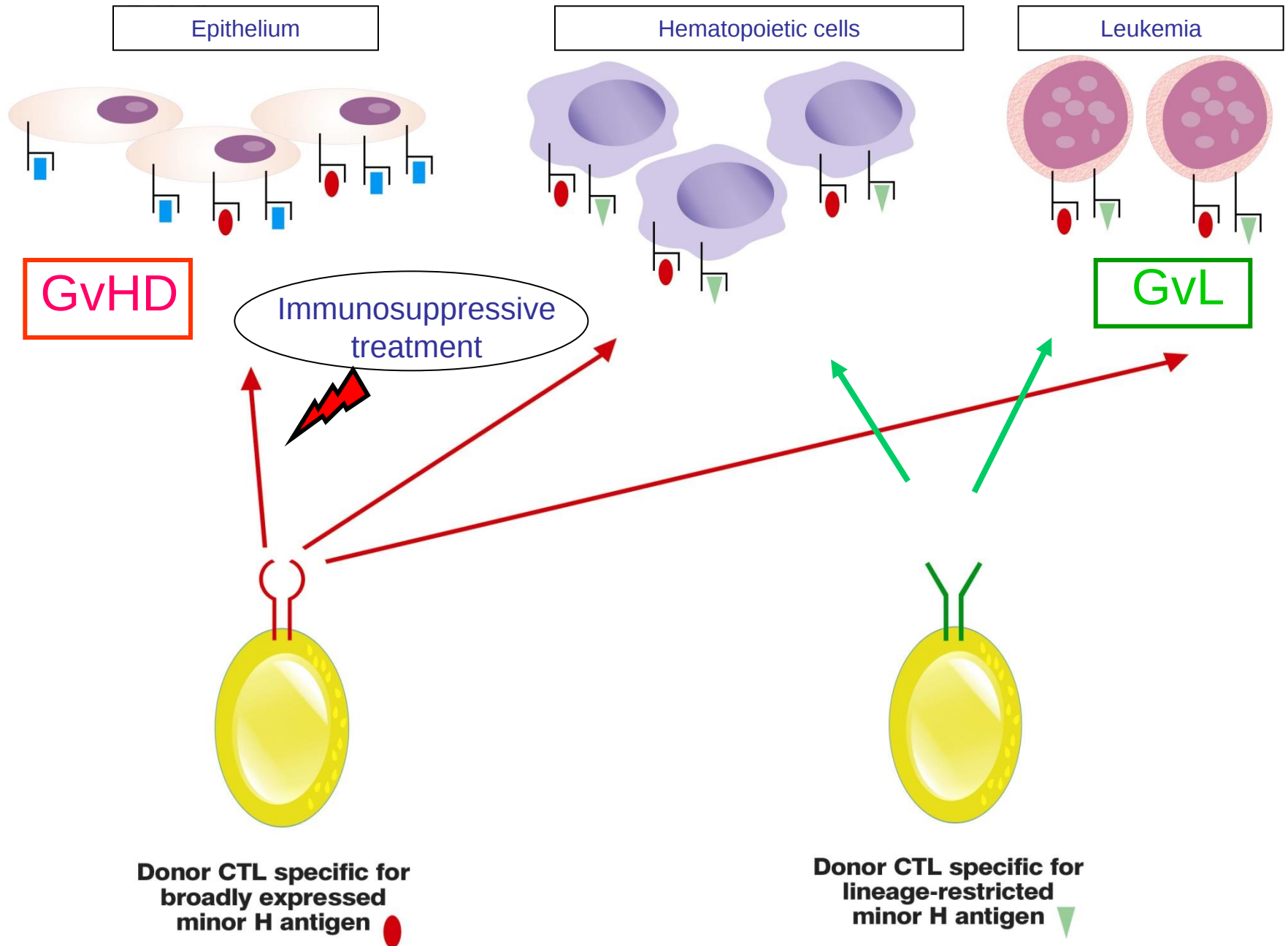
I linfociti T del donatore sono responsabili dei tre maggiori effetti biologici:

- Attecchimento
- Graft *versus* Leukemia/Tumor Effect
- Graft *versus* Host Disease

Graft vs Host Disease

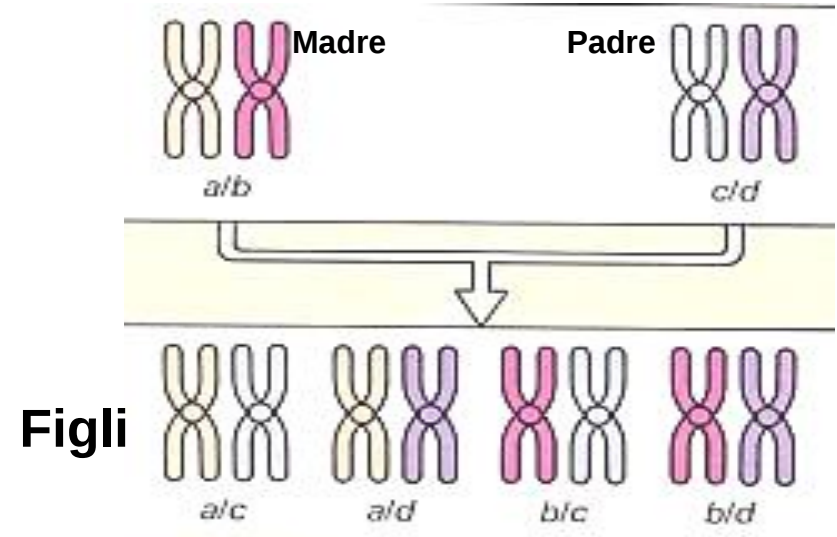
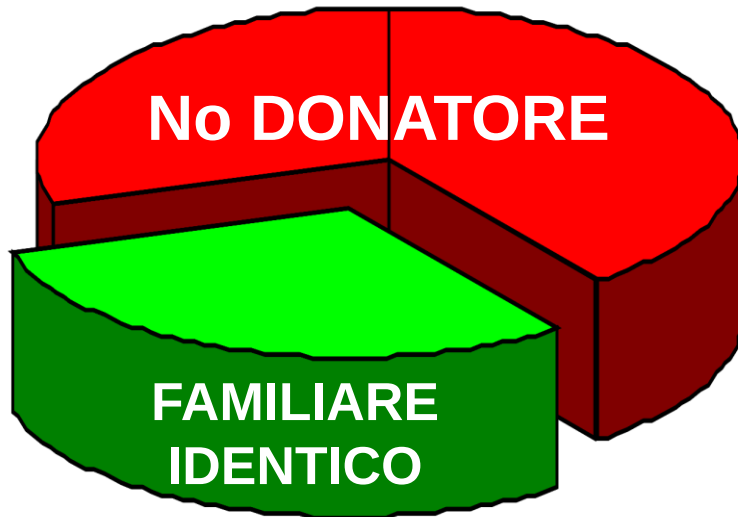
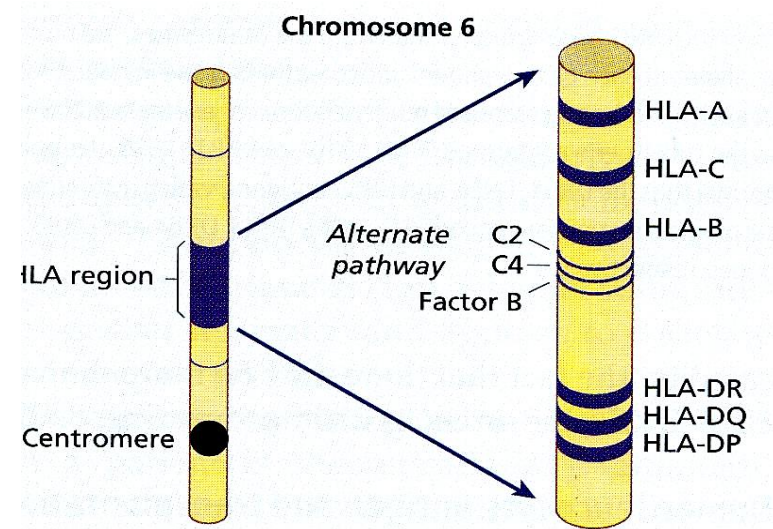
- Aggressione immunologica di tessuti del ricevente da parte dei Linfociti T del donatore che riconoscono differenze antigeniche del sistema HLA.
- Si manifesta in due forme, in genere associate e in sequenza
 - **Acuta** (precoce entro 100 giorni dal TMO)
 - **Cronica** (da 100 giorni a mesi dopo il TMO)

GvL effect and GvHD

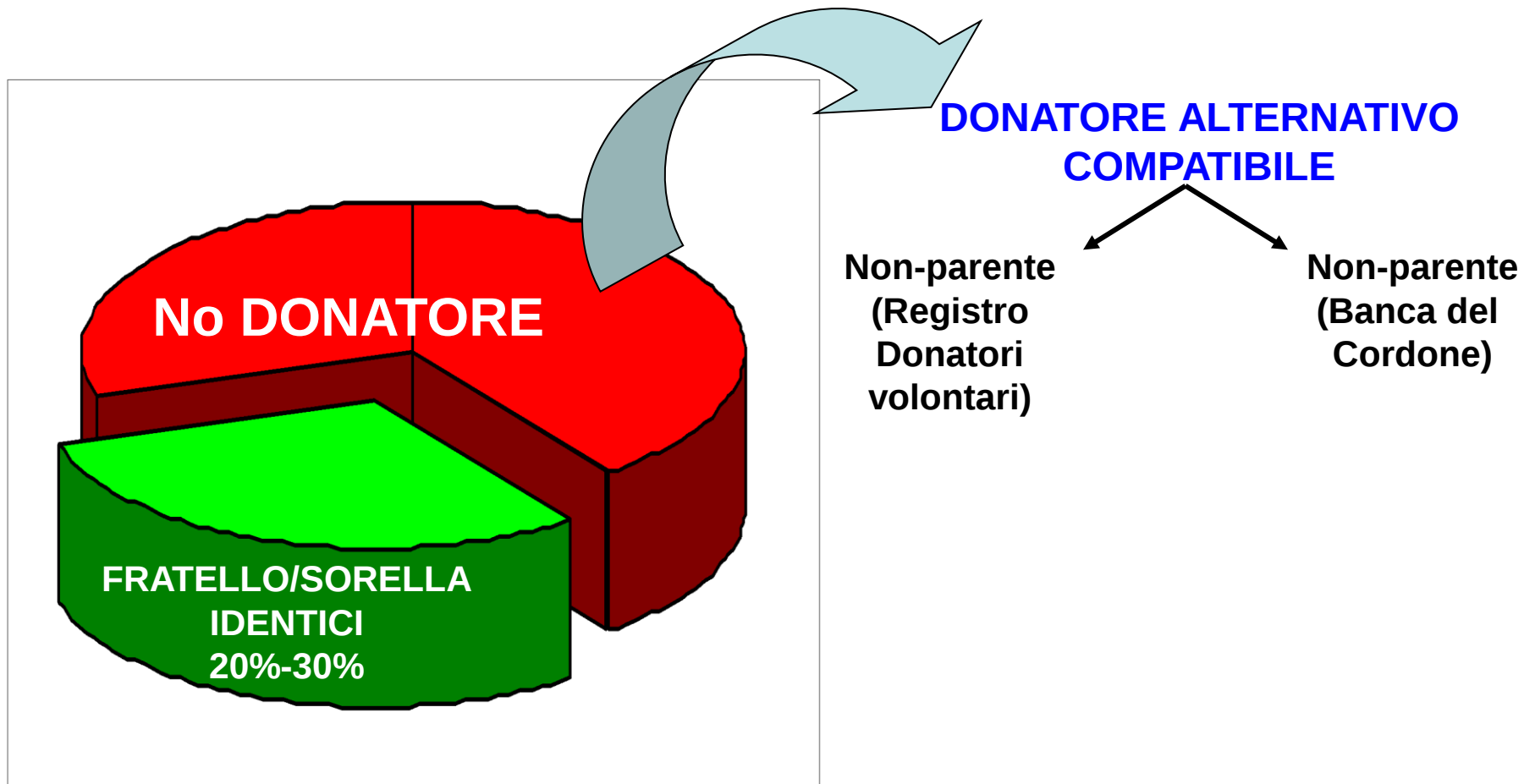




PROBABILITA' di AVERE UN DONATORE



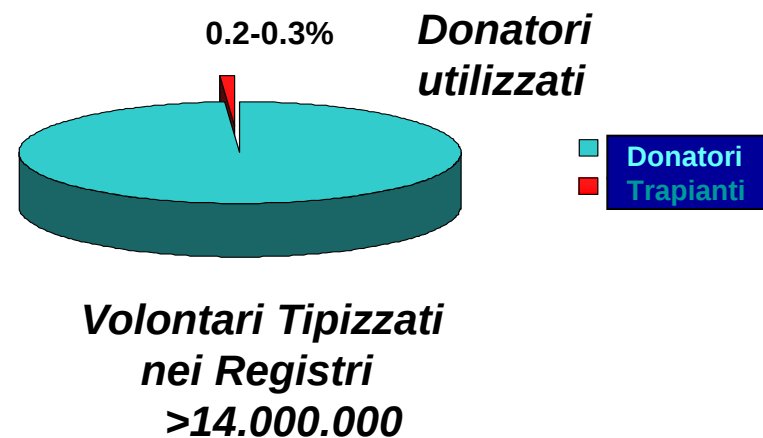
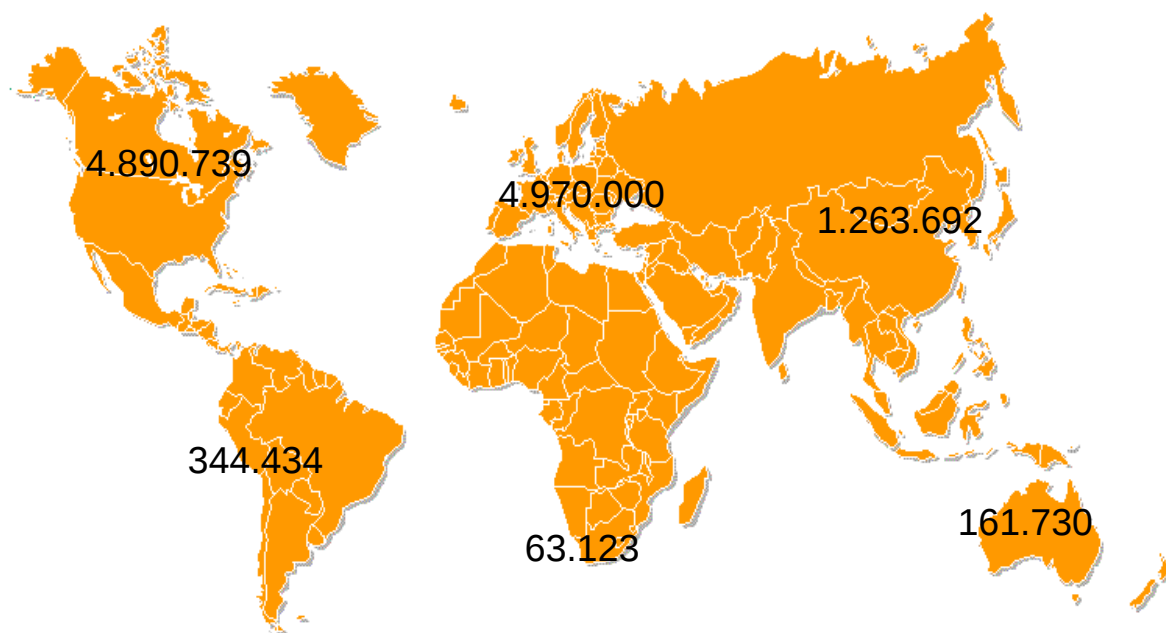
PROBABILITA' DI AVERE UN DONATORE





Distribuzione donatori di CSE nel mondo

(dati al 31-dic-2007)



Tempo necessario per identificazione donatore idoneo

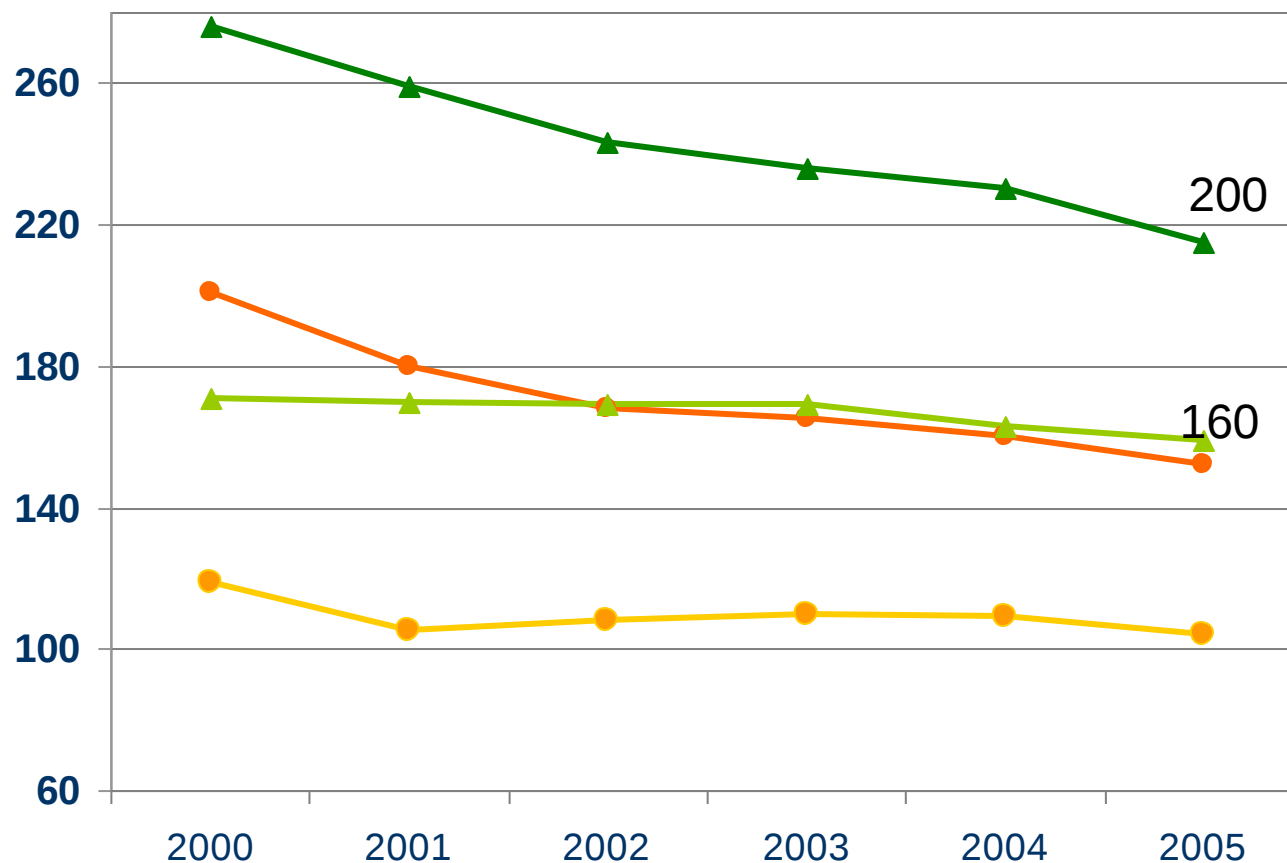
Tempo di ricerca

Test di compatibilità finale:

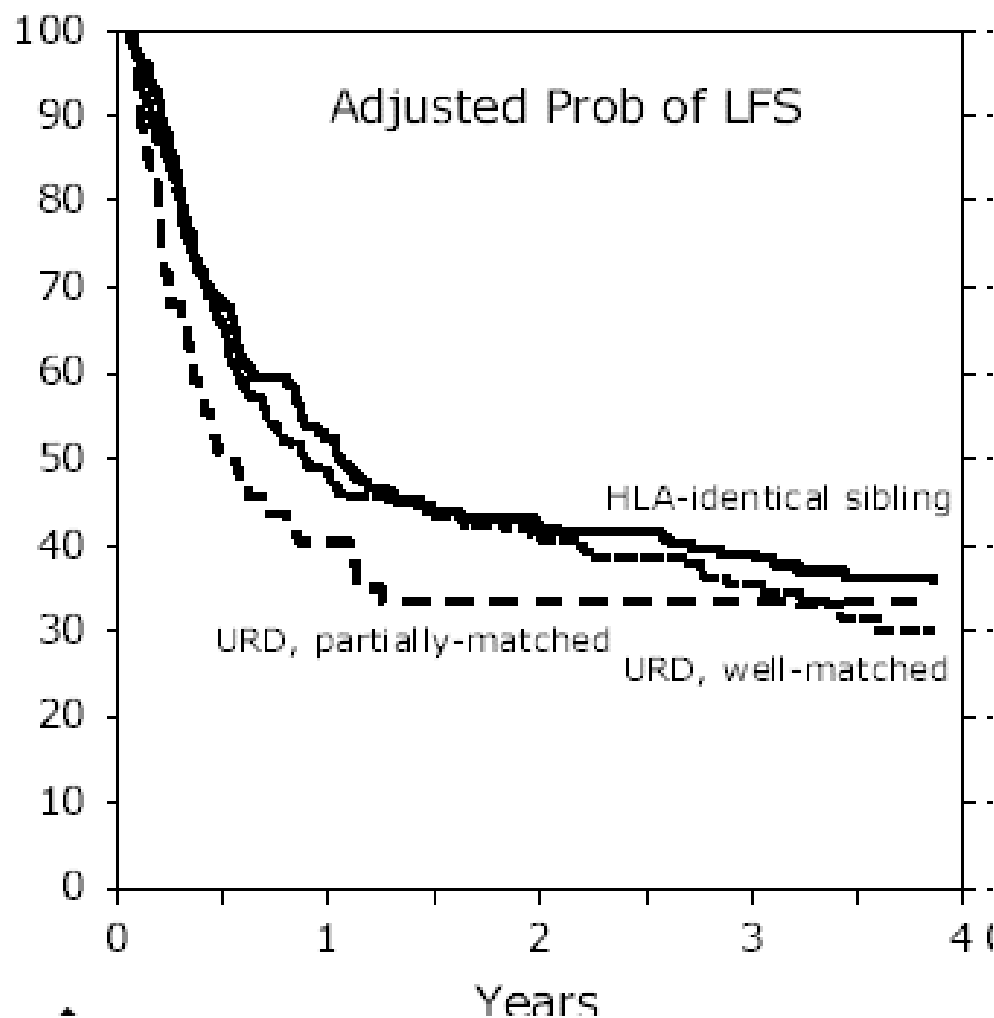
- media
- mediana

Trapianto:

- media
- mediana

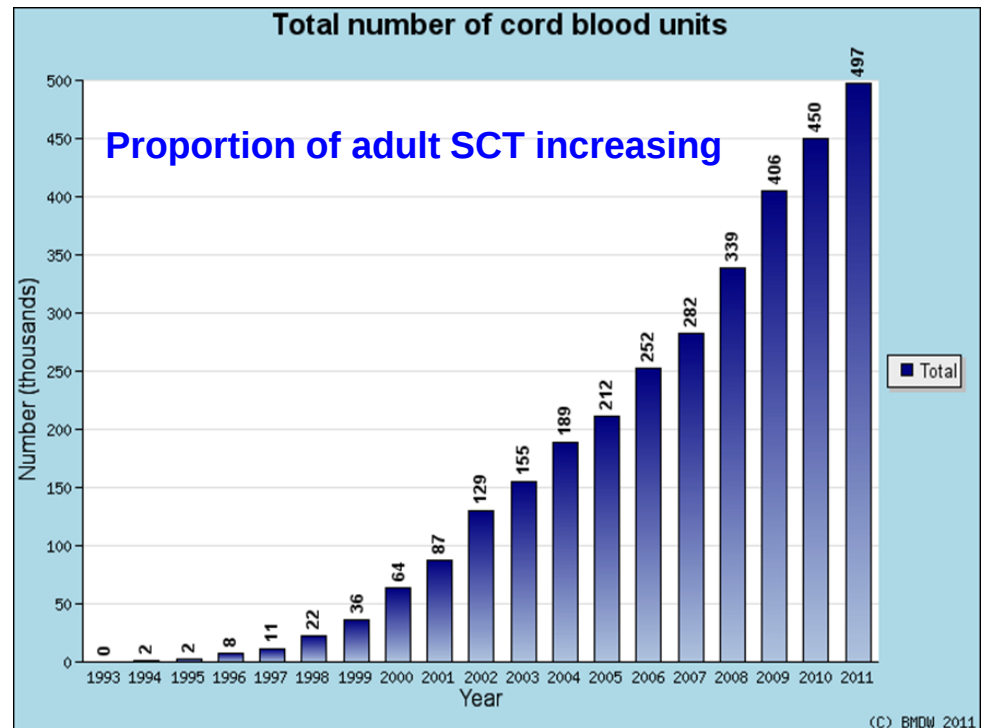


Sopravvivenza dopo trapianto da donatore HLA-identico familiare (n=226) e non (n=358) in pazienti con Leucemia Acuta alto rischio



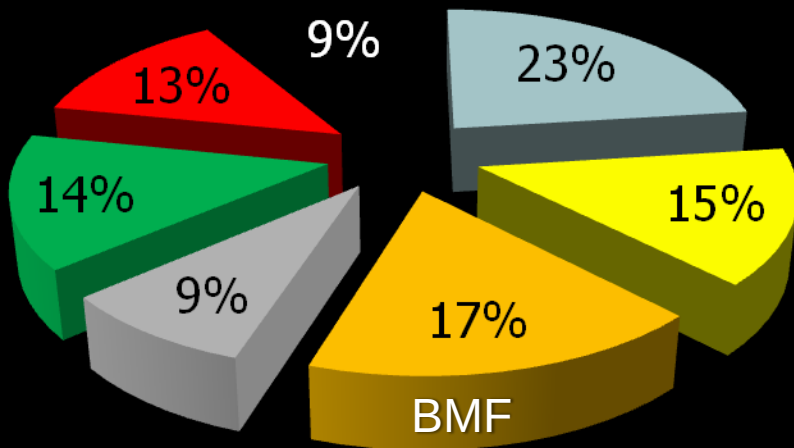
CBT - State of the art

- Initial transplants in children, extended to adults
- >25,000 UCB transplants performed worldwide
- > 500,000 UCB donated to public storage banks
- 43 Banks in 28 countries



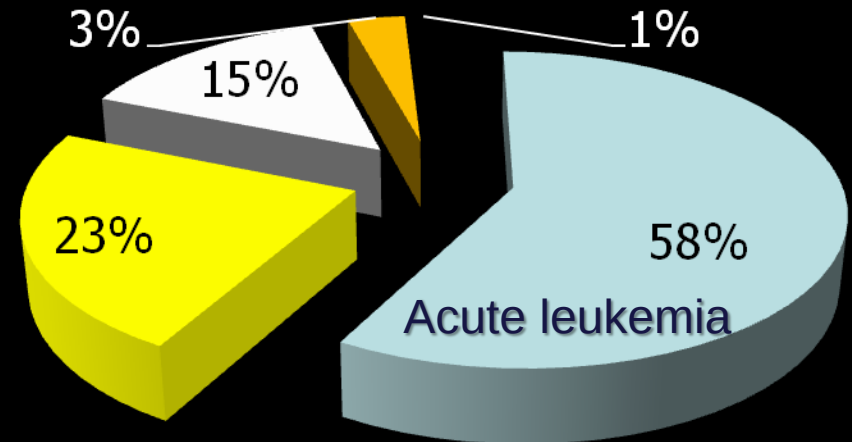
Transplants by diagnoses

Children

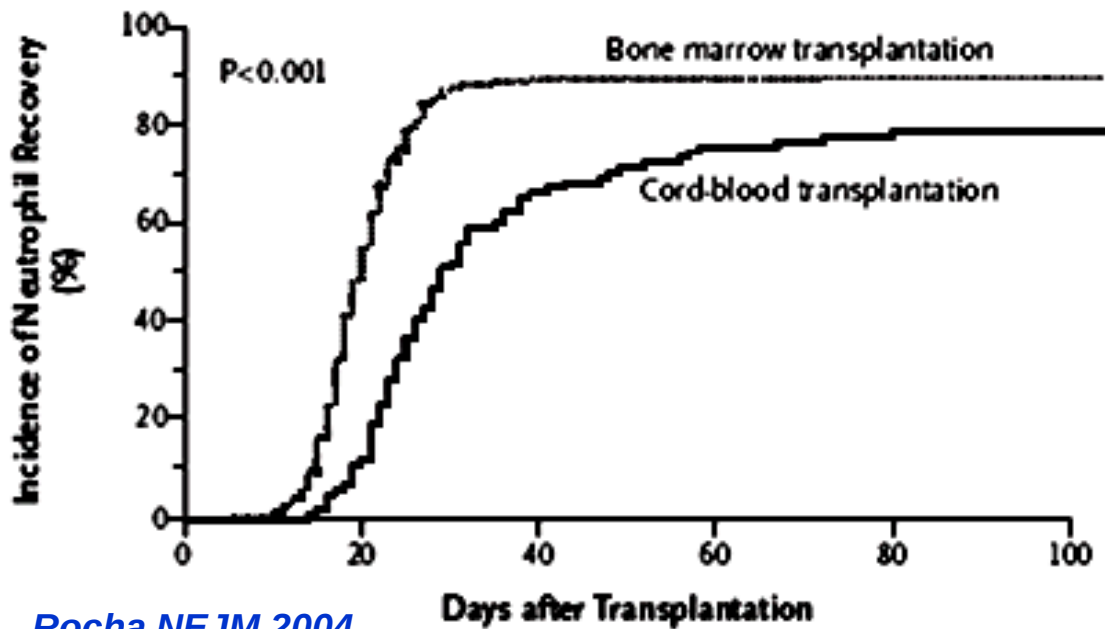


- Acute leukaemias
- MDS/CML
- BMFS
- Haemaglobinopathy
- SCID
- Metabolic disease
- Other

Adults



- Acute leukaemias
- MDS/CML/CLL
- Lymphoma and myeloma
- BMFS
- Other

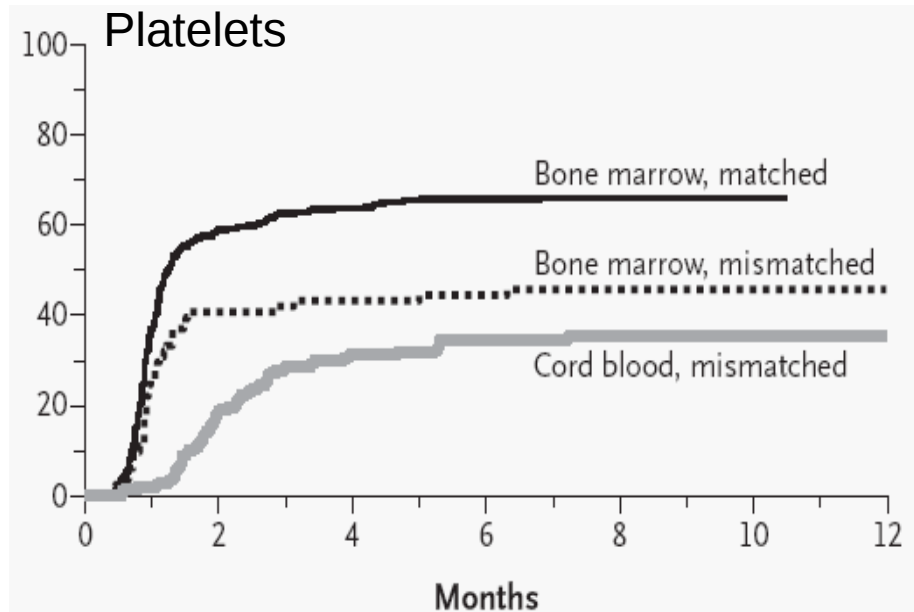
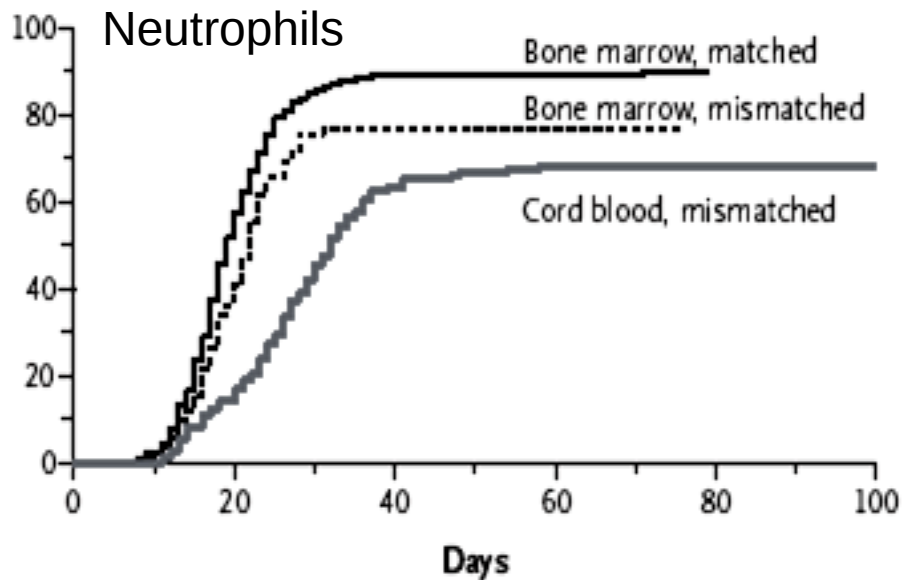


Rocha NEJM 2004

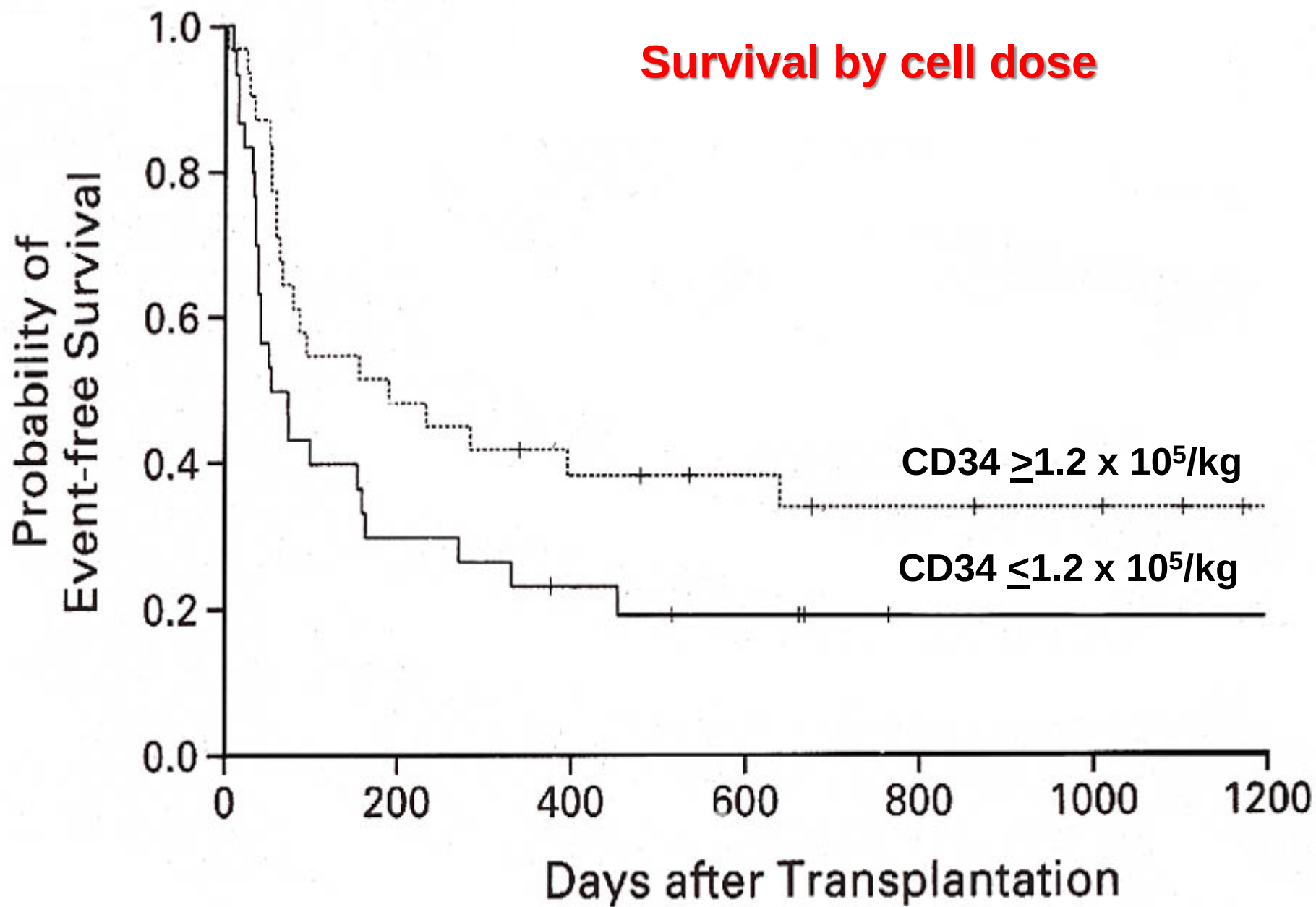
**Unrelated Cord
Blood Transplant**

Engraftment

Matched Units,

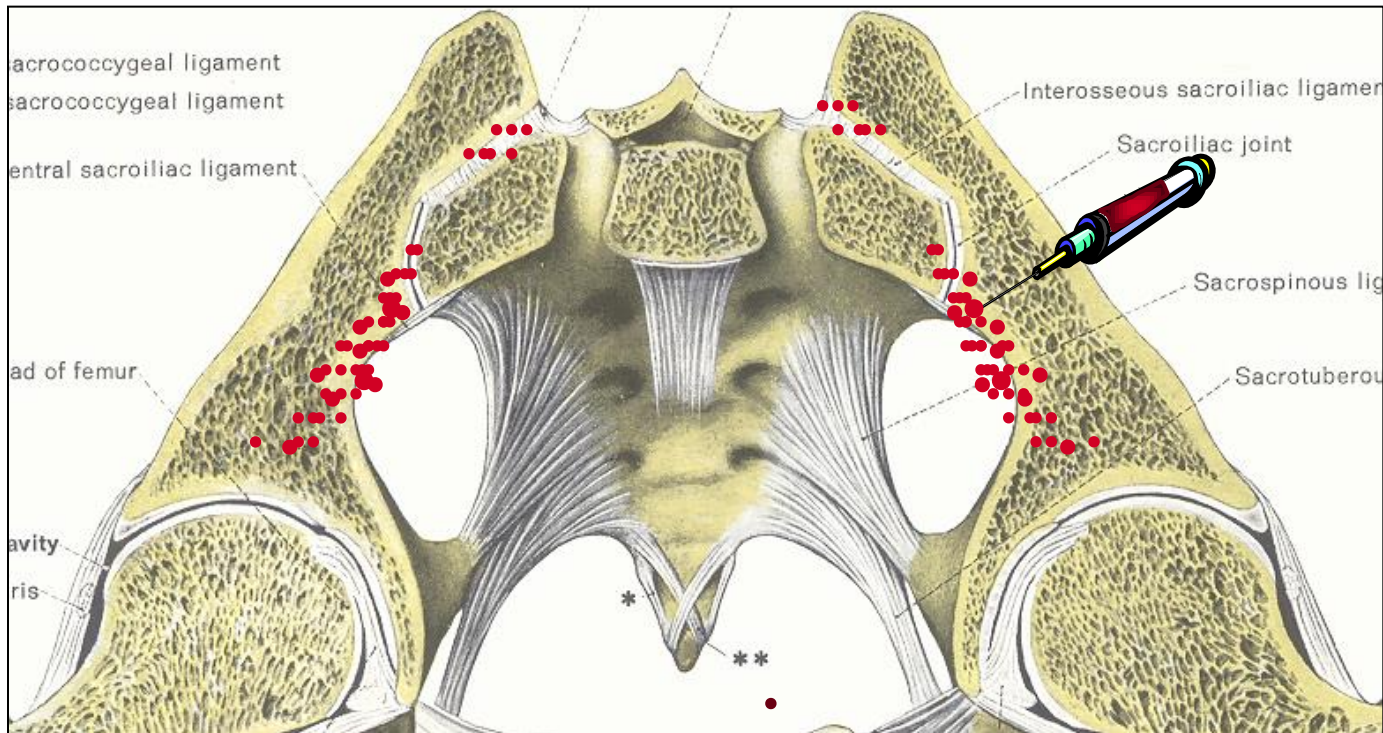


Laughlin, NEJM 2004



Intra Bone Marrow Injection

- ✓ reduces non specific SC losses,
- ✓ optimizes SC homing to the BM microenvironment



Come migliorare i risultati dell'attecchimento

- Iniezione diretta intra-ossea
- Espansione ex vivo
- Coinfusione di cellule mesenchimali
- Coinfusione di due Unità cordonali
- Coinfusione di Aplo e CB

Complicanze donatori (50.000 donatori EBMT)

1:100 lievi

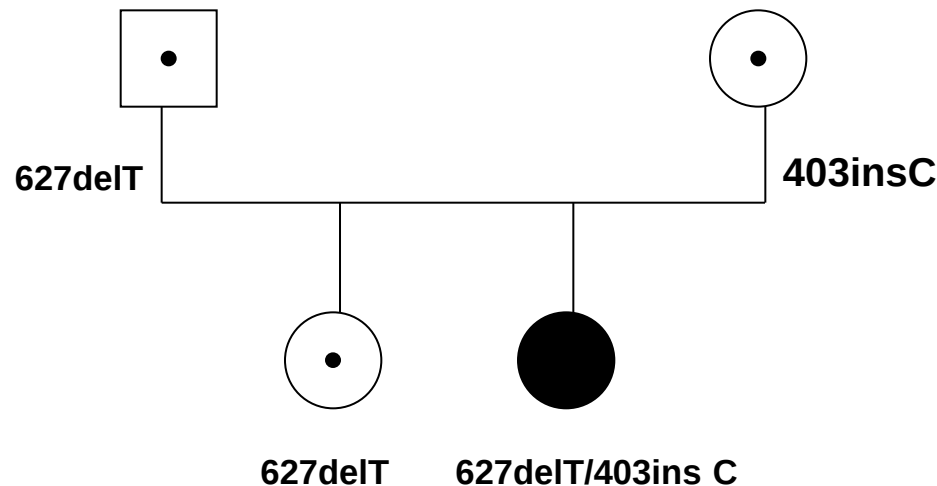
1:1000 gravi

1:10.000 fatali:

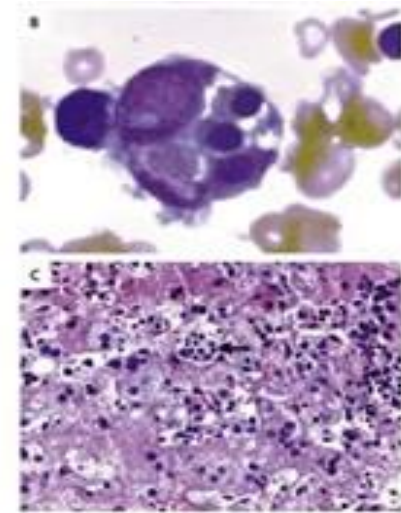
- midollo: 1 / 27000 donazione
- periferiche: 4 / 23.000 donazioni
 - 0 / 25.000 UD
 - 5 / 25.000 familiari

Analisi genetica paziente e famiglia

mutazioni gene Munc13-4



♀ C. G. 2 aa



**SINDROME EMOFAGOCITICA PRIMITIVA o
LINFOISTIOCITOSI EMOFAGOCITICA
da doppia eterozigosi per mutazioni Munc13-4**



ELSEVIER

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

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



14

Tissue regeneration potential in human umbilical cord blood

Hadar Arien-Zakay, PhD, Post-Doc student^{a,b,1}, Philip Lazarovici, PhD,
Chairman^{b,2}, Arnon Nagler, MD, MSc, Director of Hematology Division^{a,*}

^aDivision of Hematology and Cord Blood Bank, Chaim Sheba Medical Center, Tel-Hashomer, Israel

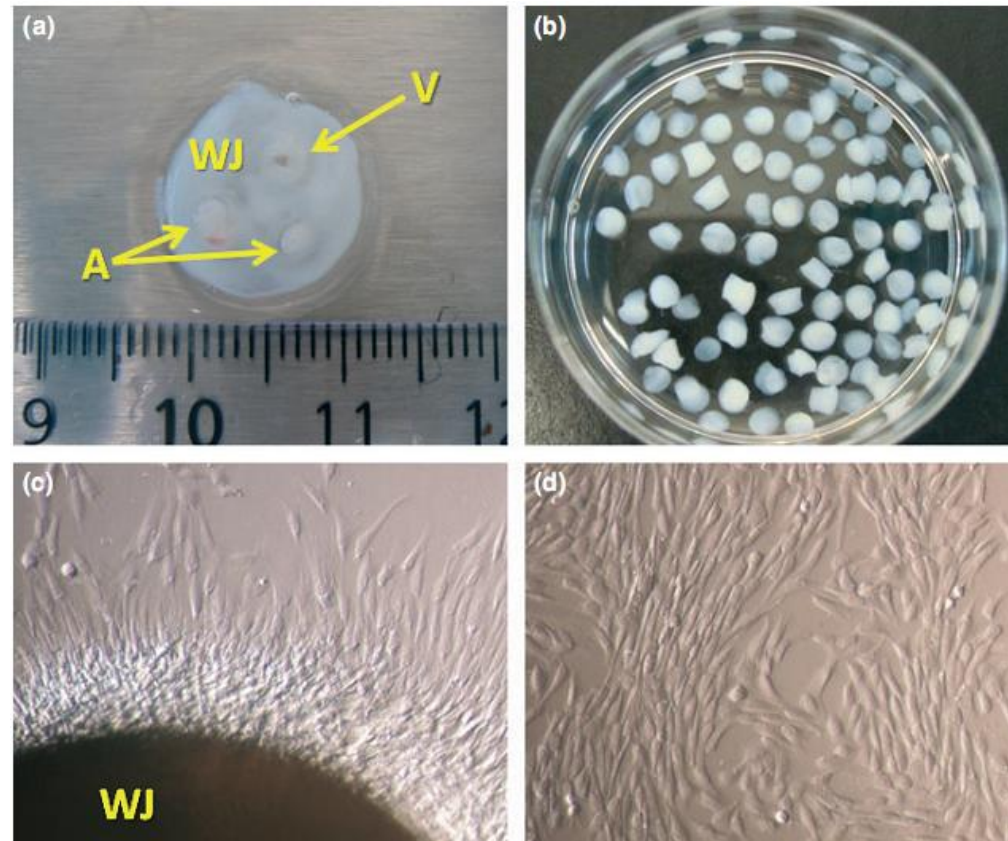
^bSchool of Pharmacy, Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

The umbilical cord: a rich and ethical stem cell source to advance regenerative medicine

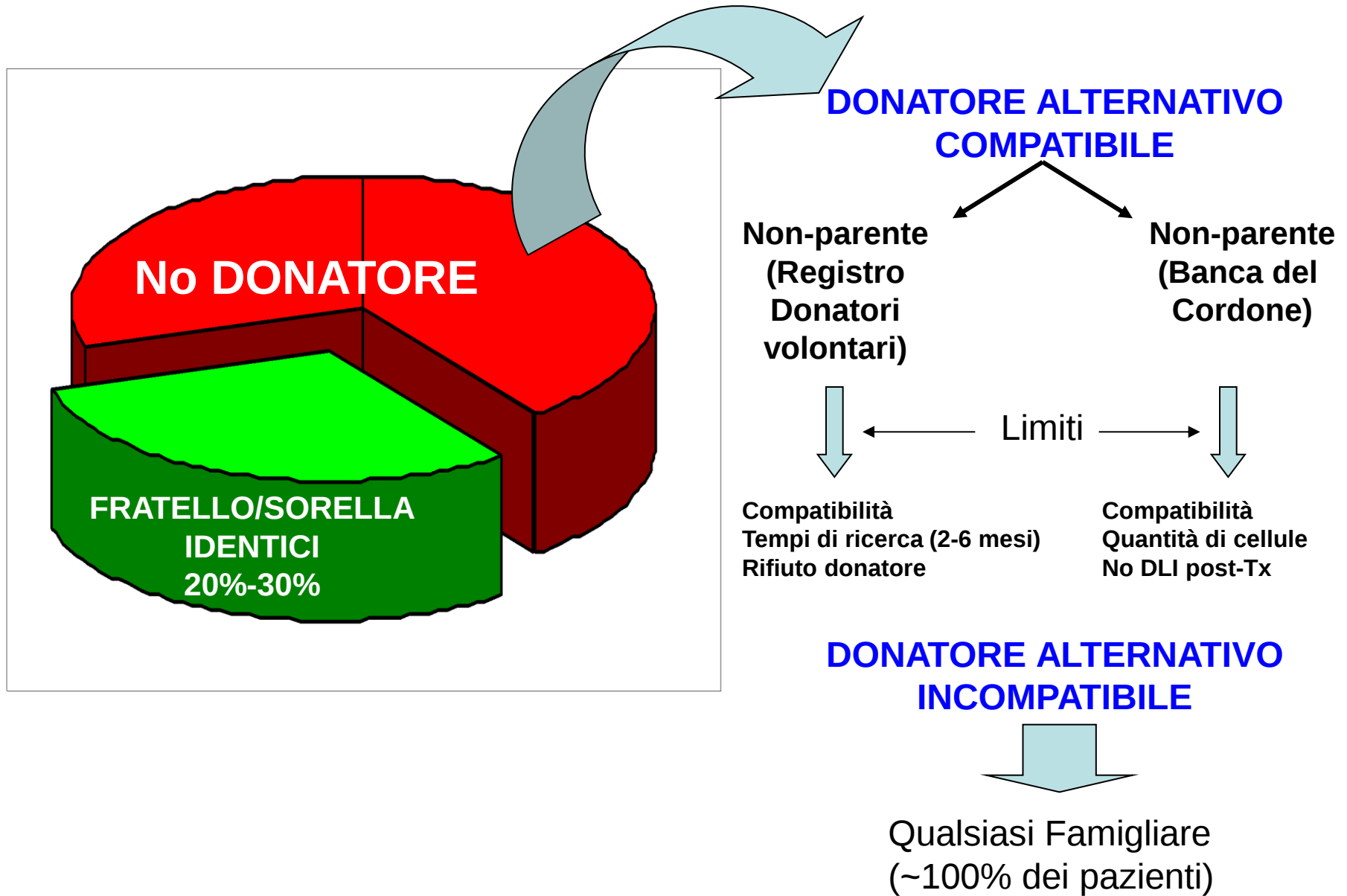
N. Forraz and C. P. McGuckin

CTI-LYON, Cell Therapy Research Institute, Parc Technologique de Lyon St Priest, St Priest-Lyon, France

Figure 1. Umbilical cord Wharton's jelly as a source of mesenchymal stem cells. (a) Sagittal section of a 1 cm diameter umbilical cord with Wharton's jelly (WJ) surrounding two arteries (A) and one vein (V). (b) 10 mm³ biopsy pieces of Wharton's jelly. (c) Wharton's jelly piece (WJ) in serum-free culture growing-out mesenchymal stem cells. (d) Mesenchymal stem cells from umbilical cord at 80% confluence in serum-free culture.



PROBABILITA' DI AVERE UN DONATORE

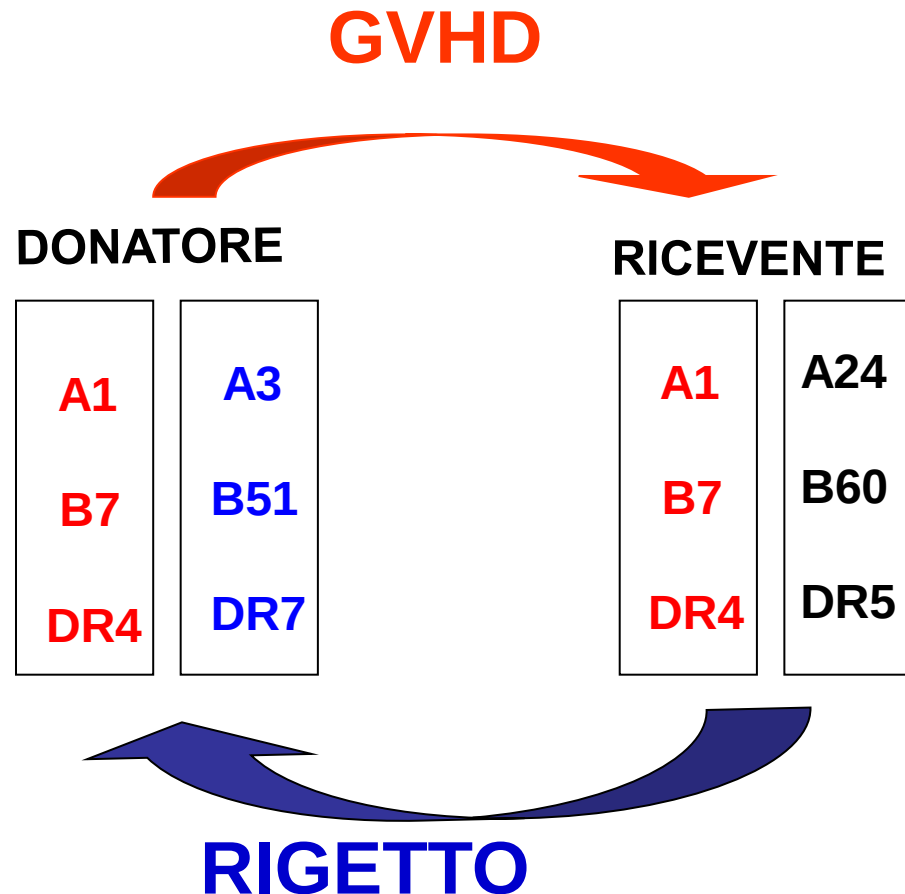


Donatore Familiare Incompatibile

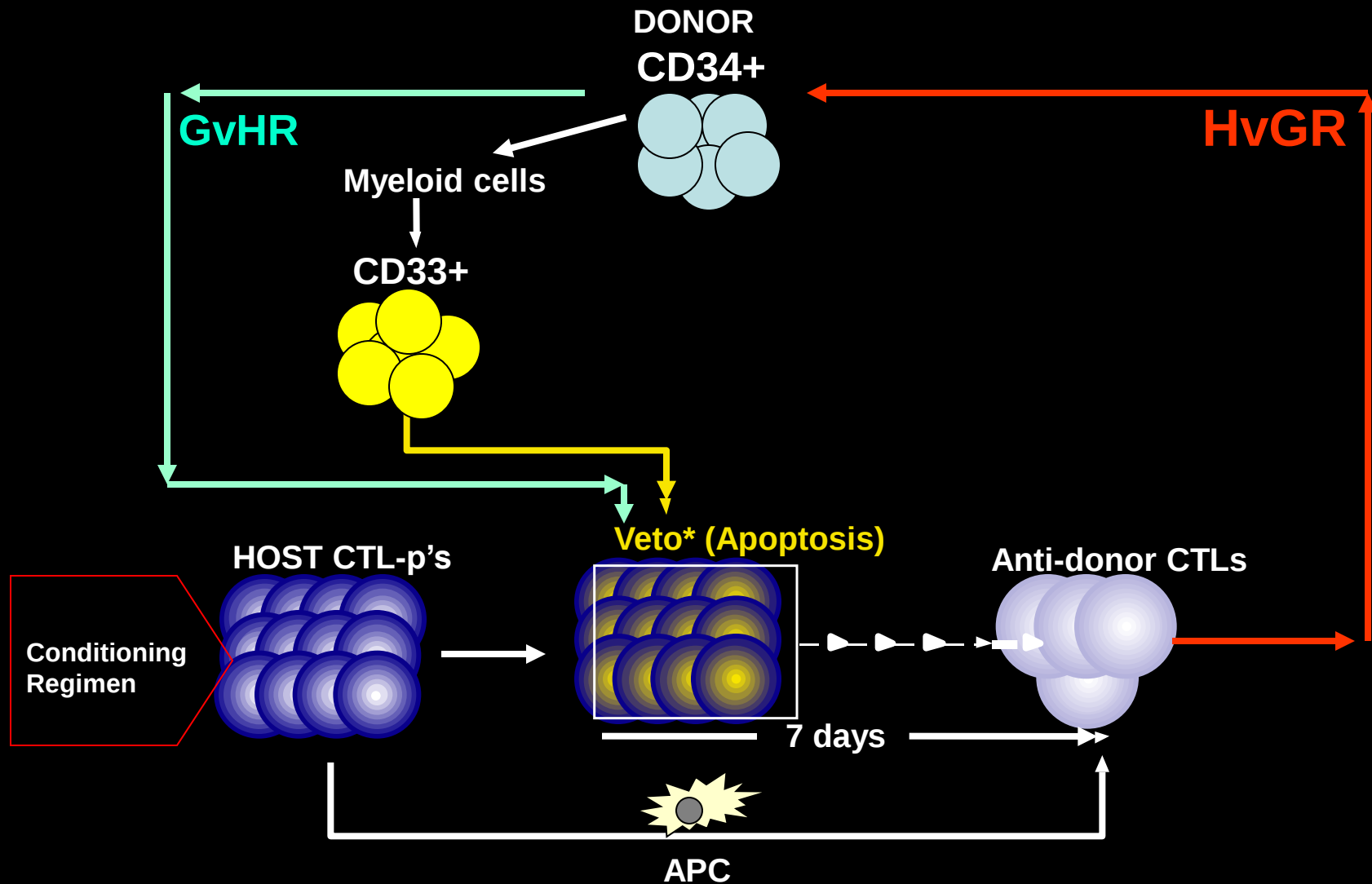
Vantaggi

- **IMMEDIATAMENTE** disponibile per tutti i pazienti in attesa di trapianto
- **Scelta** tra genitori, figli, zii, cugini, ecc
- **Impiego di altro donatore in caso di**
 - **Rigetto del primo**
 - **Scarsa raccolta di cellule**
- **Possibilità di infondere anche a distanza di anni altre cellule staminali o linfociti (vaccino)**

PROBLEMI DEL TRAPIANTO DA DONATORE FAMIGLIARE INCOMPATIBILE PER UN APLOTIPO



Immune modulation in vivo by megadose CD34 transplants



*Rachamin et al. Transplantation 1998

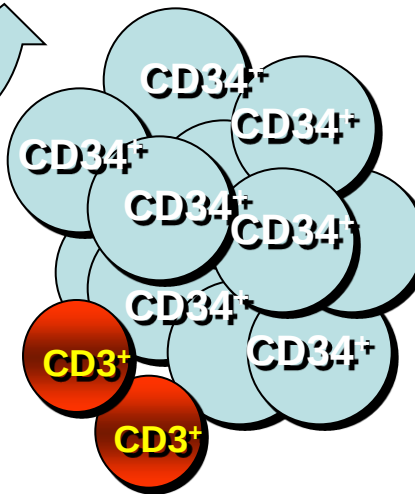
*Gur et al. Blood 2002

“Megadose” stem cell transplant

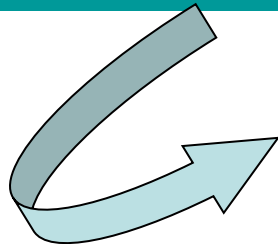
CD34⁺ cells
($\geq 10 \times 10^6/\text{kg}$)

Donor mobilization
G-CSF 12 $\mu\text{g}/\text{kg}/\text{die}$
Leukapheresis
x 4 consecutive days

Negative or Positive
Selection of CD34⁺ cells



Extensive T-cell Depletion
($\text{CD3} \leq 1 \times 10^4/\text{kg}$)



MANIPOLAZIONE CELLULE STAMINALI

1993-1995



*Aversa et al Blood 1994

1995-1998



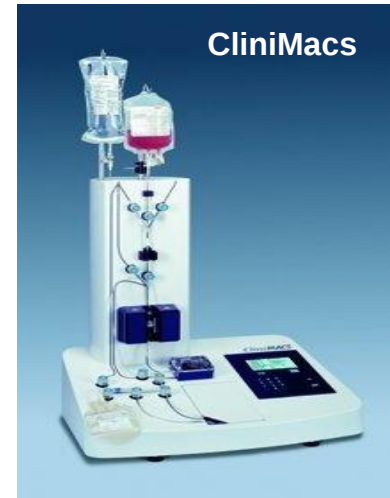
CD34⁺ selection
(CEPRATE SC)



°Aversa et al. NEJM 1999

1999 →

One Step
CD34⁺ Cell
Selection



^Aversa et al. JCO 2005

Median infused
cells

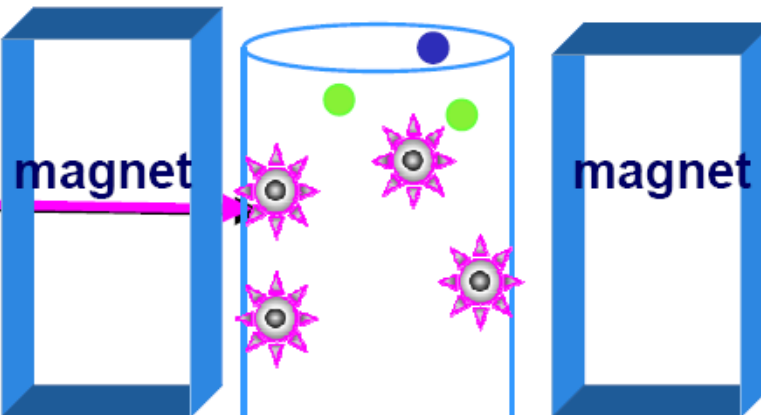
CD34⁺ 12 x 10⁶/kg
CD3⁺ 1 x 10⁴/kg
CD20* 4 x 10⁴/kg

Strategy for depletion of $\alpha\beta$ + T-cells

Chaleff S. et al.: A large scale method for the selective Depletion of $\alpha\beta$ T-lymphocytes from PBSC for allogeneic Transplantation. Cytotherapy, 2007



waste
($\alpha\beta$ T cells)



graft

$\gamma\delta$ T-cells

CD34+ and CD34-
progenitors

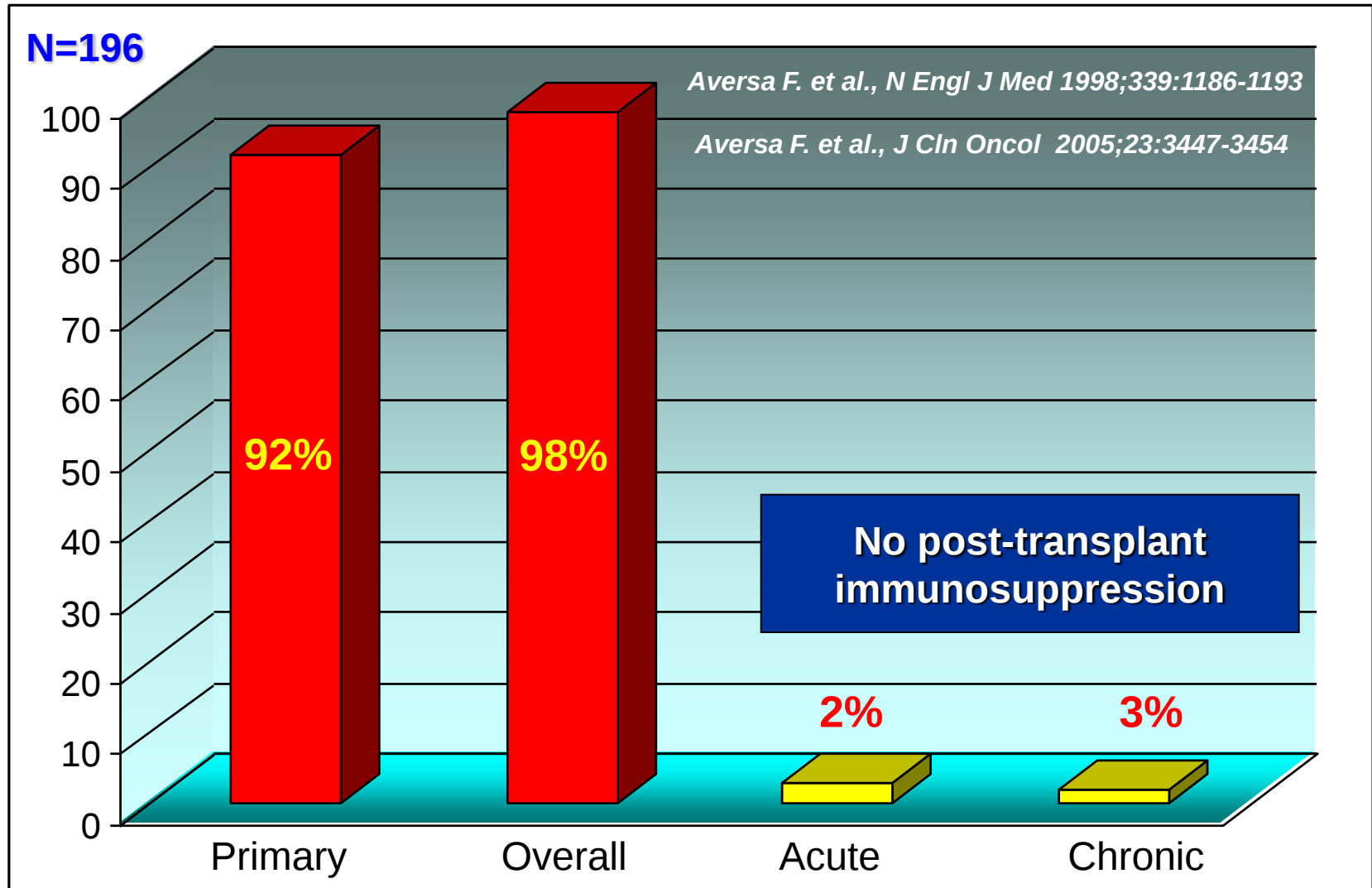
NK cells

dendritic cells



Engraftment

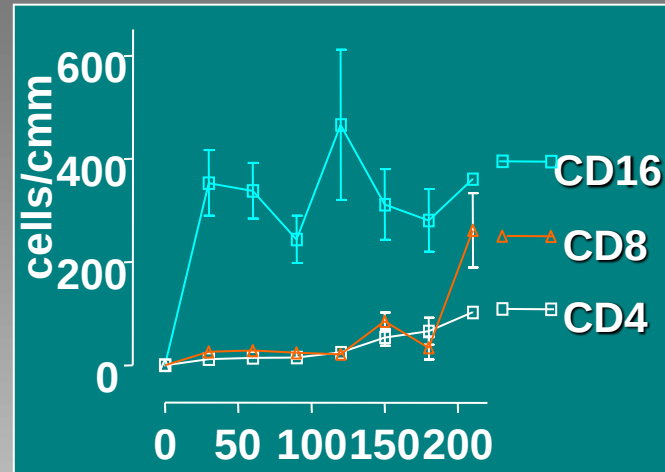
GvHD



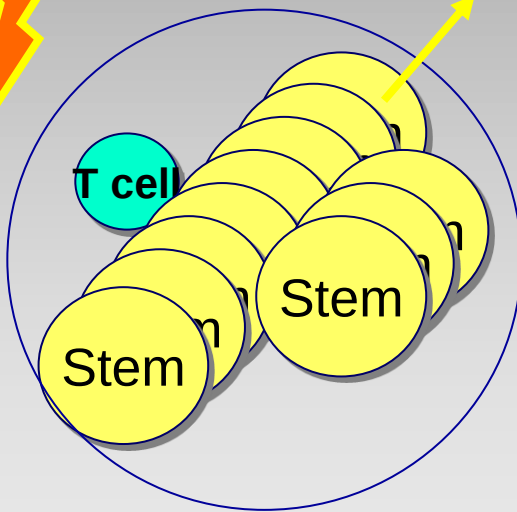
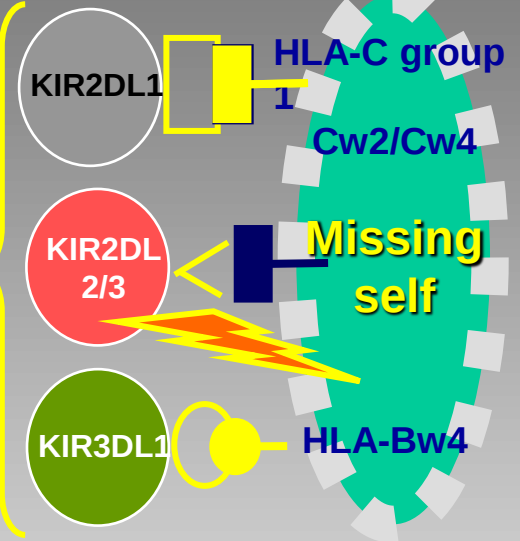
Dal trapianto aploidentico
Nuove acquisizioni biologiche

Post-transplant generation of alloreactive NK repertoire

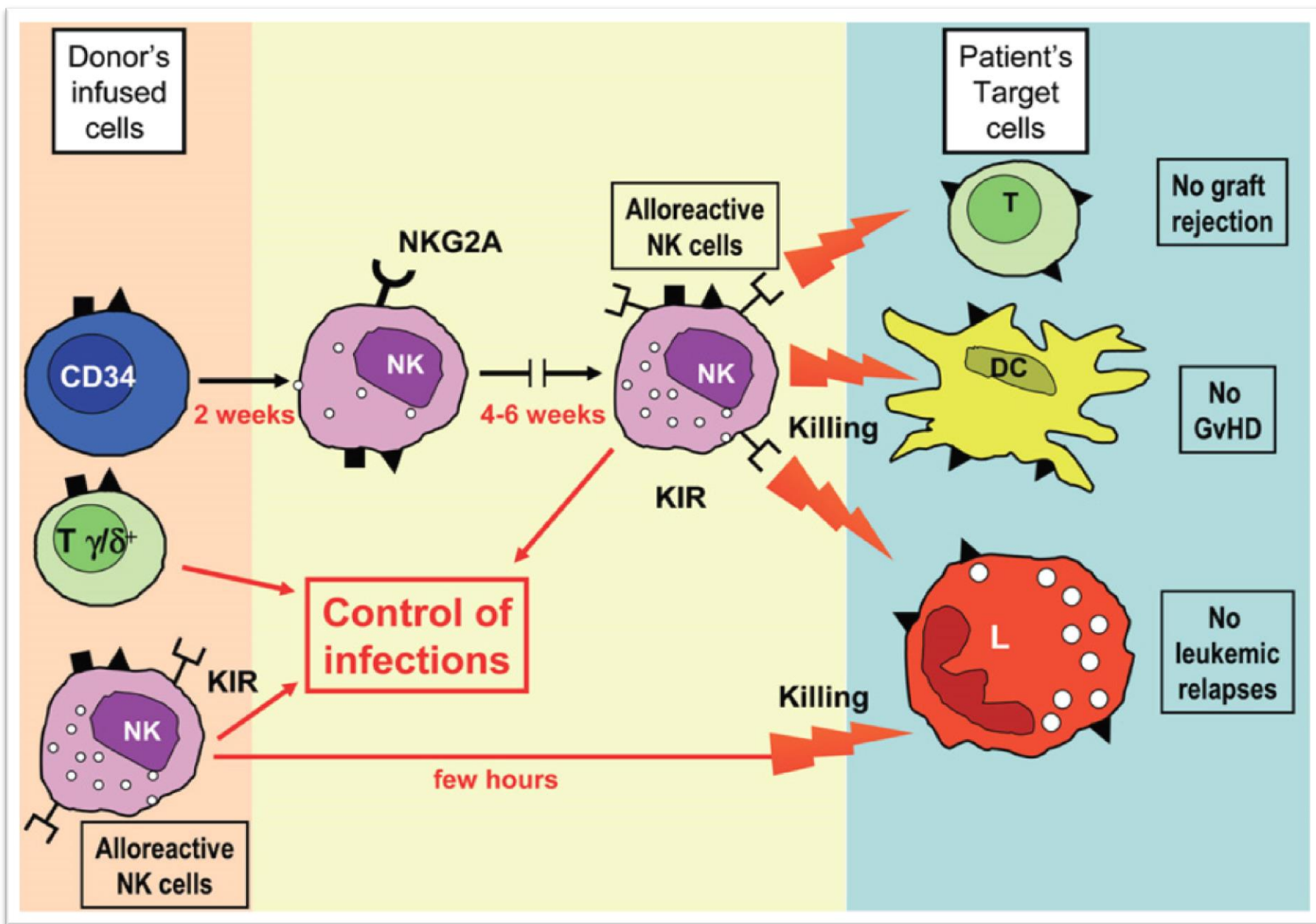
High-intensity conditioning



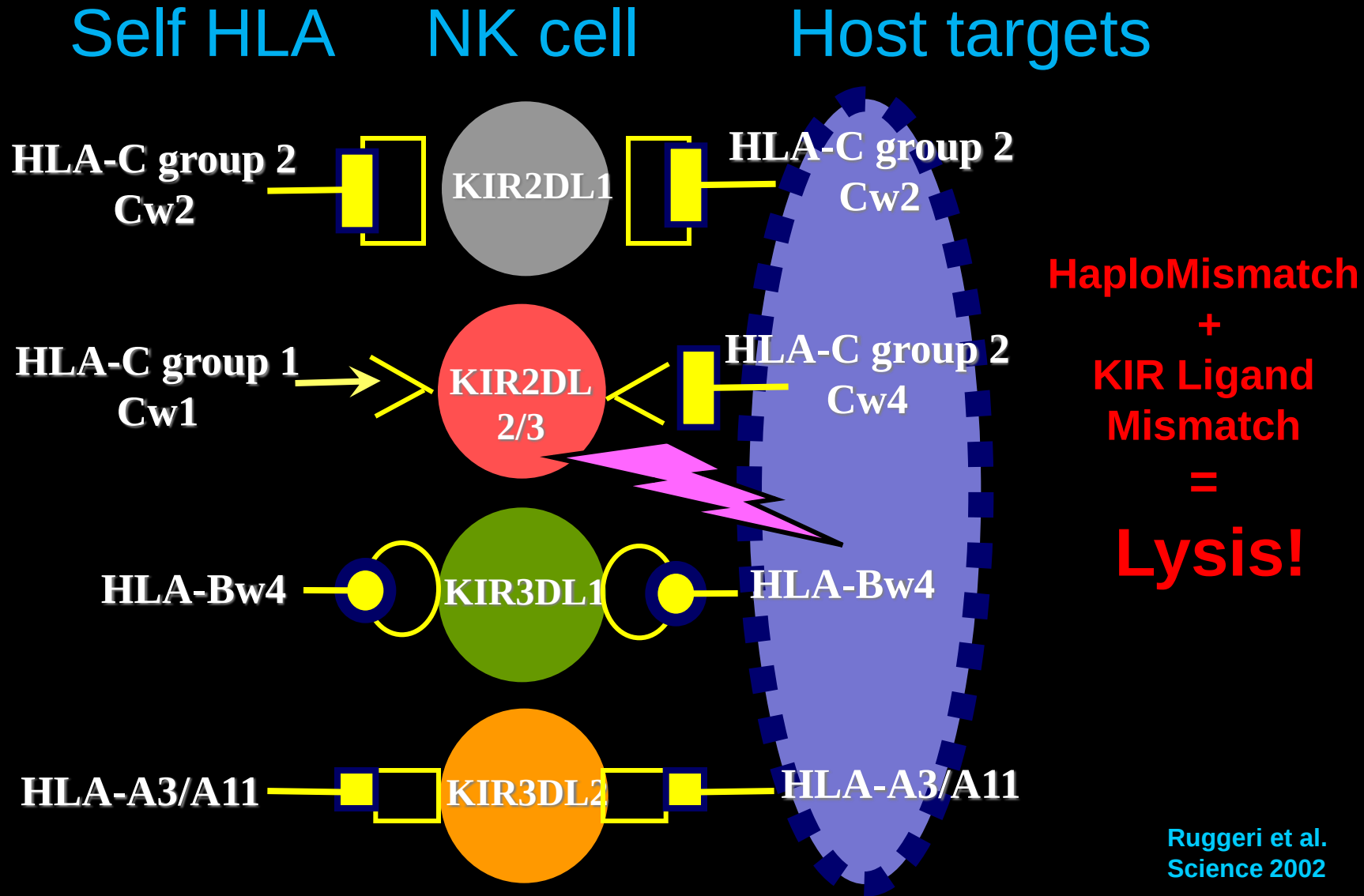
NK repertoire Host targets



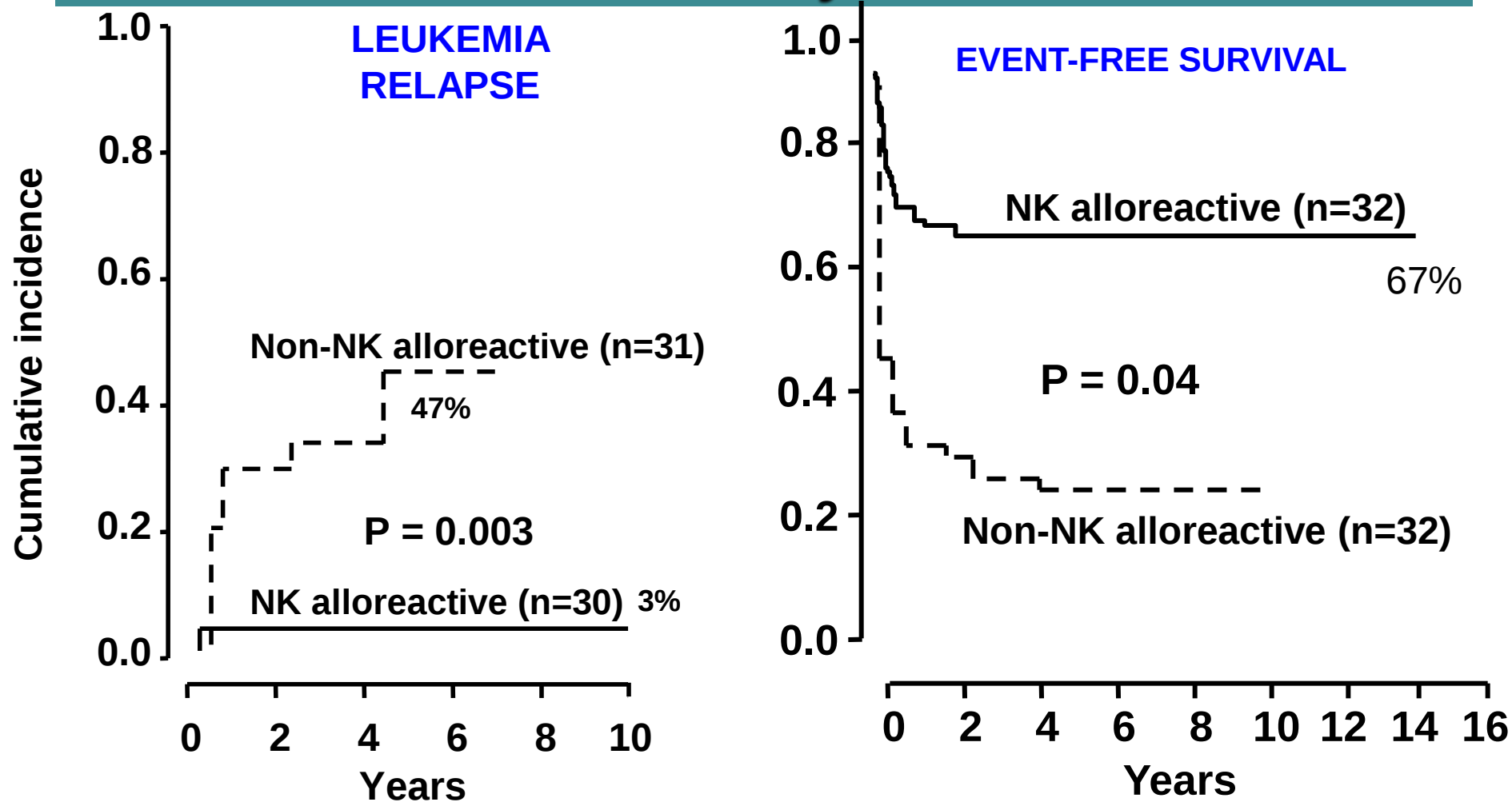
Mega-dose stem cells from “allo NK” donor
No post-transplant immune suppression



Donor vs recipient NK cell alloreactivity in HLA haplotype-mismatched transplants

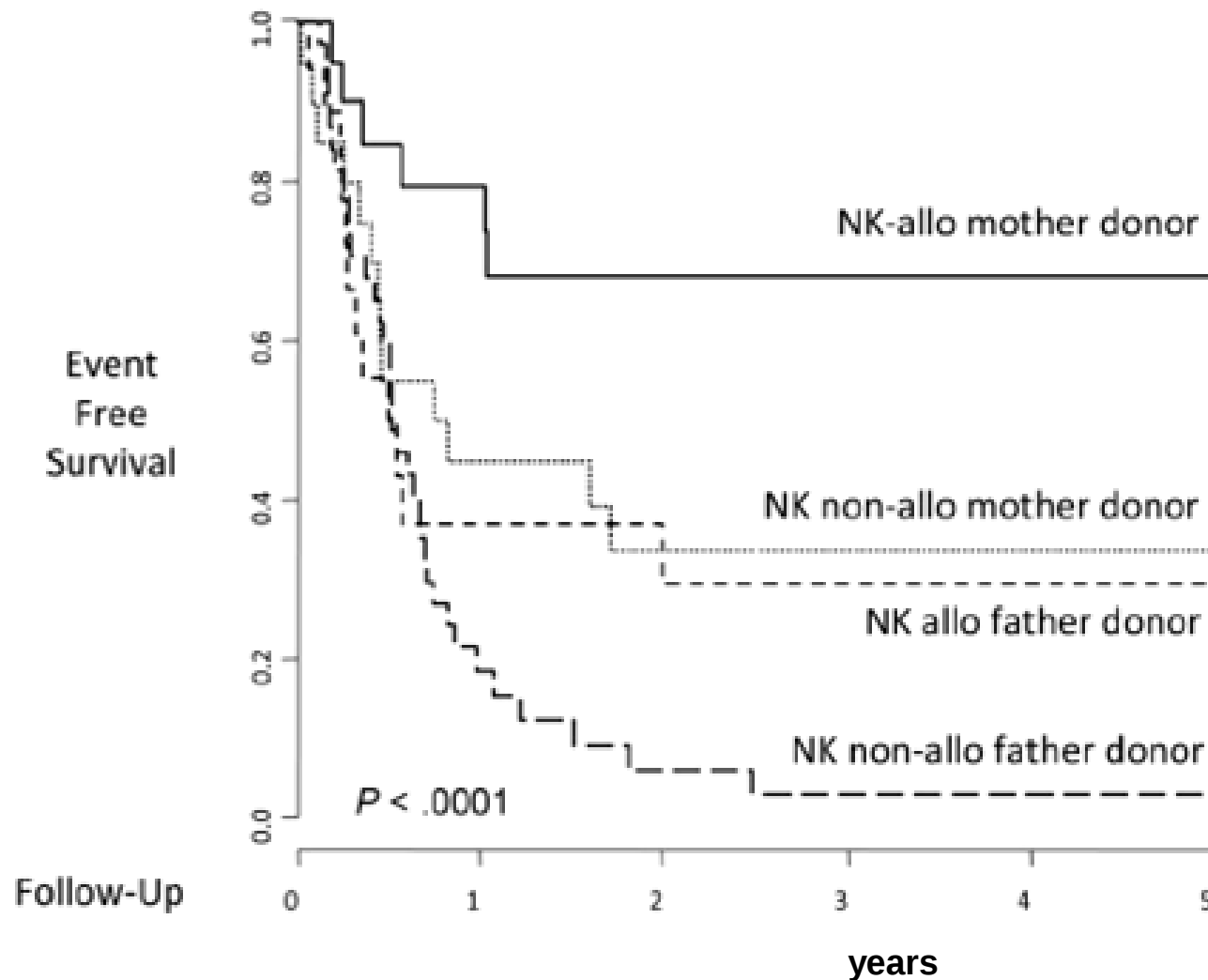


Relapse, EFS and NK-cell alloreactivity in AML



Survival after T cell-depleted haploidentical stem cell transplantation is improved using the mother as donor

Martin Stern,¹ Loredana Ruggeri,² Antonella Mancusi,² Maria Ester Bernardo,³ Claudia de Angelis,² Christoph Bucher,⁴ Franco Locatelli,³ and Franco Aversa,² and Andrea Velardi²



Patients = 118
Years of study
1993-2006



Tolerogenic ef hematopoietic

Masahiro Hirayama, Eiich

Department of Pediatrics and Cell Tran



Mother
NIMA/IMA



Father
NIPA/IPA

ntigens in

it International ISSN 0934-0874

REVIEW

The influence antigens on o

Daniëlle E. M. van den

Department of Immunohematolo



Patient
IMA/IPA



Sibling
NIMA/IPA



Sibling
NIPA/IMA



Sibling
NIMA/NIPA

arental

H. J. Claas

lands

Algoritmo per pazienti candidati al TMO

**Chemioterapia di
Induzione**

Test HLA

**Famigliare
HLA-identico**

TMO

**No Donatore
Famigliare identico**

**Ricerca
MUD/CB (2 mesi)**

Well-matched

MUD

No well-matched

Cordone

Aplo

