“Fuente de Progenitores Hemopoyéticos en el Trasplante Alogénico "

A. Urbano Ispizua

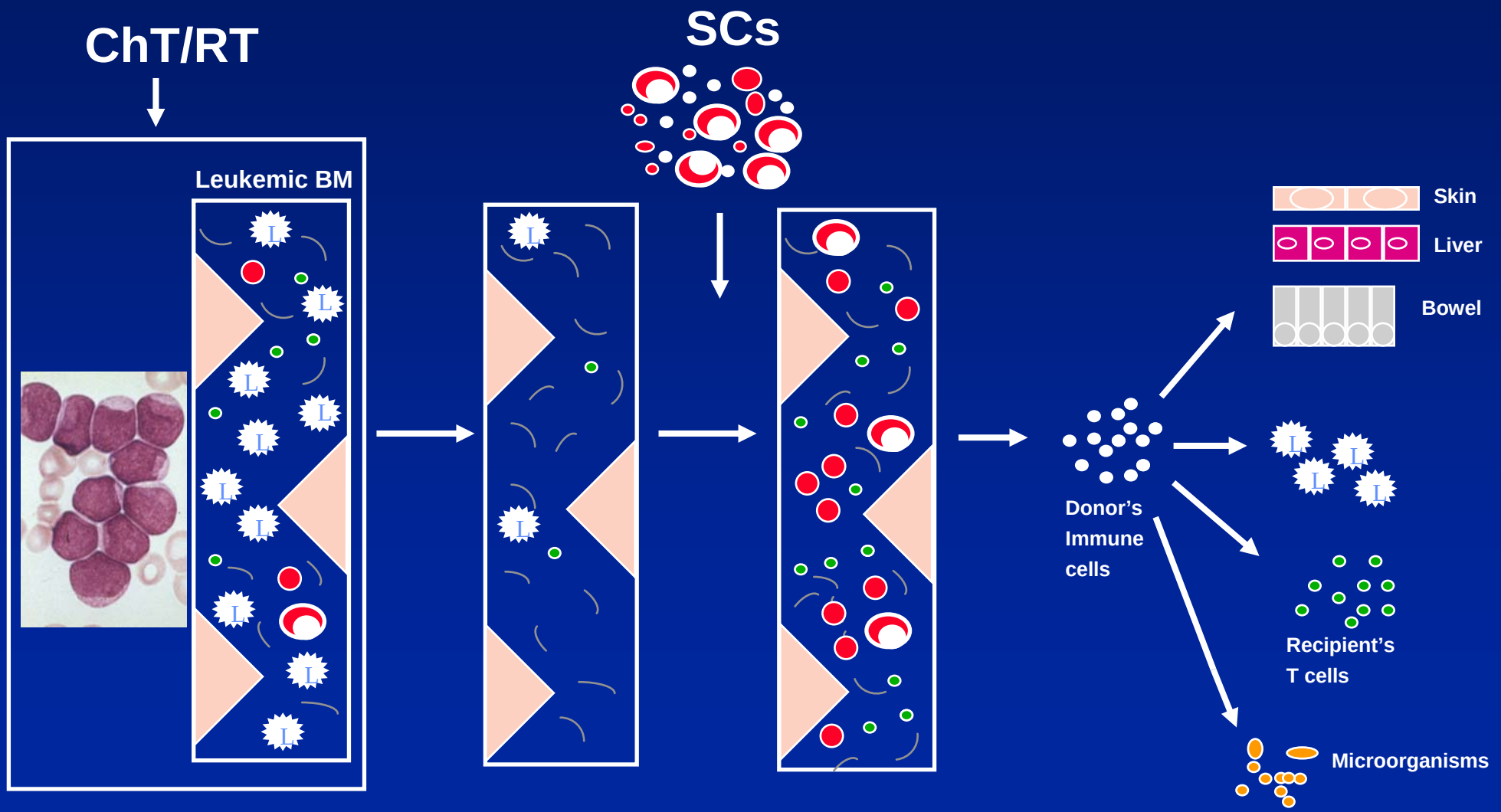
La Serena, 26 de setiembre de 2008

In the beginning, there was bone marrow

Fuente de progenitores para trasplante

1.- Introducción
2.- Uso en Europa
3.- Procedimiento de obtención
4.- Composición celular
5.- Resultados clínicos

Allogeneic SCT



Differences in Stem cell sources (BM, PB, UC)

- Anatomical
- Biological
- G-CSF effect
- Absolute cell numbers

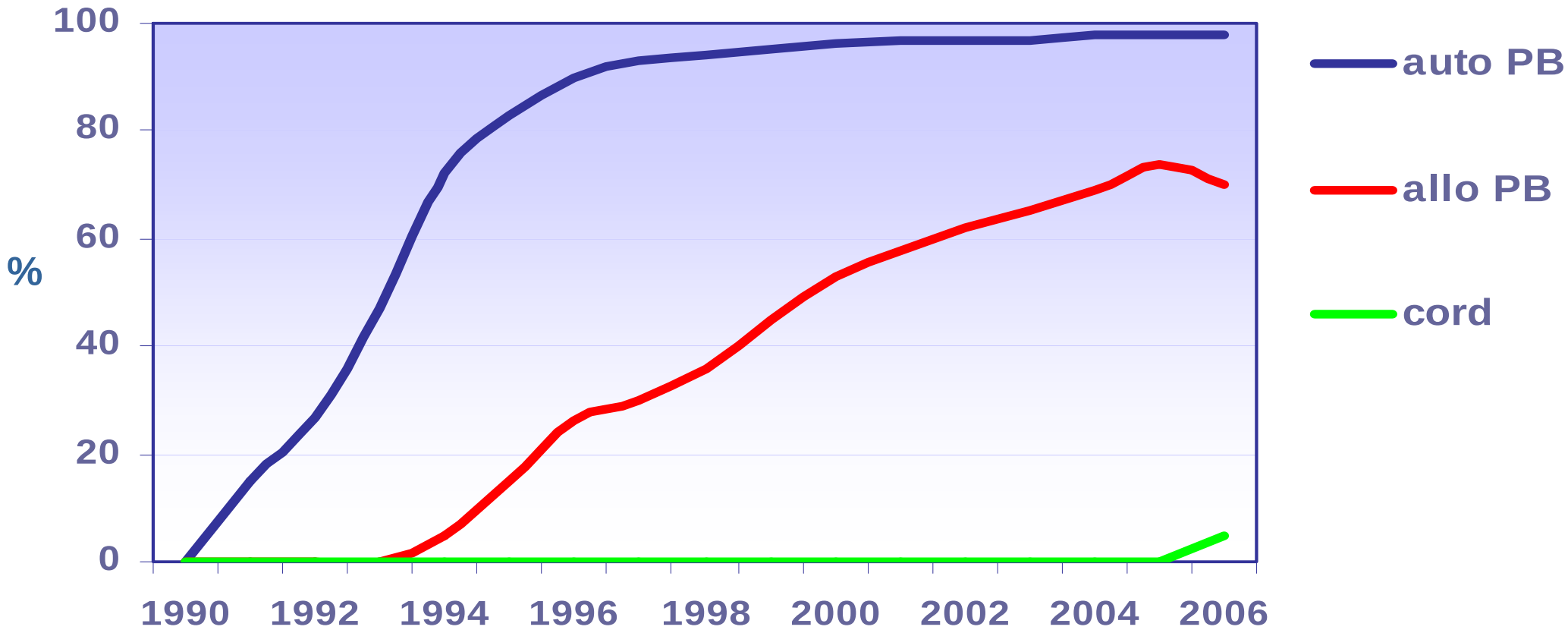
Stem cell sources

	CD34/MNC	Vol. of Harvest
UC	1%	0.1 L
BM	0.8%	1-1.5 L
PB (G-CSF)	0.6%	10-20 L

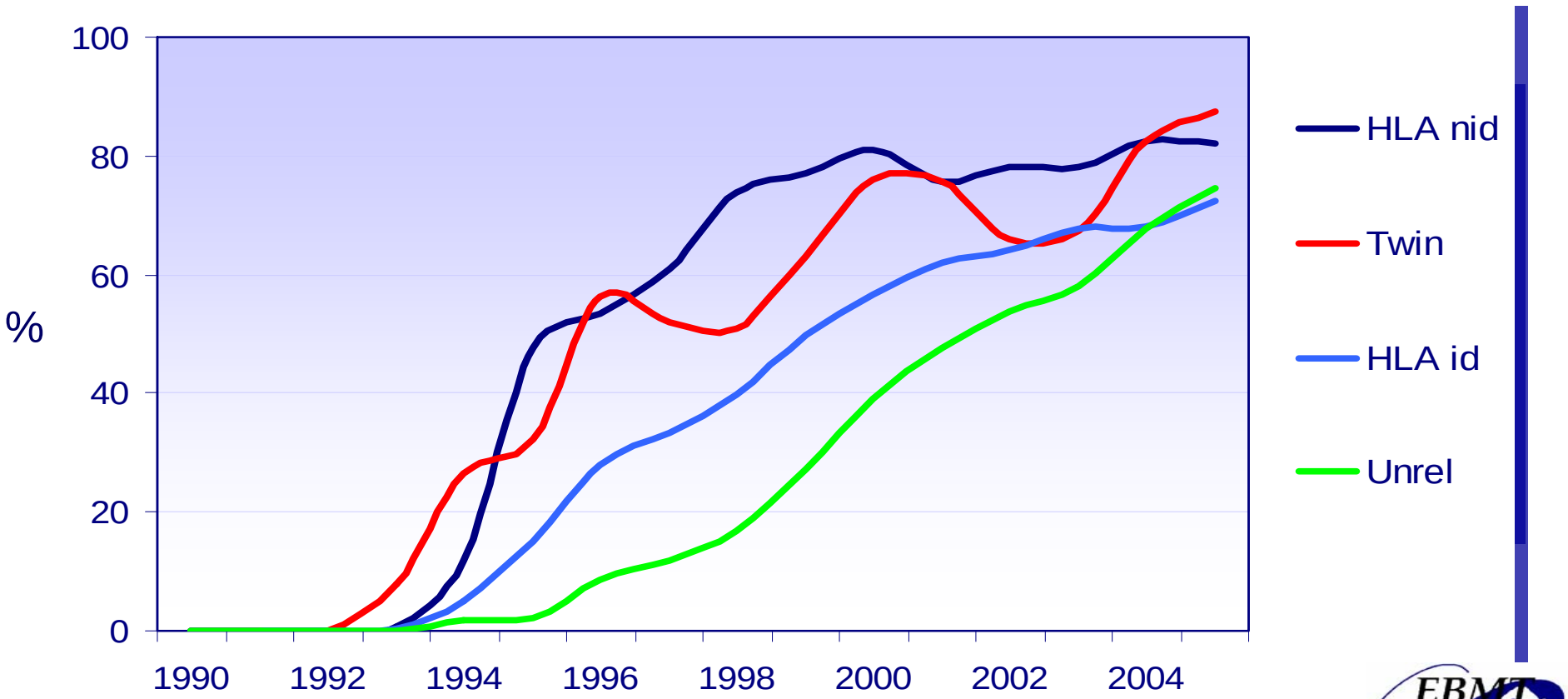
Comparison of Stem cell sources for transplantation

Current use in Europe

EBMT Activity Survey on HSCT 1990-2006
changes in PBSC and Cord

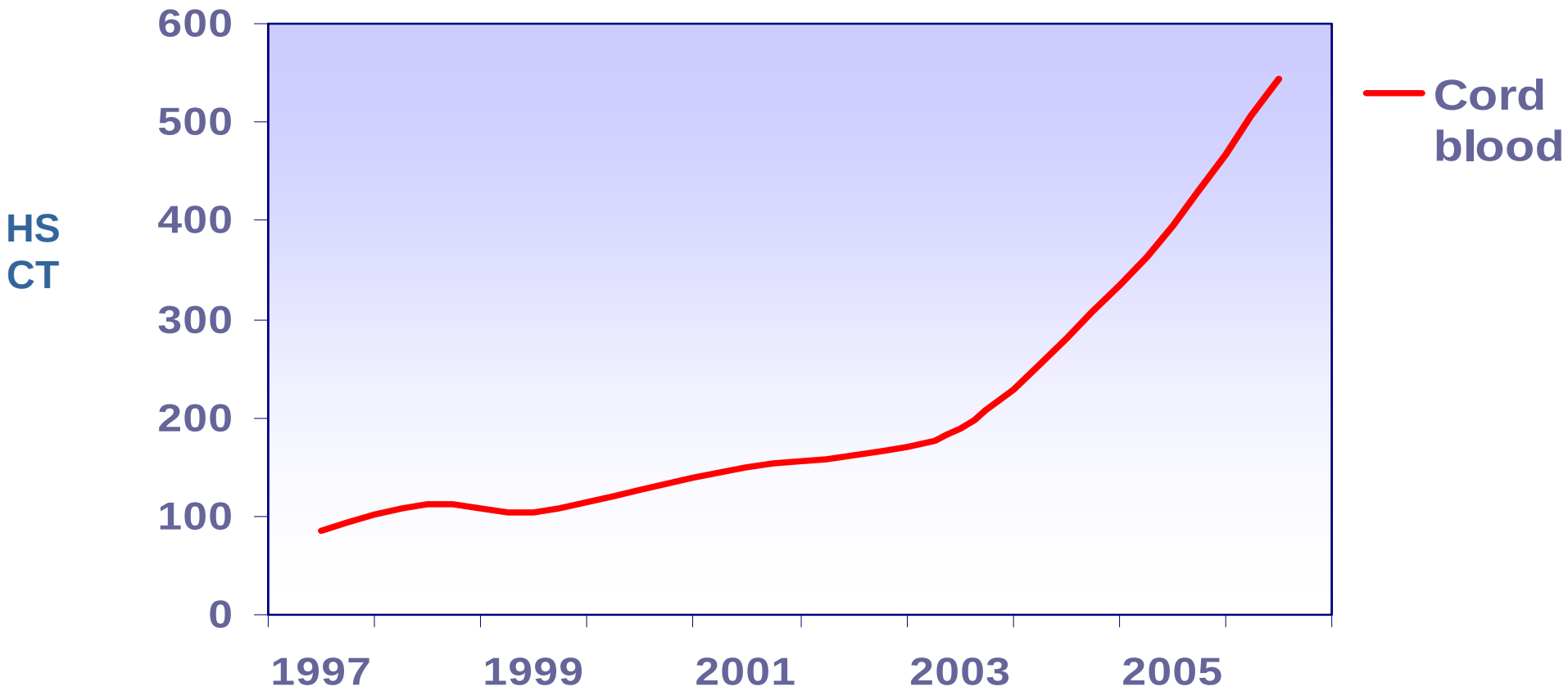


EBMT Activity survey on HSCT 1990 – 2005: changes in stem cell source by donor type

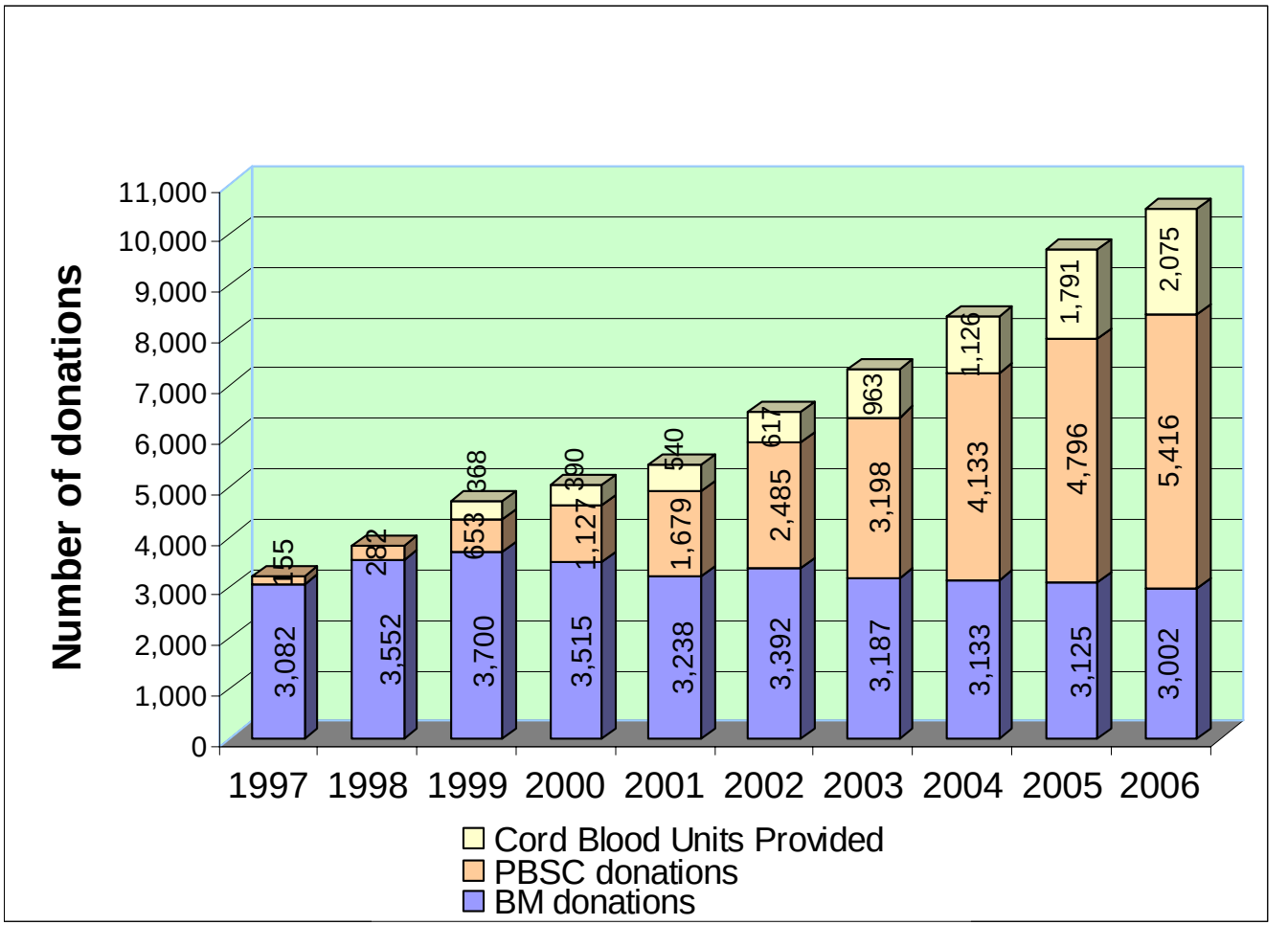


EBMT Activity Survey on HSCT 1990–2006

Cord blood HSCT



Number of stem cell products released for unrelated transplantation

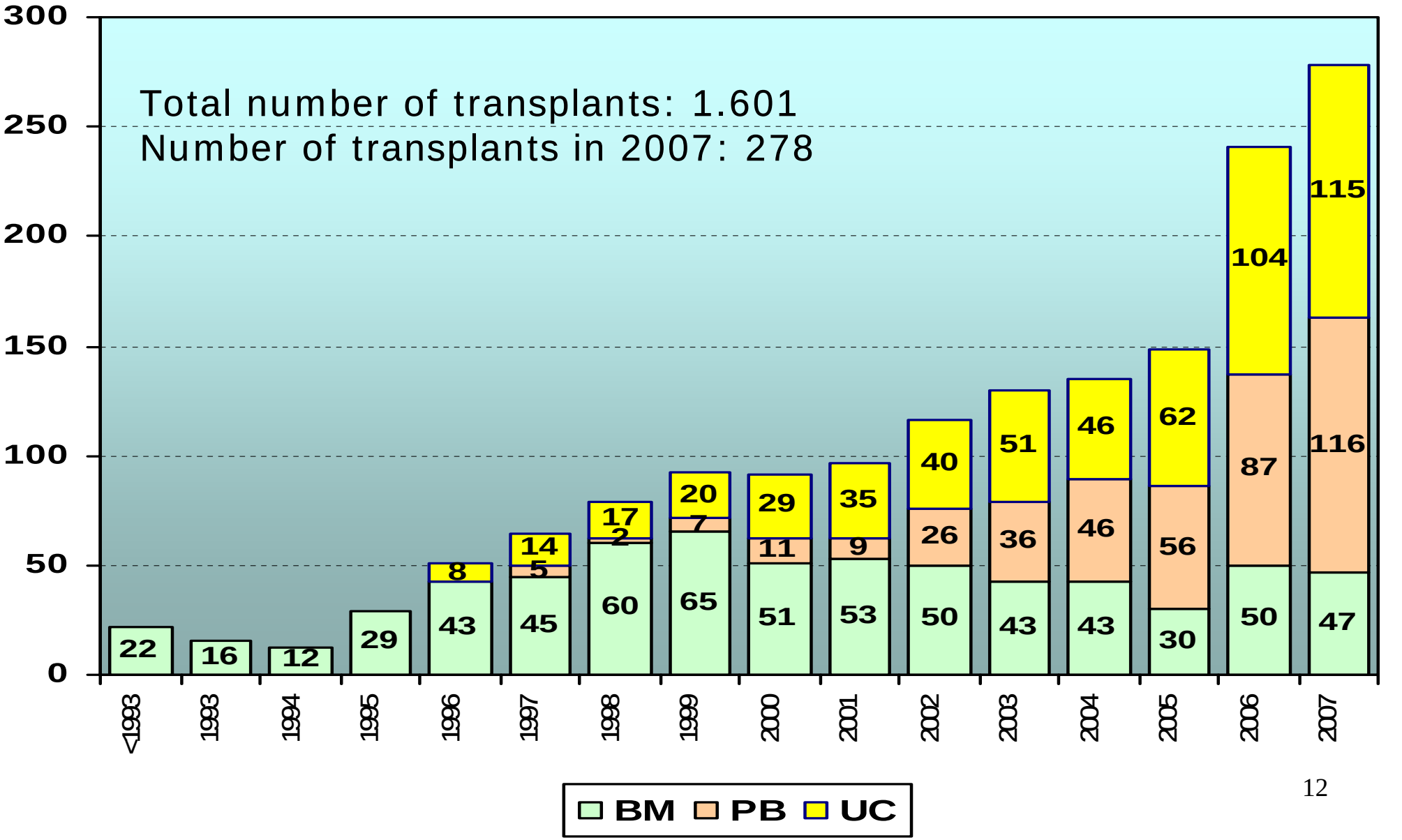


→ UC 20%

→ PB 52%

→ BM 28%

REDMO


Total number of transplants: 1.601
Number of transplants in 2007: 278
300
250
200
150
100
50
0
22
16
12
29
43
8
45
5
14
60
2
17
65
7
20
51
11
29
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62
50
87
104
47
116
115
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1993
1994
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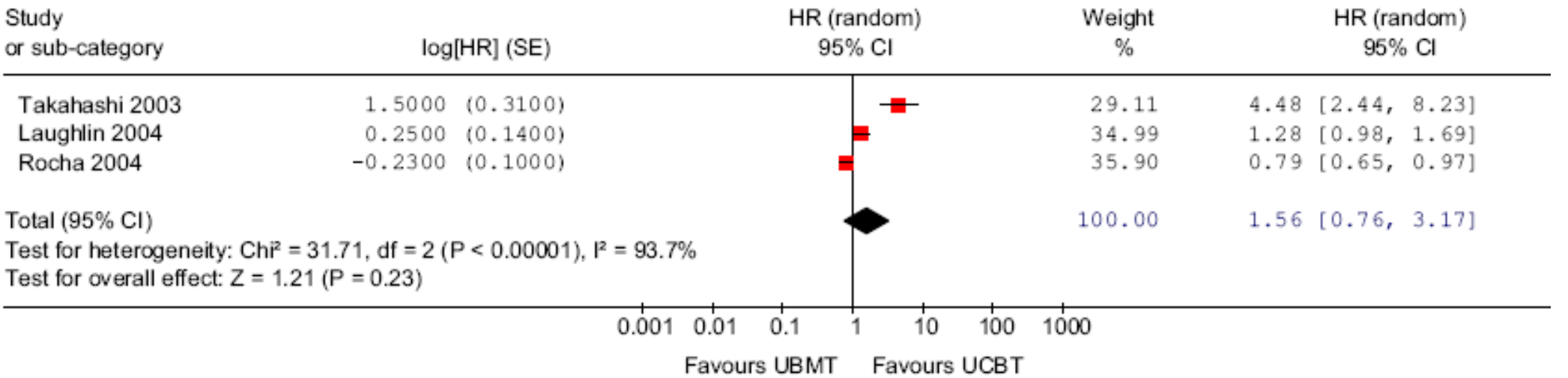
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
BM
PB
UC

A Meta-Analysis of Unrelated Donor Umbilical Cord Blood Transplantation versus Unrelated Donor Bone Marrow Transplantation in Adult and Pediatric Patients

William Ying Khee Hwang,[1] Miny Samuel,[2] Daryl Tan,[1] Liang Piu Koh,[3] Winston Lim,[4] Yeh Ching Linn[1]

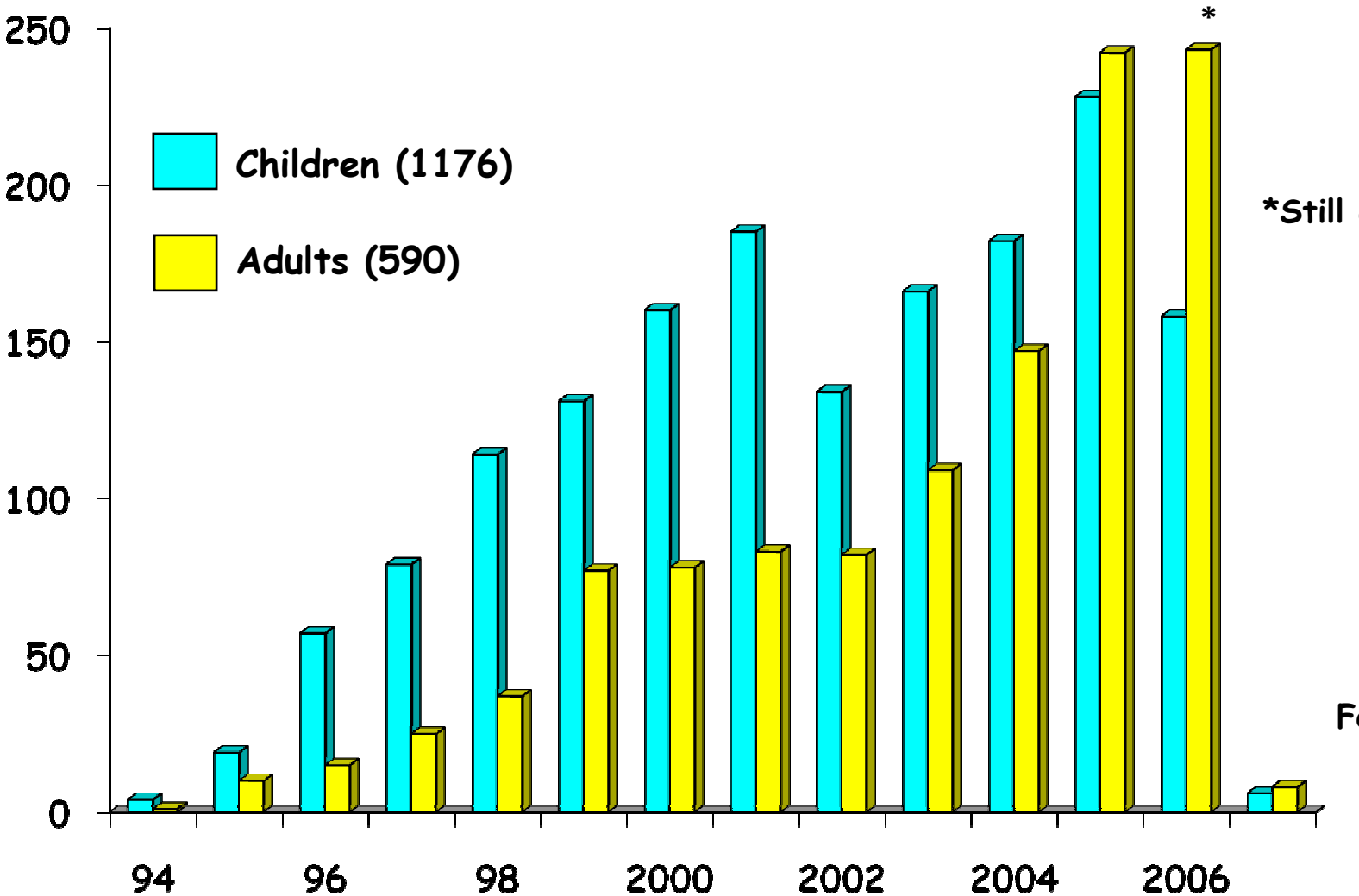
Biology of Blood and Marrow Transplantation 13:444-453 (2007)

Review: Umbilical cord transplant for haematological diseases
Comparison: Umbilical cord blood transplantation (UCBT) Vs Matched unrelated donors (UBMT)
Outcome: Disease free survival in Adults



Single Unrelated CBT according to the recipient age/year reported to Eurocord

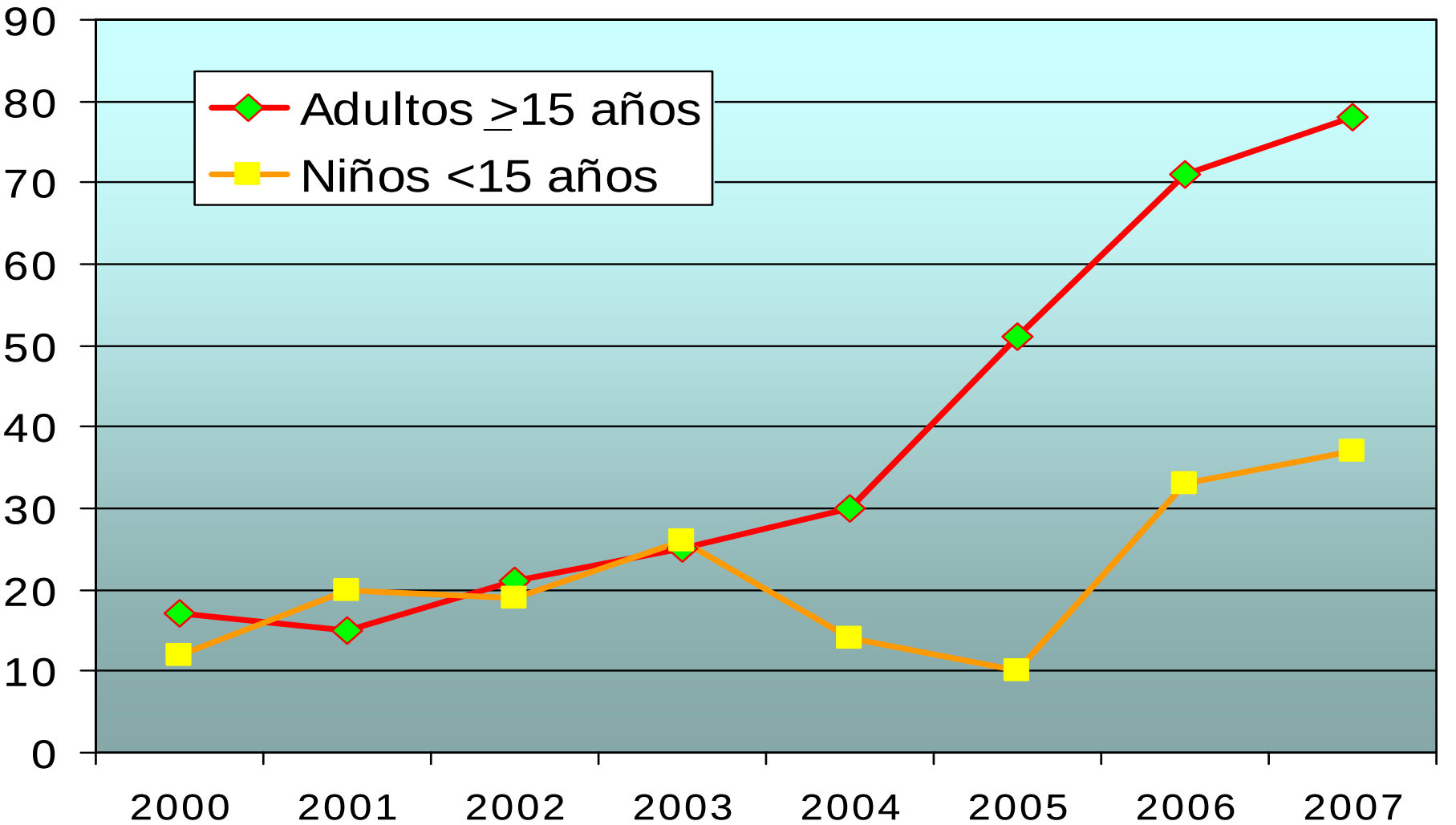
W. Fibbe 2007



*Still collecting data

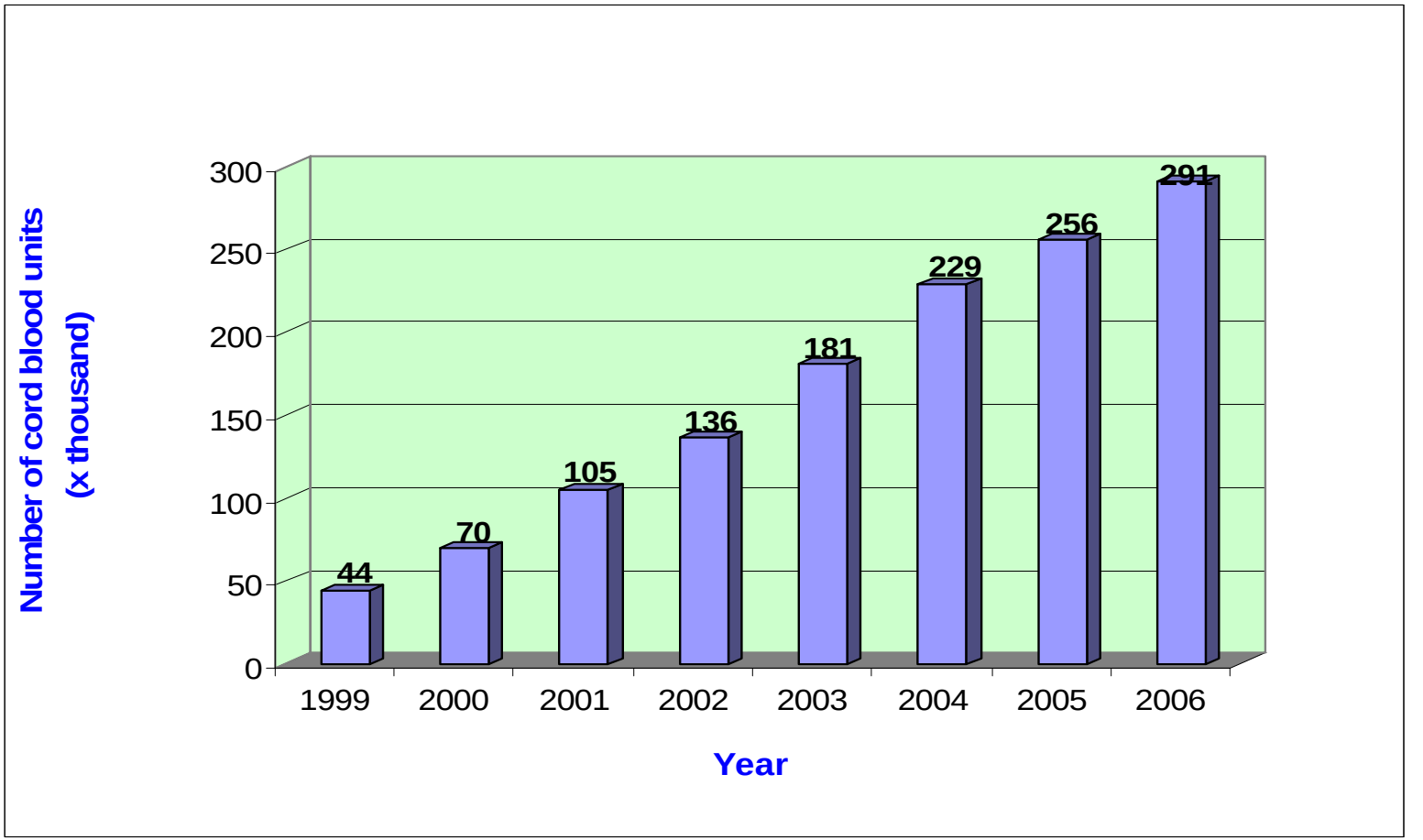
February 2007

Actividad TPH de SCU España
(relación niños / adultos)



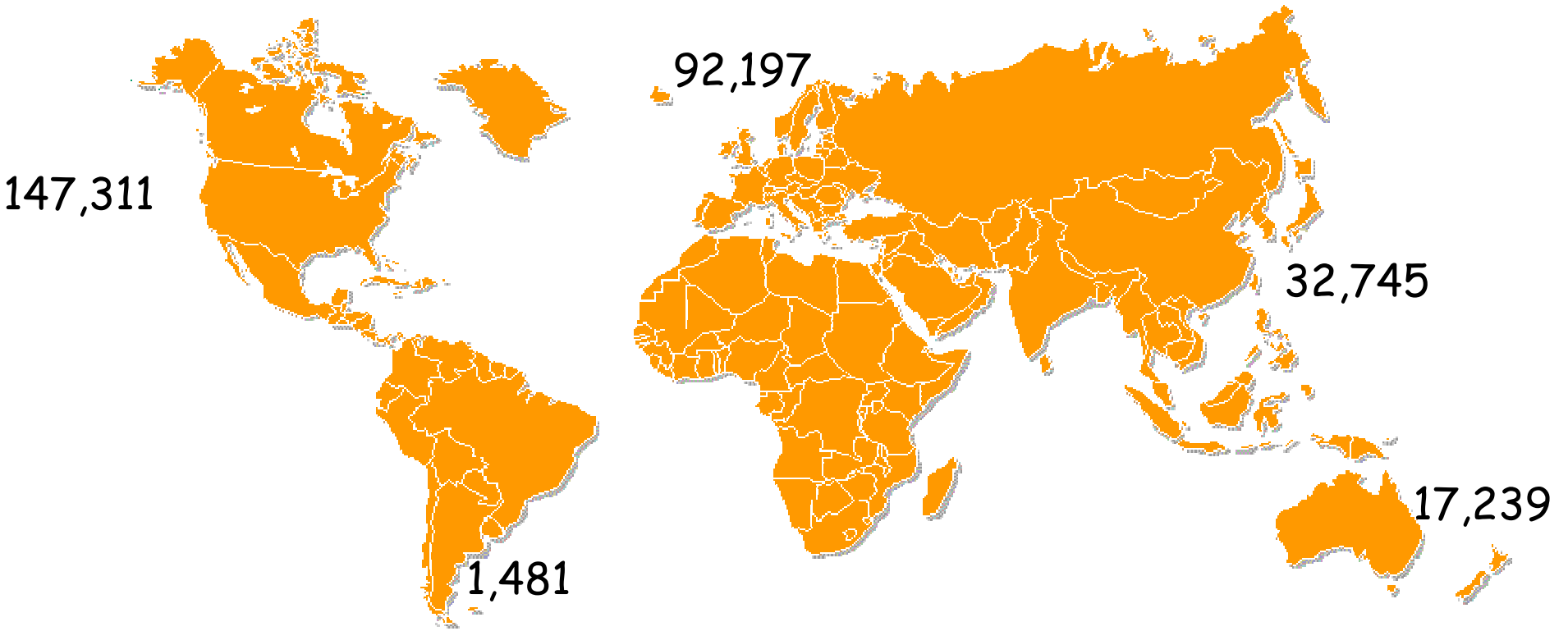
Number of Cord Blood Units available for Unrelated Transplantation

W. Fibbe 2007



UNRELATED CORD BLOOD BANK/REGISTRIES

Worldwide Storage of Cord Blood Units

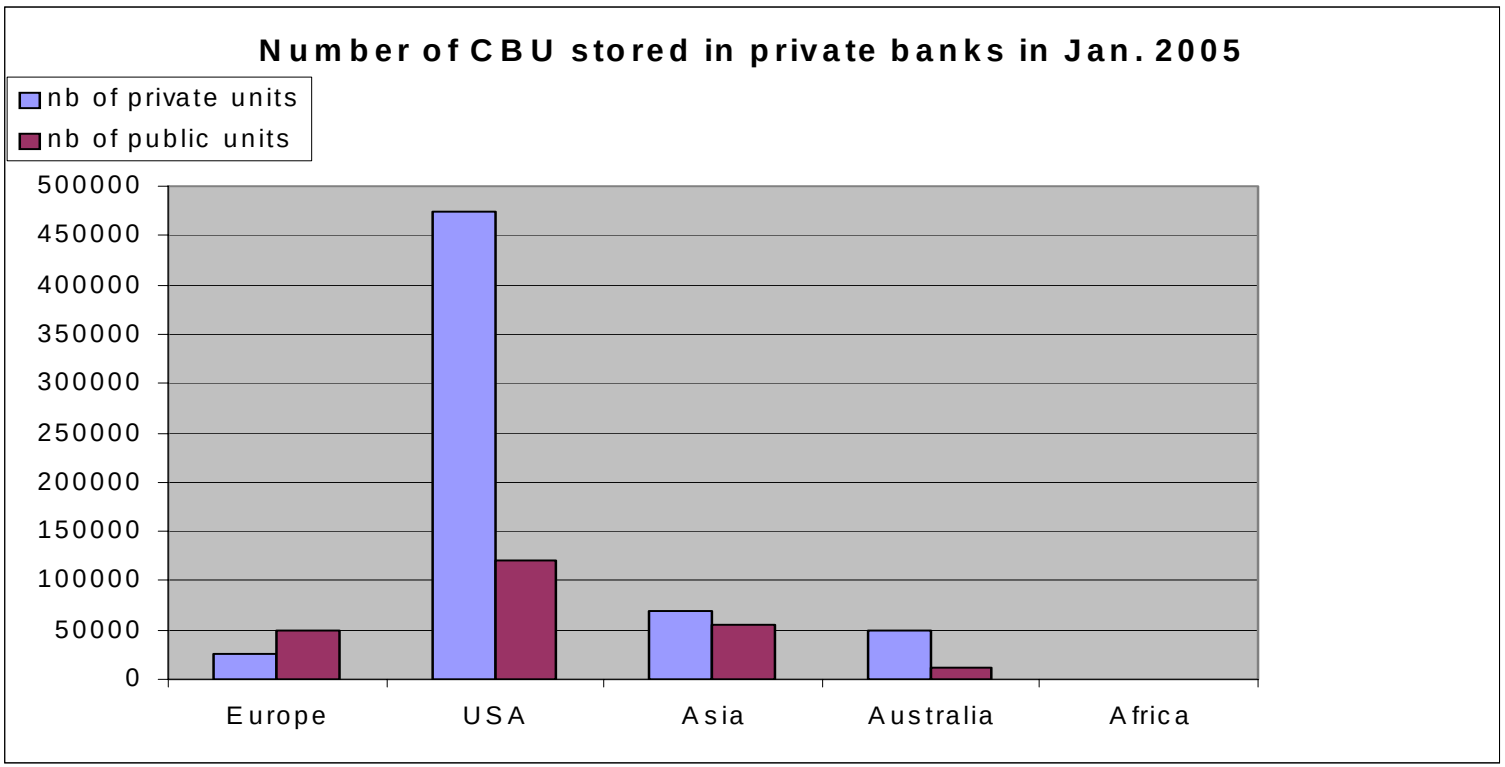


UNRELATED CORD BLOOD BANKS/REGISTRIES

Number of Units Stored in Private Banks

134 private banks; estimated 780,000 CB units stored

W. Fibbe 2007



Source: BMDW, ESSEC, June 2005
Gregory Katz-Benichou. Int. J. Healthcare Technology and Management, Vol. 8, No. 5, 2007

"*storage of CB for personal use is not recommended*"

ASBMT Committee report. Biol Blood Marrow Transpl 14:356-363 (2008)

INTERNATIONAL Herald Tribune

LONDON: Monday august 28, 2006

“Soccer dads tackle injury by storing baby stem cells”

Top British footballers are storing stem cells from their newborn babies as a potential future treatment for their own injuries on the pitch.

"We decided to store our new baby's stem cells for possible therapeutic reasons, both for our children and possibly for myself," the paper quoted a Premier League player as saying. "As a footballer, if you're prone to injury, it can mean the end of your career, so having your stem cells - a repair kit, if you like - on hand makes sense."

El Mundo

LA INFANTA LEONOR, HEREDERA DEL TRONO ESPAÑOL

Los príncipes Felipe y Letizia congelan células madre de su hija

Es para atender posibles enfermedades futuras, según confirmó la Casa Real española.

"Se trata de una práctica habitual" de la clínica Ruber Internacional donde se produjo el parto, señaló el vocero.

Opina el especialista Javier Sanpedro que "la sangre del cordón umbilical contiene células óptimas para el trasplante de médula ósea, una técnica bien establecida para el tratamiento de **la leucemia**". Fuera de la familia es bajísima la posibilidad de hallar un donante cuyas células sean compatibles.

UNA DECISIÓN DE CONCIENCIA

"Cada año nacen en España 20 niños que hoy podían ser curados con sus propias células de sangre de cordón umbilical. No podíamos tomar otra opción que no fuera contactar con Bioteca y garantizarnos una protección para el futuro de nuestro hijo"

JOSÉ ABEL • PADRE EN MARZO DE 2006

bioteca
la Vida en sus manos

LA SOLUCIÓN ESTÁ EN EL MOMENTO DEL PARTO

La solución pasa por utilizar las células madre contenidas en el cordón umbilical de un recién nacido.

Las células madre son células indiferenciadas, que poseen una enorme capacidad de multiplicarse y de transformarse en nuevos tejidos.

En un nuevo ser en gestación, en el que los tejidos tienen que ser creados de inicio, es natural que exista una gran cantidad de éstas células en circulación en su sangre. En el momento del parto, muchas de éstas células se encuentran en el cordón umbilical, de donde pueden ser fácilmente recogidas, en un proceso completamente seguro e indoloro tanto para la madre como para el bebé.

El uso de las células madre, ya ha probado ser de gran importancia en el tratamiento de un gran número de enfermedades graves, habiendo sido realizados a día de hoy más de 6.000* transplantes con sangre de cordón umbilical

*Fuente: NETCORD

DIARIO REGIONAL DE ANDALUCÍA

IDEAL

Domingo 7 de septiembre de 2008
Precio 1,90 euros
Director Eduardo Peralta de Ana

EL TIEMPO HOY
Mañana
Tarde
Noche
Temperaturas sin cambios

GRANADA

GRANADA 7
Un inmigrante marroquí muere al caer desde siete metros en un invernadero de Albuñol en el que trabajaba sin arnés

GRANADA 8 y 9
Suspendidos los exámenes de moto en septiembre para reformar los circuitos ante las nuevas pruebas

DEPORTES 42 y 43
Un gol de Villa da el triunfo a España en el primer partido de clasificación para el Mundial

El SAS se desentiende de las peticiones para conservar el cordón umbilical tras el parto

No deja extraer para uso privado células que podrían curar enfermedades de los hijos porque **sólo está permitida la donación anónima**

PÁGS 2 Y 3

La ley para una muerte digna divide a médicos, políticos y ciudadanos

La iniciativa de la Junta ya ha recibido el «no» de la Iglesia

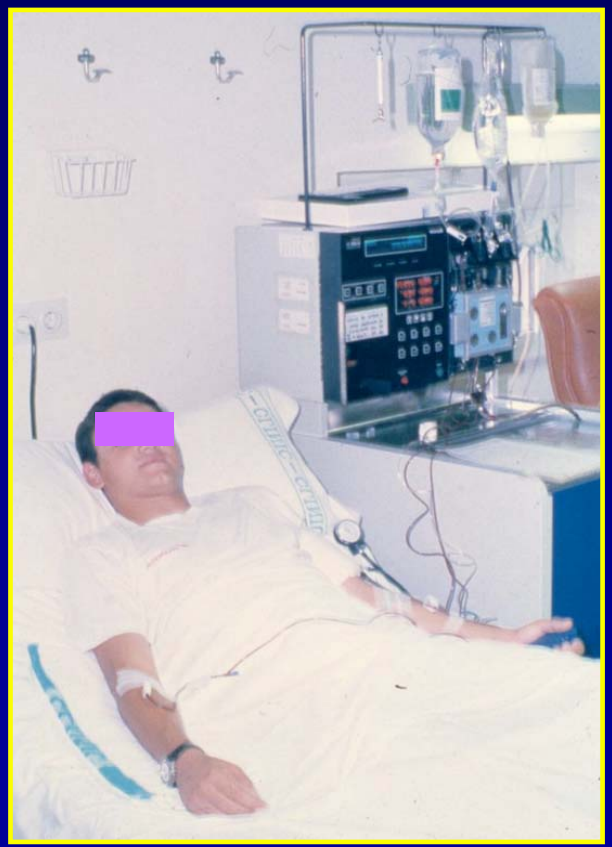
Comparison of Stem cell sources for transplantation

Procedure of harvest

Stem cell harvest

BM

PB



UC

G-CSF: Donor aspects

- **Rarely severe adverse events**
  - Splenic rupture 1/5,000-1/10,000
  - Cardiovascular events (of 3,286 donations 2 strokes and one myocardial infarction)
  - Flares underlying auto-immune disorders
- **Concern of G-CSF induced leukemia**
  - In Breast Cancer
  - In Severe congenital neutropenia

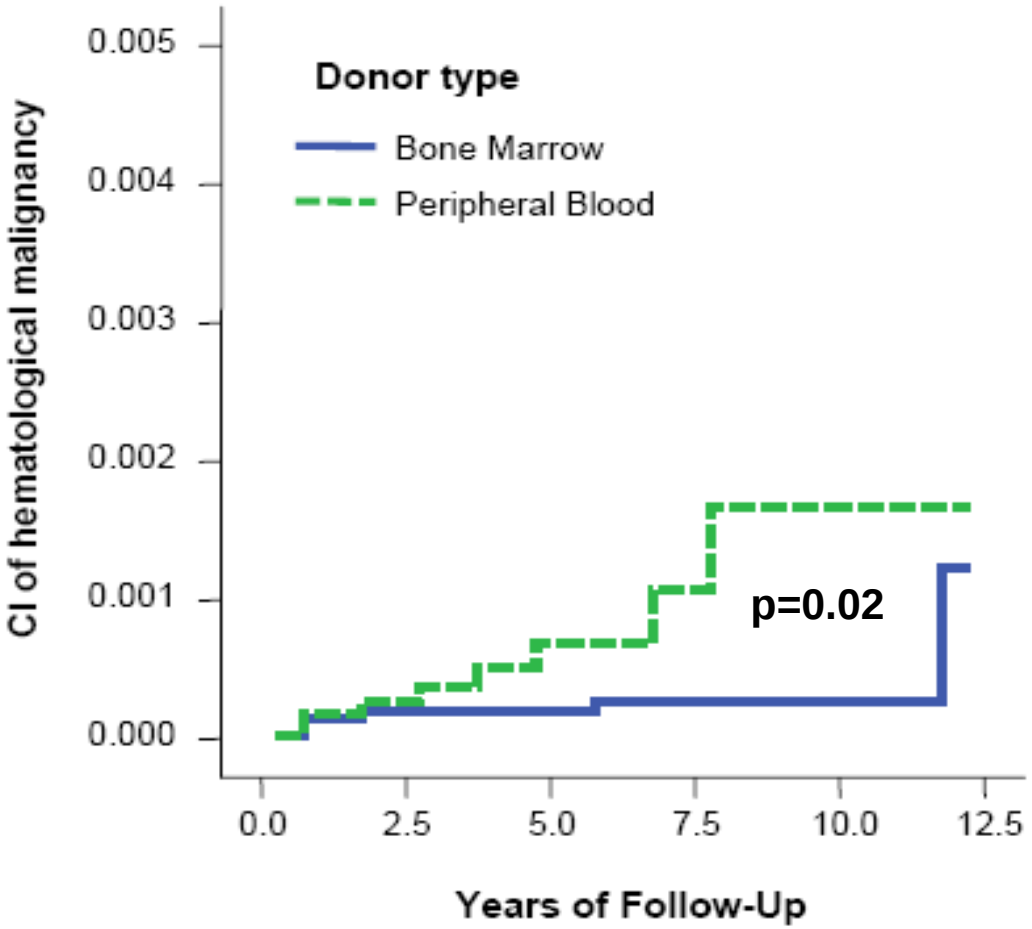
Severe donor events after allo- HSC donation

Halter J, Kodera Y, Urbano Ispizua A, et al. Hematologica, in press

- 51,024 first allogeneic (50% BM/PB)
  - 5 donor deaths
    - 1 BM, 4 PB
  - 37 SAEs
    - 12 BM, 25 PB (p=0.01)
  - 20 Hematological malignancies
    - 8 BM, 12 PB (p=0.02)

Severe donor events after allo- HSC donation

Halter J, Kodera Y, Urbano Ispizua A, et al. Hematologica, in press



Severe donor events after allo- HSC donation

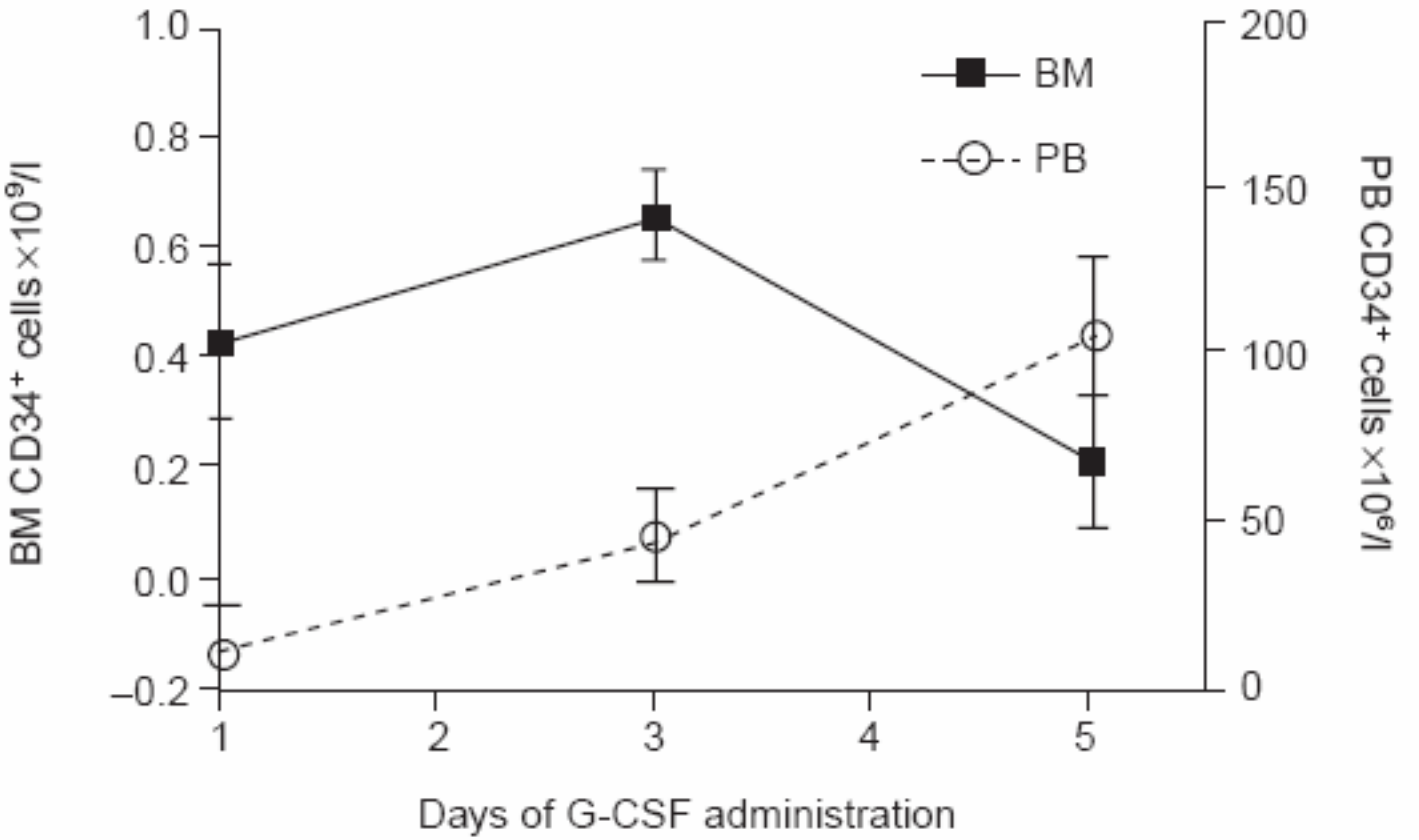
Halter J, Kodera Y, Urbano Ispizua A, et al. Hematologica, in press

Event	Total
Death	1/10.000 **PB=BM**
SAE	1/1.500 **PB>BM (x2)**
Haematological malignancies	1/3.000 **PB>BM (x3)**

Movilizing stem cells

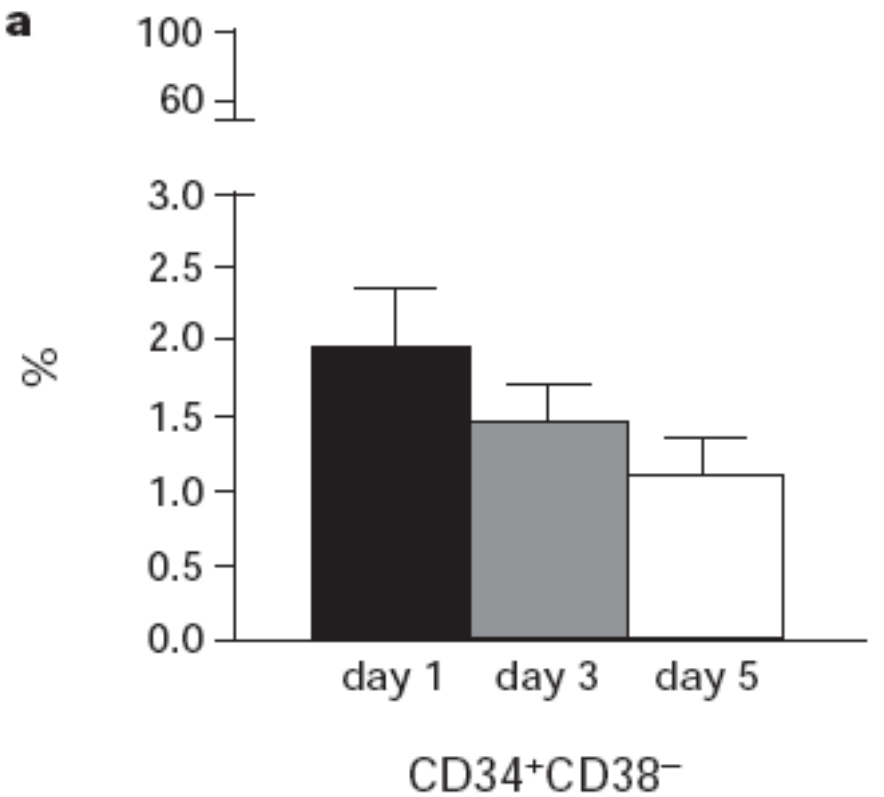
Is there an alternative to G-CSF?

G-CSF and CD34^{+} cells in BM and PB



C. Martínez BMT 1999

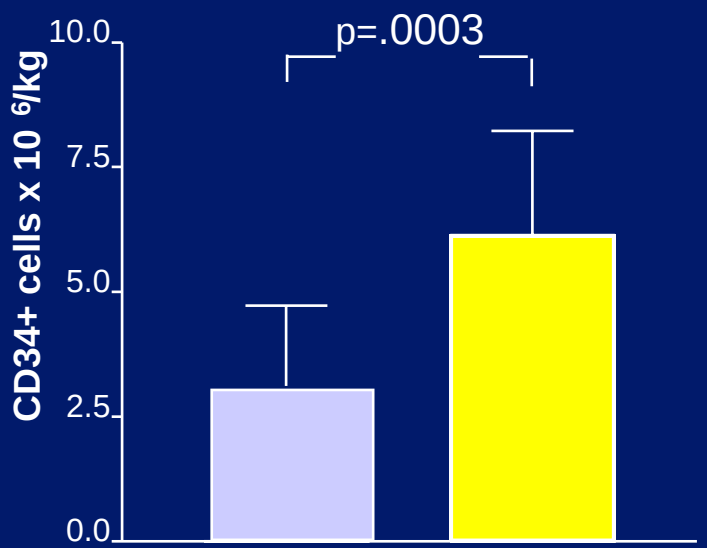
G-CSF and CD34+ cells in BM



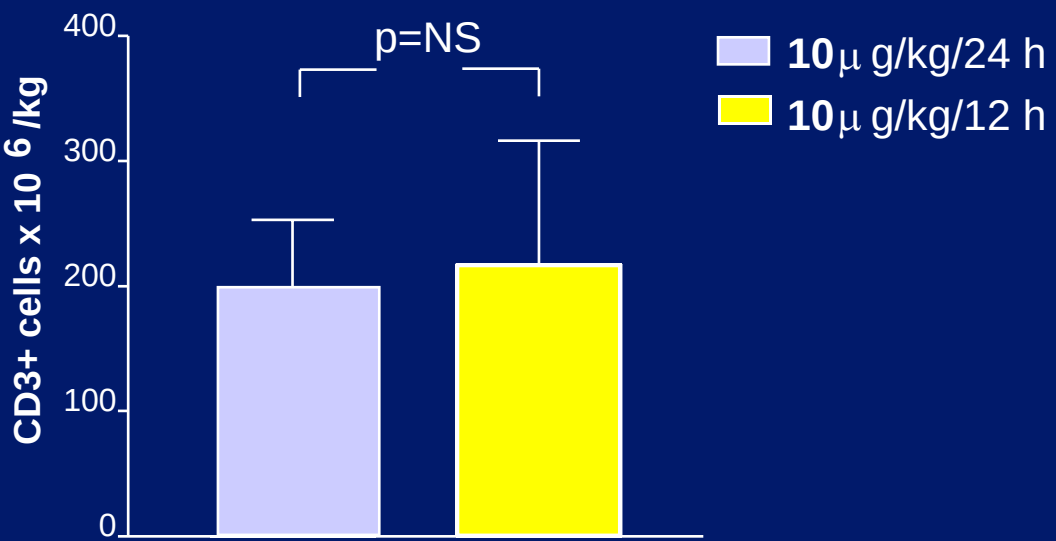
C. Martínez BMT 1999

Number of cells per apheresis depending on G-CSF dose

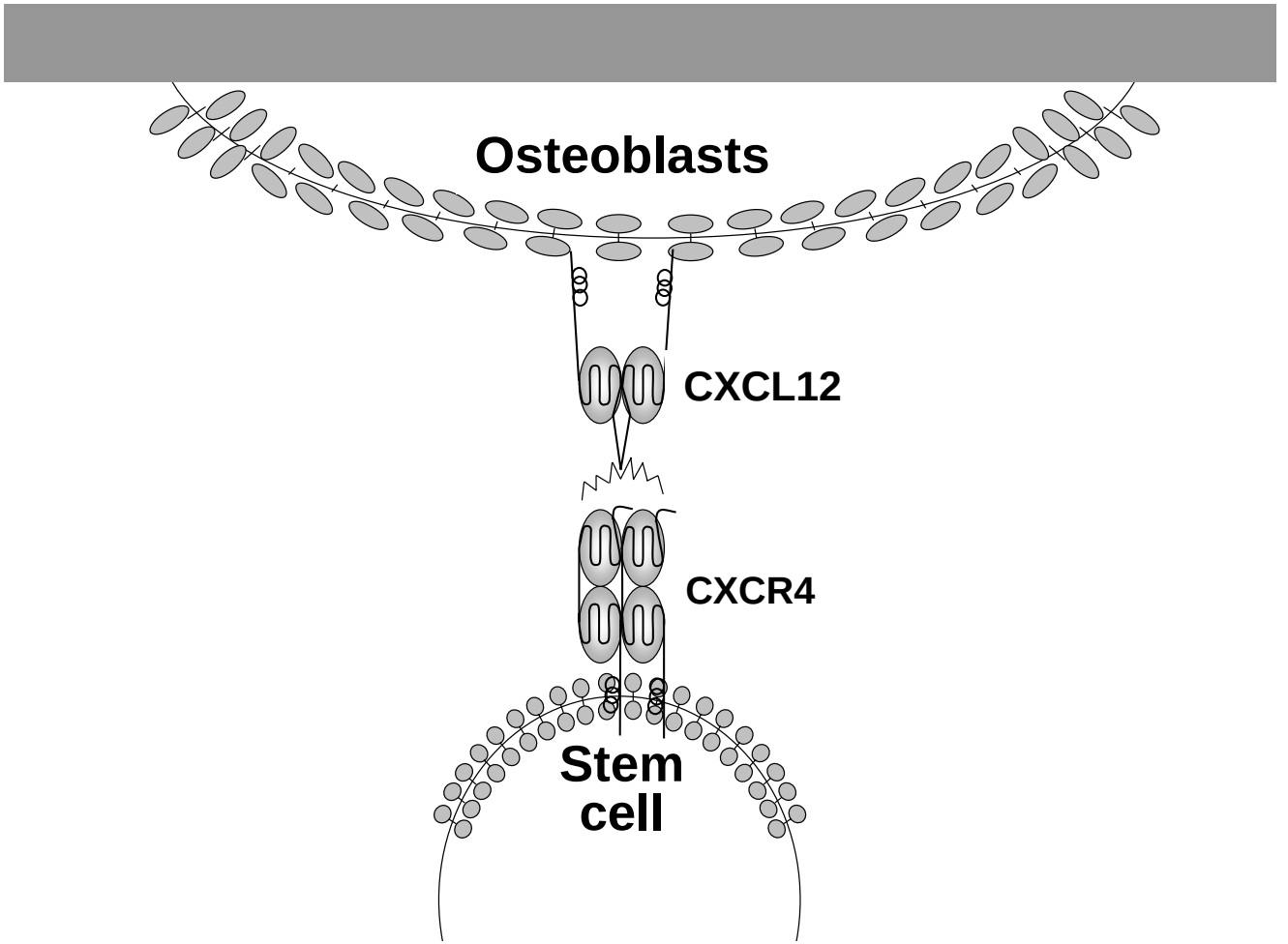
CD34+ cells



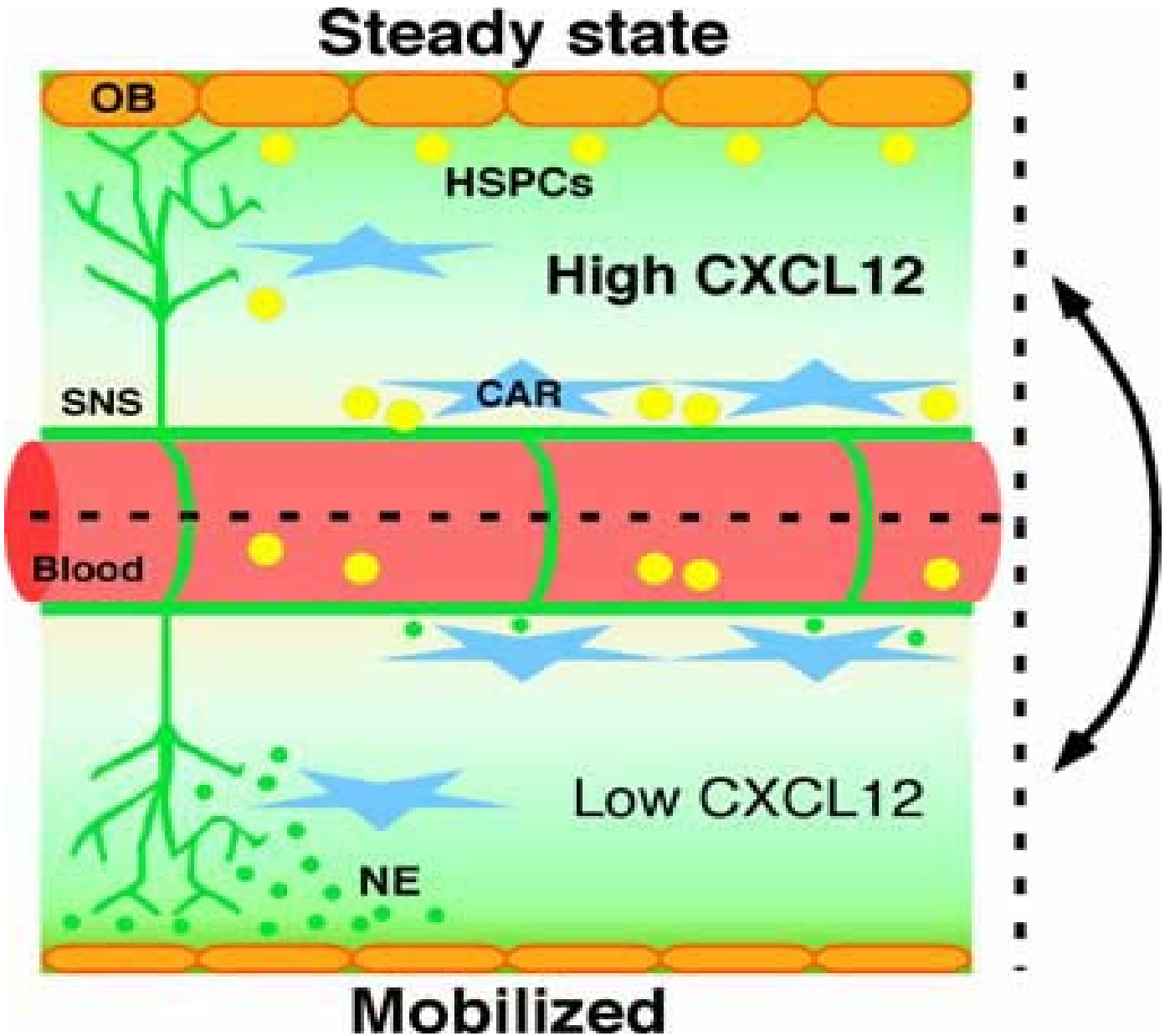
CD3+ cells



Homing and Movilization

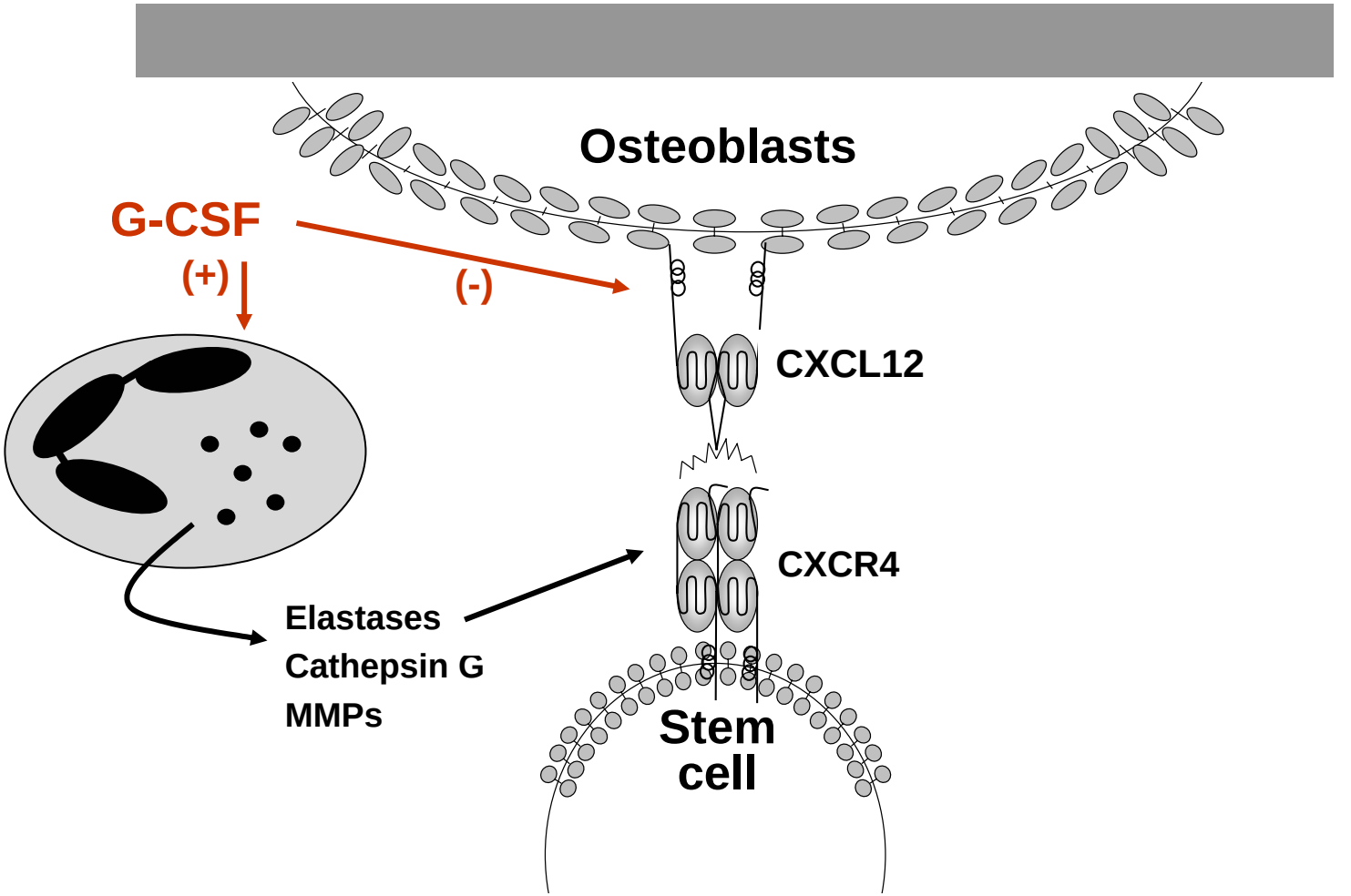


Lapidot T, Experimental Hematology 30 (2002) 973-981



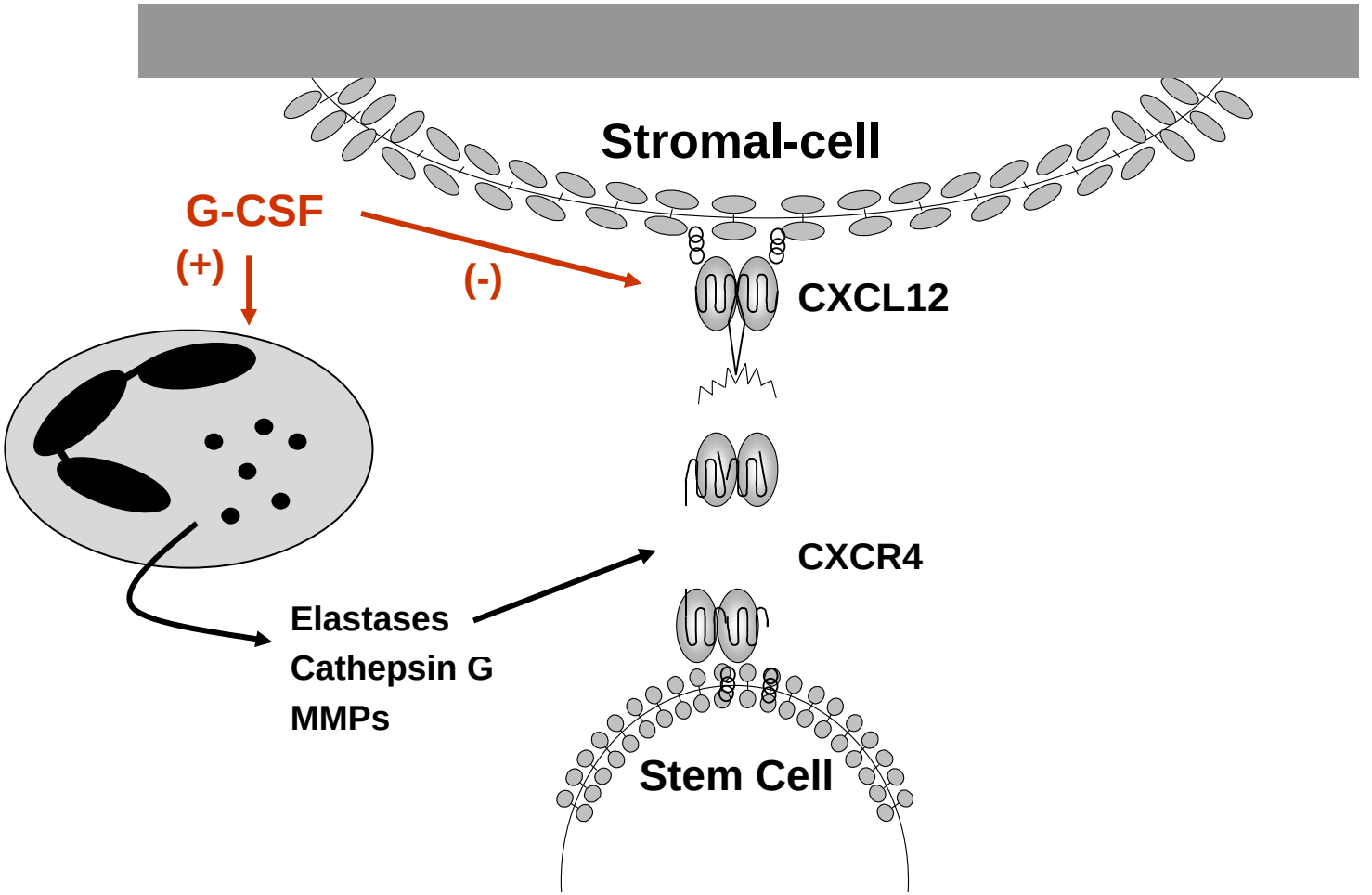
Méndez-Ferrer Simón, Nature 2008

Homing and Movilization



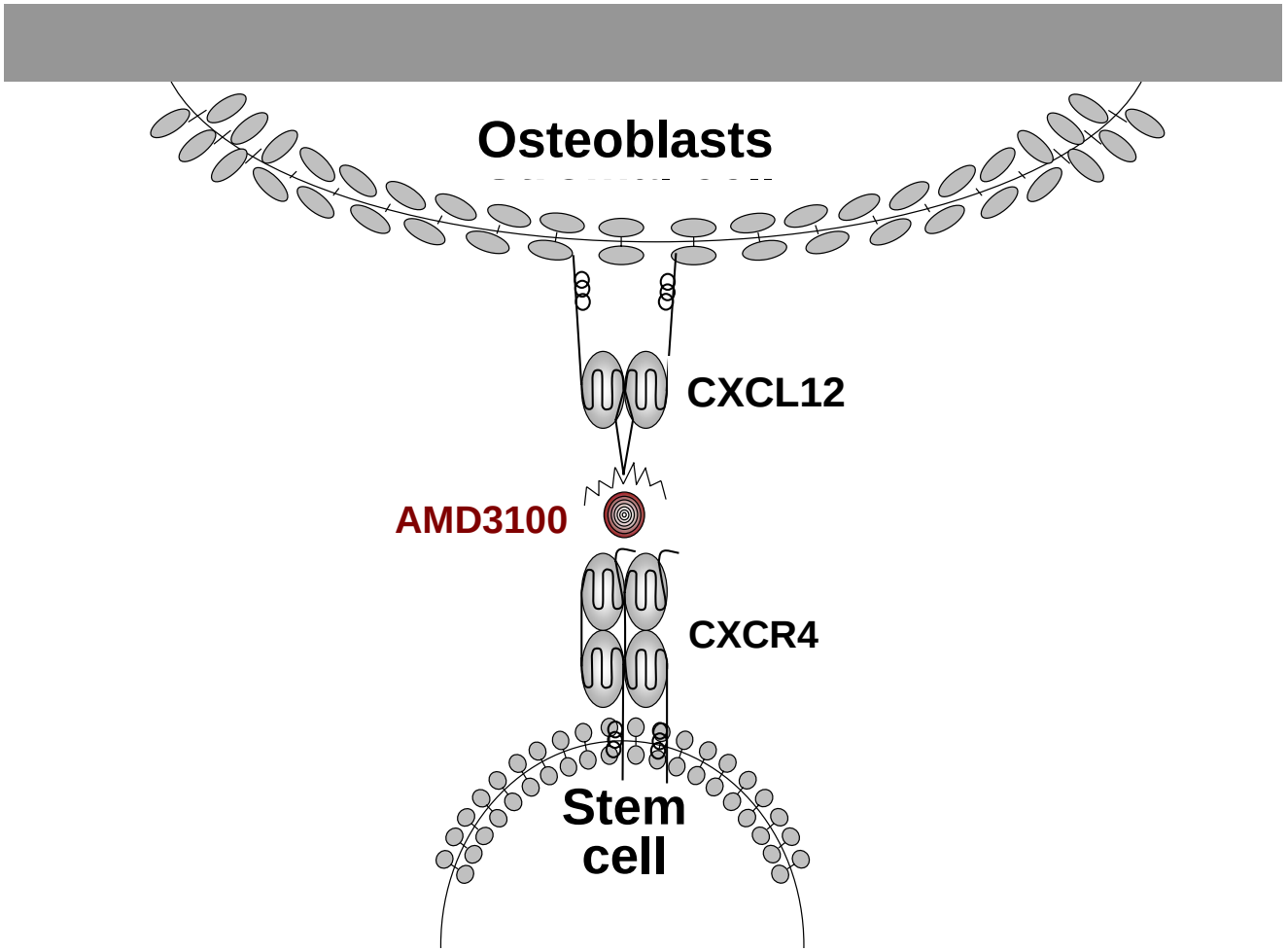
Lapidot T, Experimental Hematology 30 (2002) 973-981

G-SCF and movilization of HPC



Larochelle A, Blood 107 (2006) 3772-3778

AMD3100 and movilization of HPC



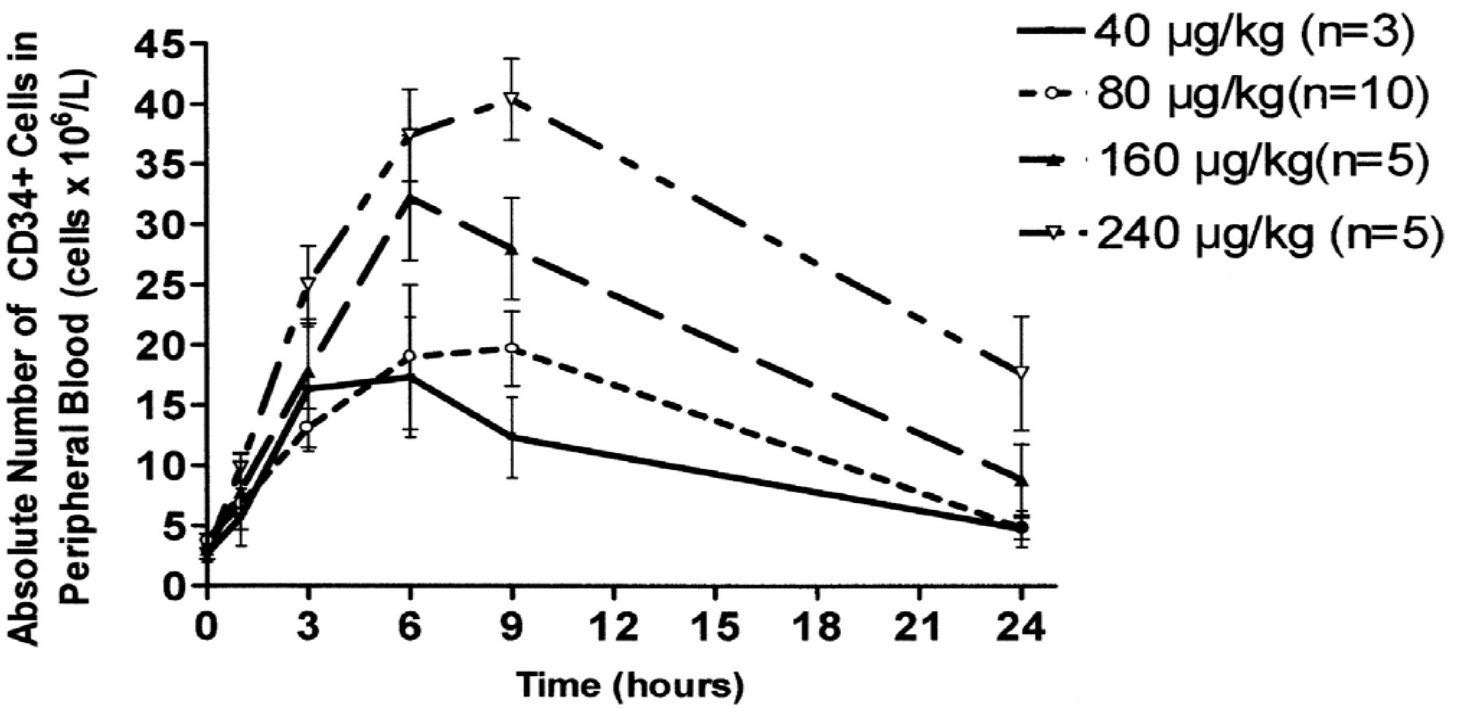
Liles WC, Blood 102 (2003) 2728-2730

Burroughs L, Blood 106 (2005) 4002-4008

Larochelle A, Blood 107 (2006) 3772-3778

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 1. Dose-response analysis of AMD3100-induced mobilization of CD34+ cells into peripheral blood. Healthy human volunteers received a single subcutaneous injection of AMD3100



Liles, W. C. et al. Blood 2003;102:2728-2730

Umbilical Cord

- **Advantages**
  - **Rapid availability**
  - **Lower risk of aGVHD**
  - **Lack of risk for the donor**

Umbilical Cord

- **Disadvantages**
  - Treatment of graft failure or relapse
  - Fewer HPC

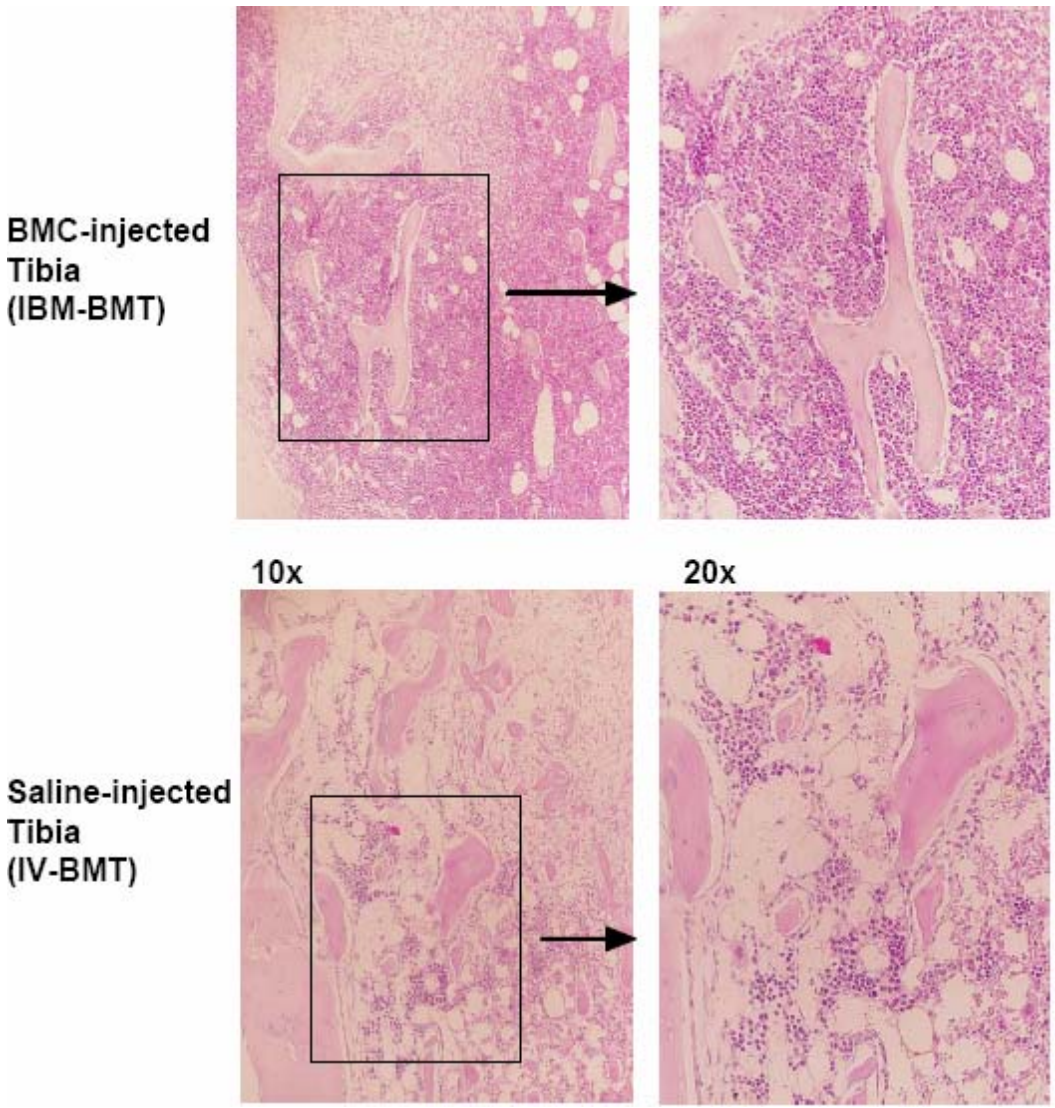
    <20% of adults with >3 x 10^7CN/kg

Overcoming CB cell dose barrier

1. Double cord blood transplants
   University of Minnesota
2. CB + Haploidentical HSC third party
   University of Madrid
3. *Ex vivo* expansion of CB cells (copper chelator)
   MD Anderson
4. Co-infusion of mesenchymal stroma cells
   University of Korea
5. *Ex vivo* expanded Treg cells
   Godfrey WR, Blood 2005; 105:750

Analyses of very early hemopoietic regeneration after BMT: Comparison Between IV and IB Marrow Routes

Li Q, Stem Cells, Feb 22, 2007



Overcoming CB cell dose barrier: Intrabone infusion

- <20% of infused stem cells home to the BM
- IBM injection has shown superior efficiency
  Castello S, Exp Hematol 2004; 32: 782
- No clinical differences in allo-BMT setting
  Hägglund H, BMT 1998; 21: 331
- IBM could be useful in CB setting
  Genova's experience (EBMT 2007)

Búsqueda Unidad CU

1. Identidad HLA
2. Dosis celular adecuada
3. Criopreservación reciente

Comparison of Stem cell sources for transplantation

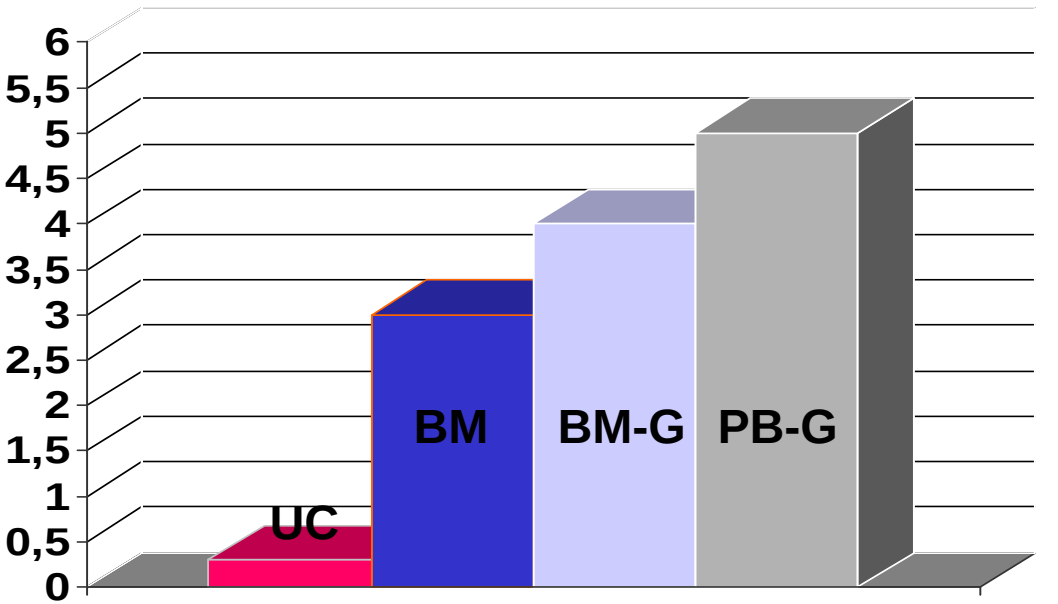
Cell composition

Cell subsets and allo-SCT

- CD34+ cells
  - Myeloid
  - Lymphoid
- T (and Treg), B cells
- Dendritic cells
- Mesenchymal stem cells

Progenitor cell collection

Healthy donor



CD34+ cells x 10^6/kg

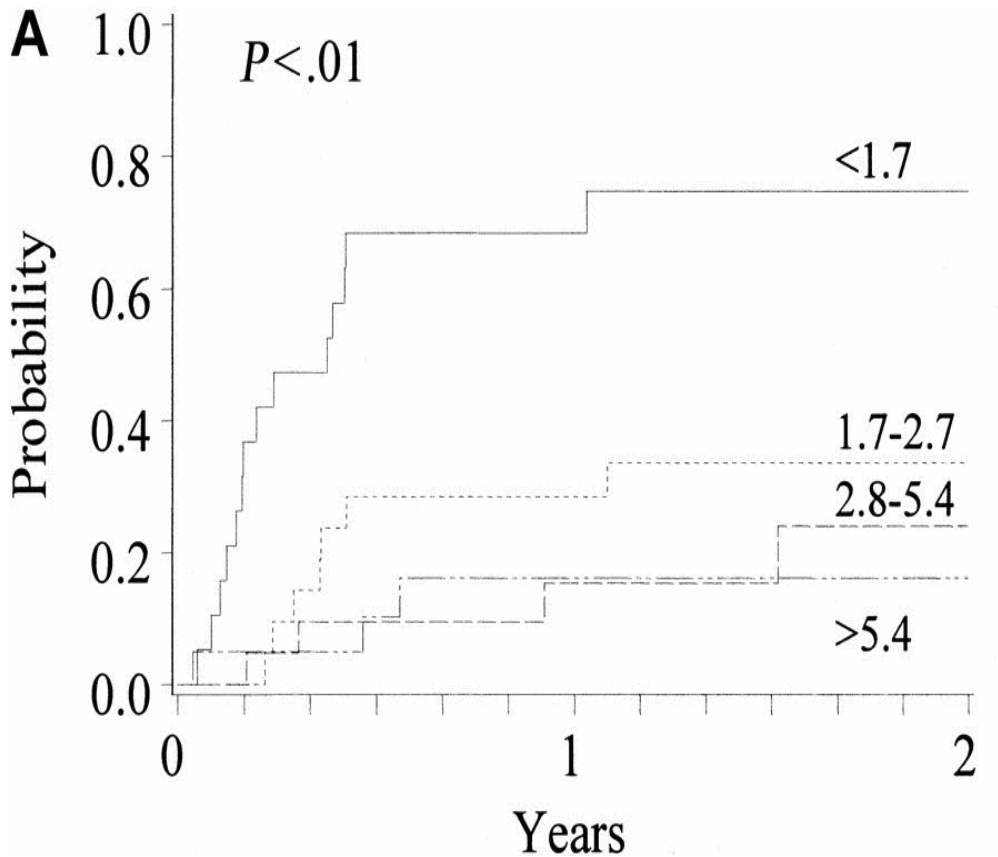
UC = 0.3

BM = 3

BM-G = 4

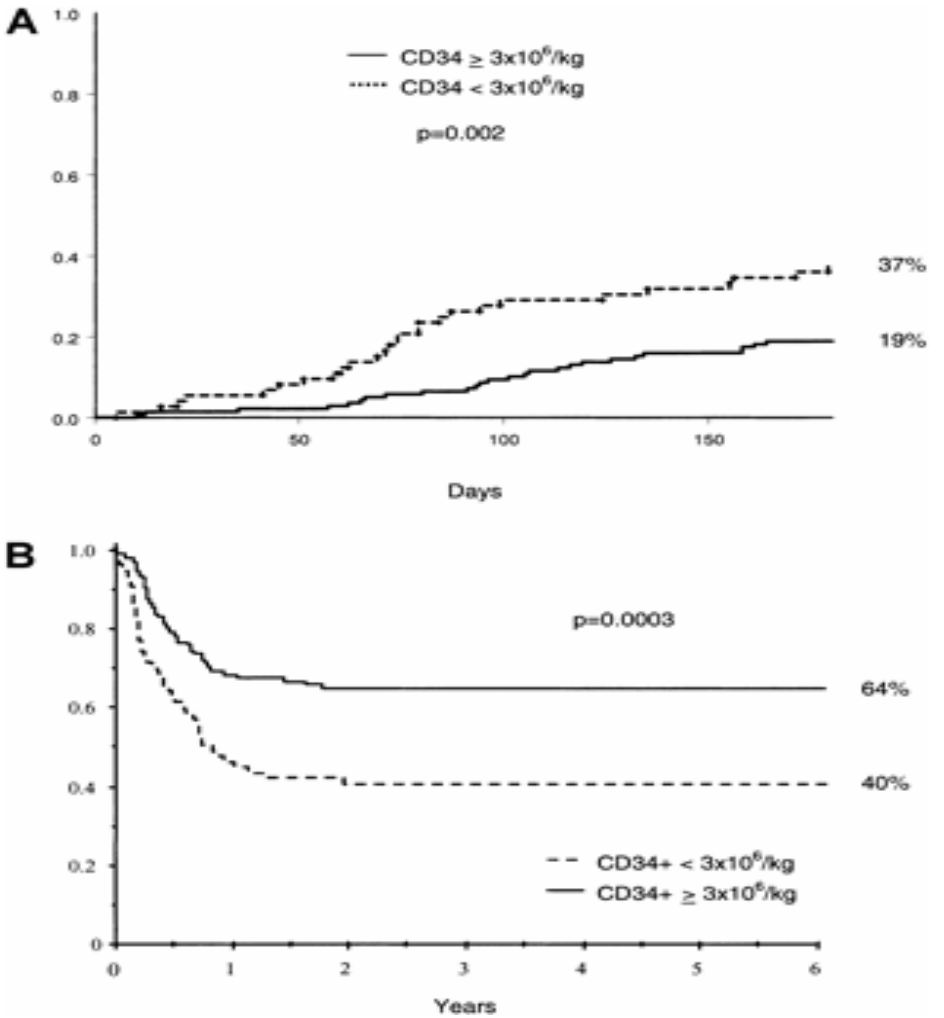
PB-G = 5

CUMULATIVE INCIDENCE OF TRM AFTER UNRELATED DONOR UCB TRANSPLANTATION (N = 102). EFFECT OF CD34 DOSE. *Wagner et al.* **Blood** *2002;100:1611*



CD34+ threshold: 1.7 × 10^5/kg

TRM (A) and Survival (B) according to CD34+ dose in allo-BMT. *Bittencourt et al. 2002*



Transplantation of mobilized peripheral blood cells to HLA-identical siblings with standard-risk leukemia (EBMT Randomized Study)

Schmitz N et al. Blood 2002;100:761

“The correlation of survival with $CD34^+$ number was significant in the BMT group (*P* = .022), but appeared nonexistent in the PBPCT group”

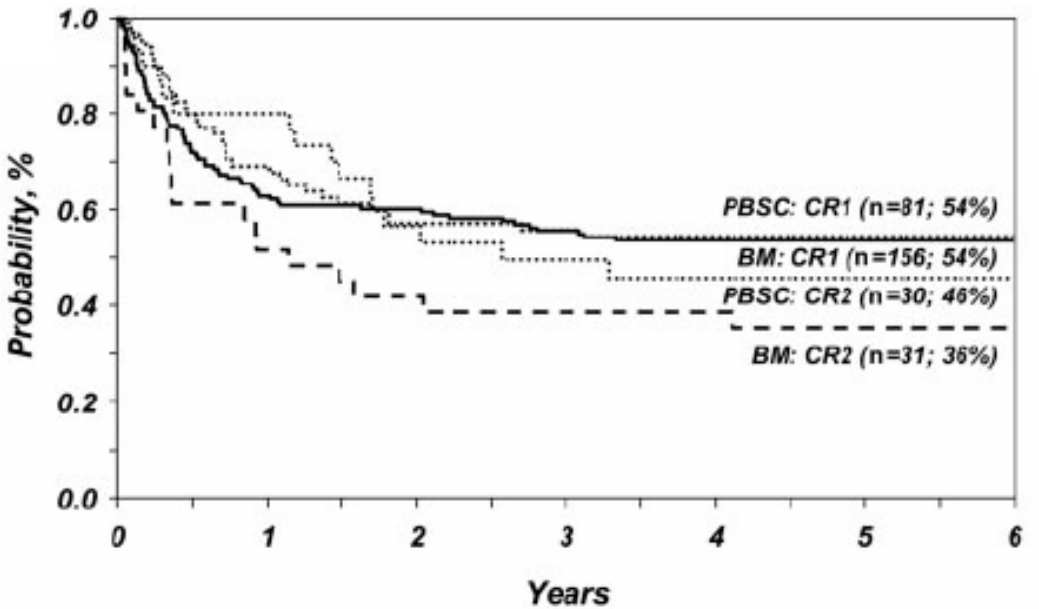
Comparison of stem cell sources for allotransplants

Clinical results BM vs PB

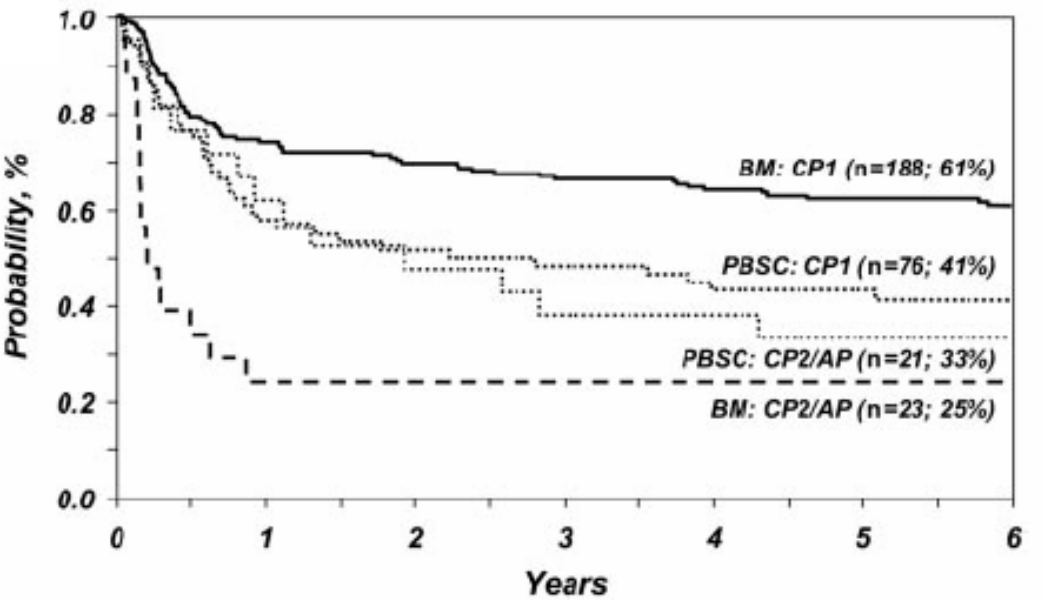
Long-term outcome of patients given transplants of mobilized blood or bone marrow: a report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation

Norbert Schmitz, Mary Eapen, Mary M. Horowitz, Mei-Jie Zhang, John P. Klein, J. Douglas Rizzo, Fausto R. Loberiza, Alois Gratwohl, and Richard E. Champlin **(Blood. 2006;108:4288-4290)**

Probability of Leukemia Free Survival



Acute Leukemia



Chronic Myeloid Leukemia

Allo-SCT

Leukemia Free Survival

	BM	PB
AL RC1	+	+
AL >RC1	±	+
CML CP1	+	-
CML >CP1	-	+

Goal of allo-SCT

- Rapid hematological recovery of allo-PBT with incidence of cGVHD of allo-BMT

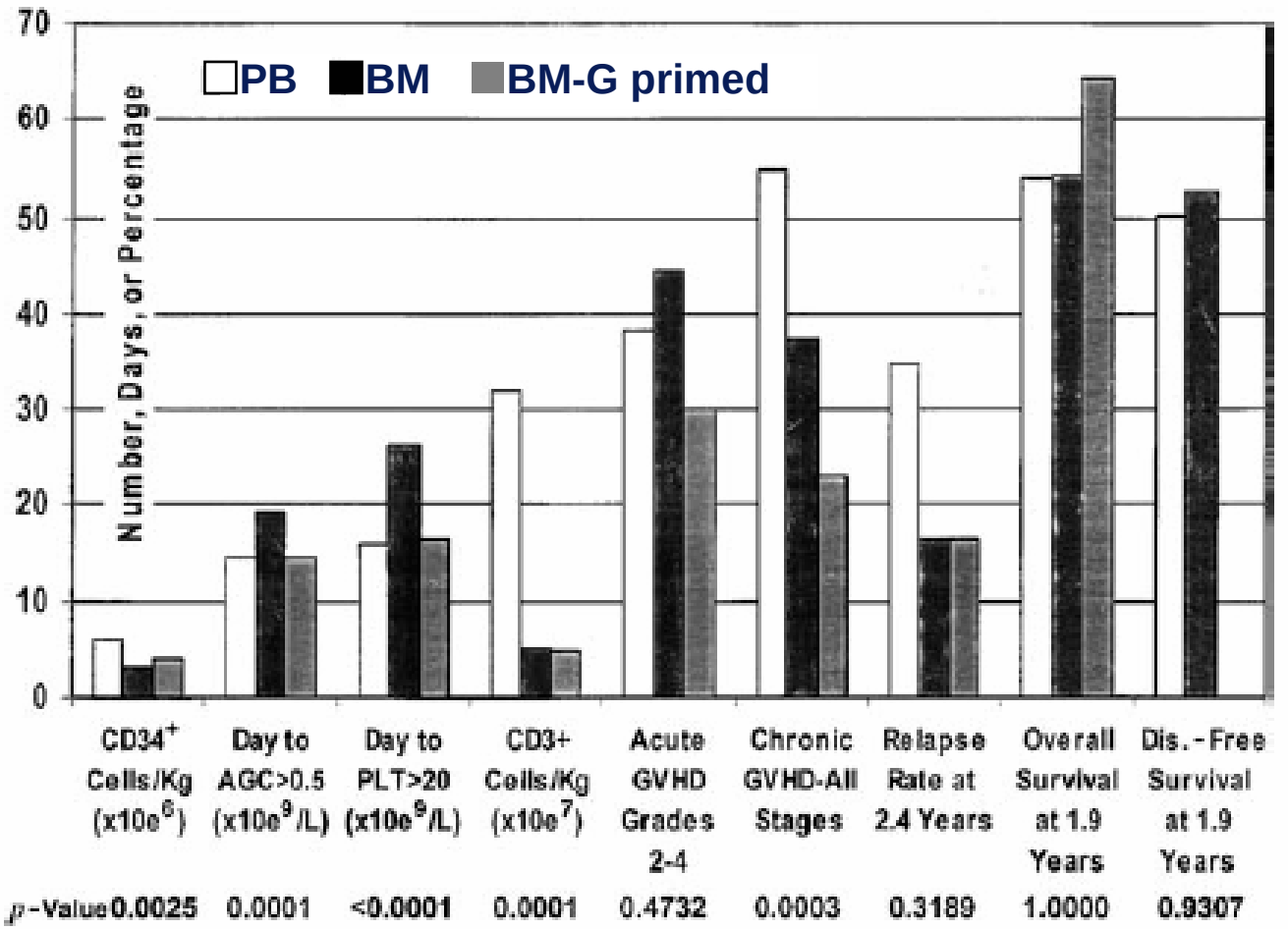
- G-CSF primed bone marrow?

ELSEVIER

Gerald J. Elfenbein[a] and Robert Sackstein[b]

EXPERIMENTAL HEMATOLOGY

Experimental Hematology 32 (2004) 327–339



Stem cell sources

Intensity of allogeneic reactions

	aGVHD	cGVHD	Relapse	Chimerism	Fight against infections
UC	±	+	+	±	±
BM	+	+	+	+	+
PB (G-CSF)	+ ±	+ +	+	+ +	+ +

Muchas gracias por su atención