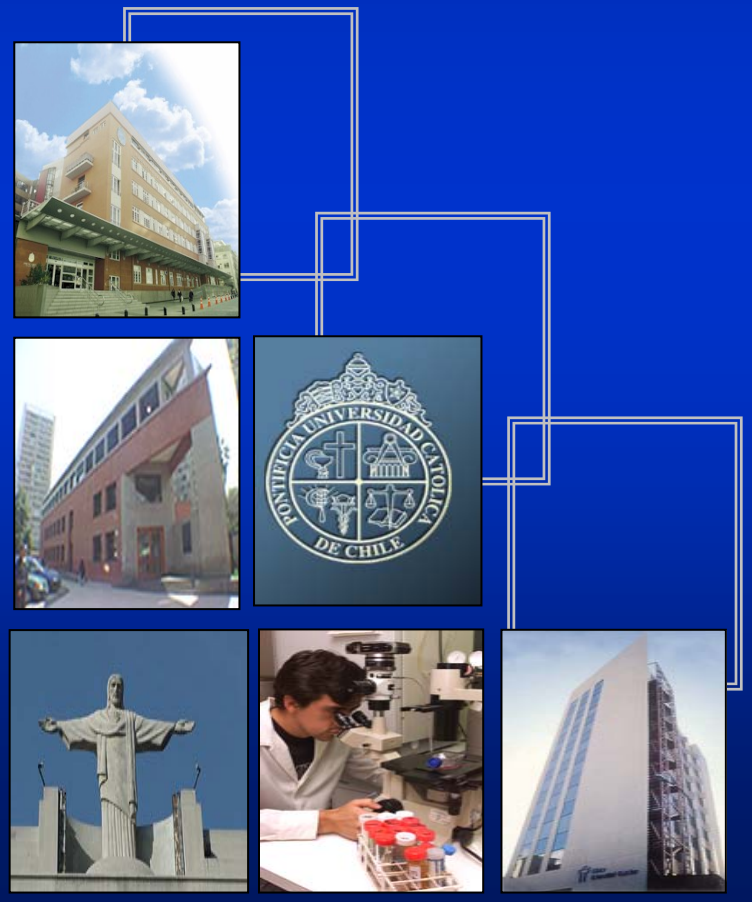
Simposio:
Experiencia de trasplante en Chile

Mantagua, 26 de Octubre de 2006



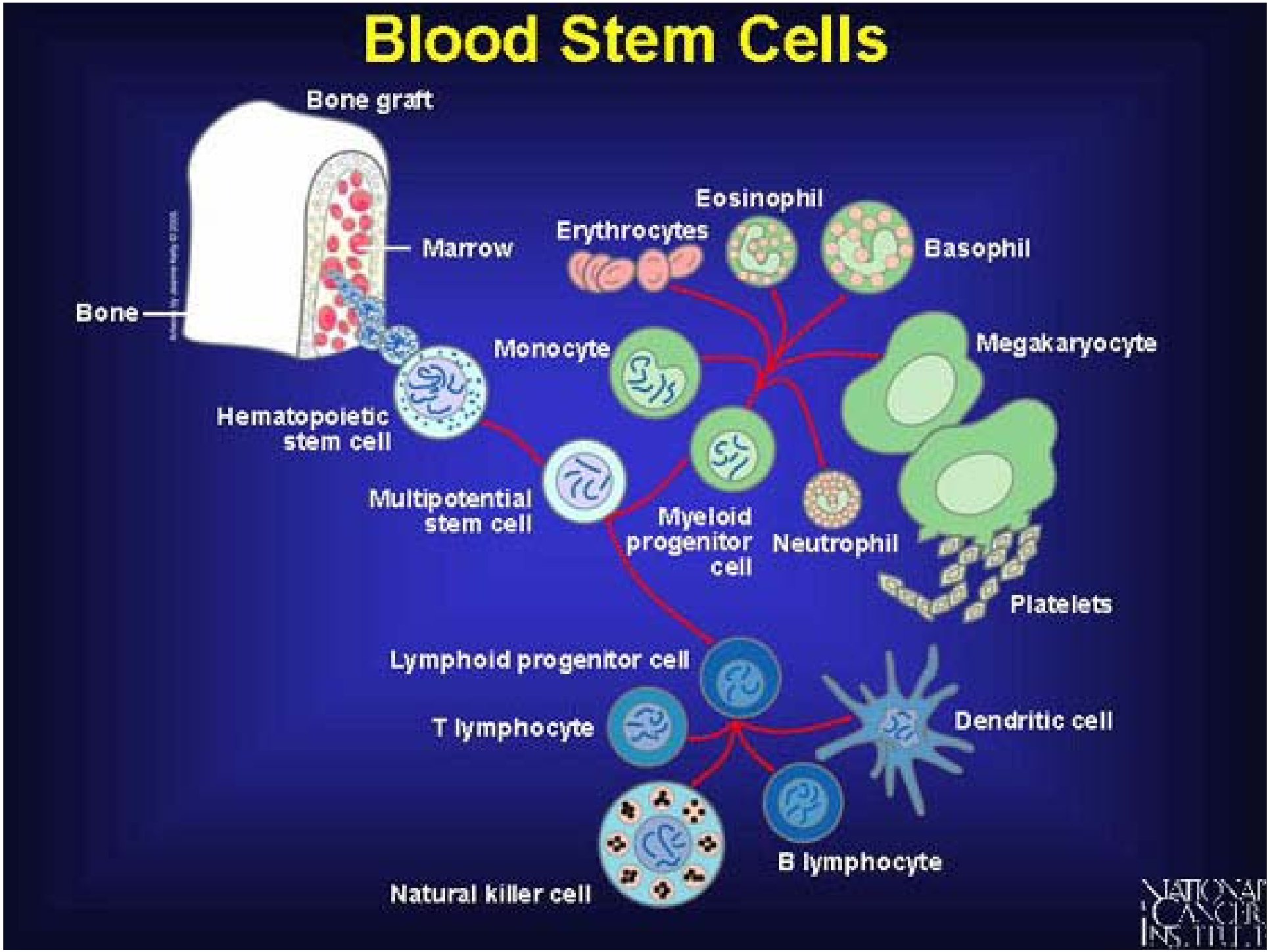
EXPERIENCIA DE TRASPLANTE EN CHILE:

GVH

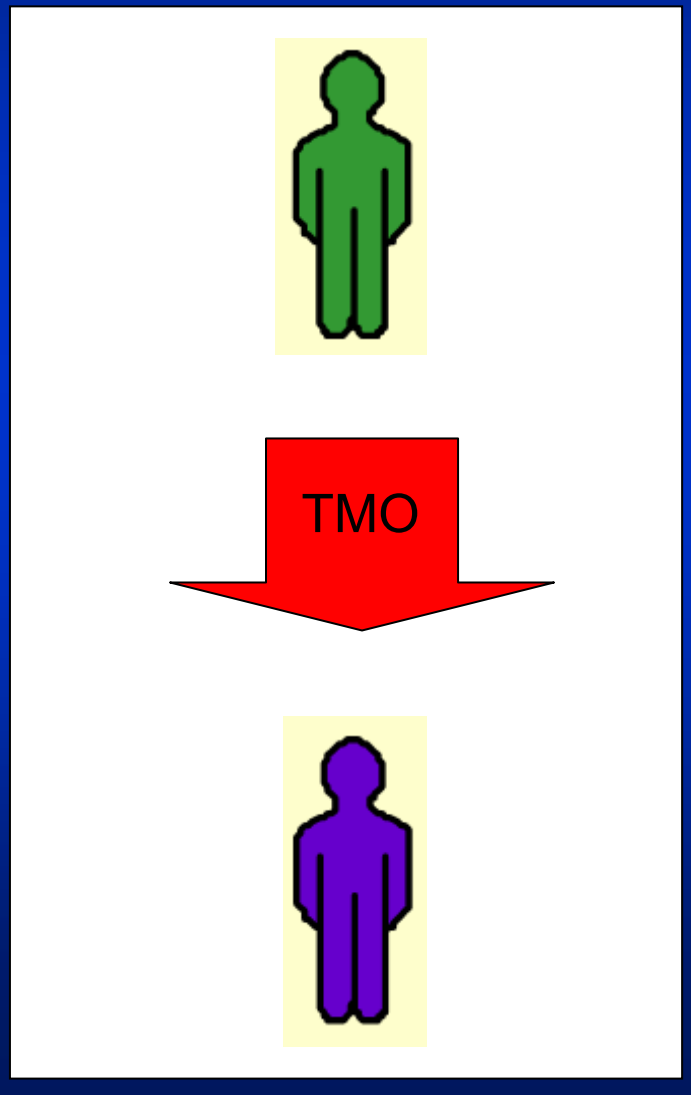
DR. BRUNO NERVI

PROGRAMA DE CANCER

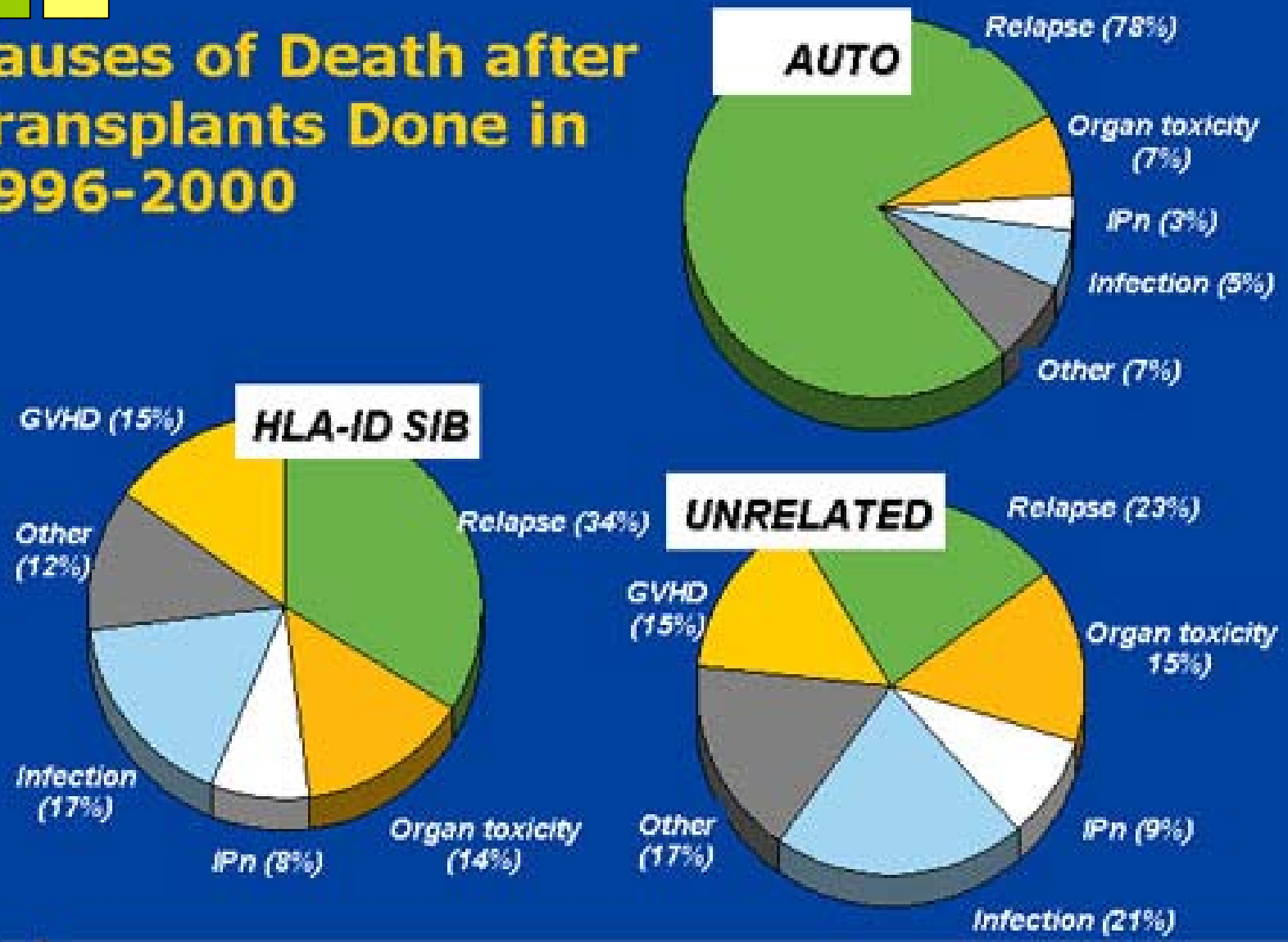
PONTIFICIA UNIVERSIDAD CATOLICA DE CHILE


Blood Stem Cells
Bone graft
Marrow
Bone
Eosinophil
Erythrocytes
Basophil
Monocyte
Megakaryocyte
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Neutrophil
Platelets
Lymphoid progenitor cell
T lymphocyte
Dendritic cell
B lymphocyte
Natural killer cell

Trasplante alogeneico de precursores hematopoyeticos

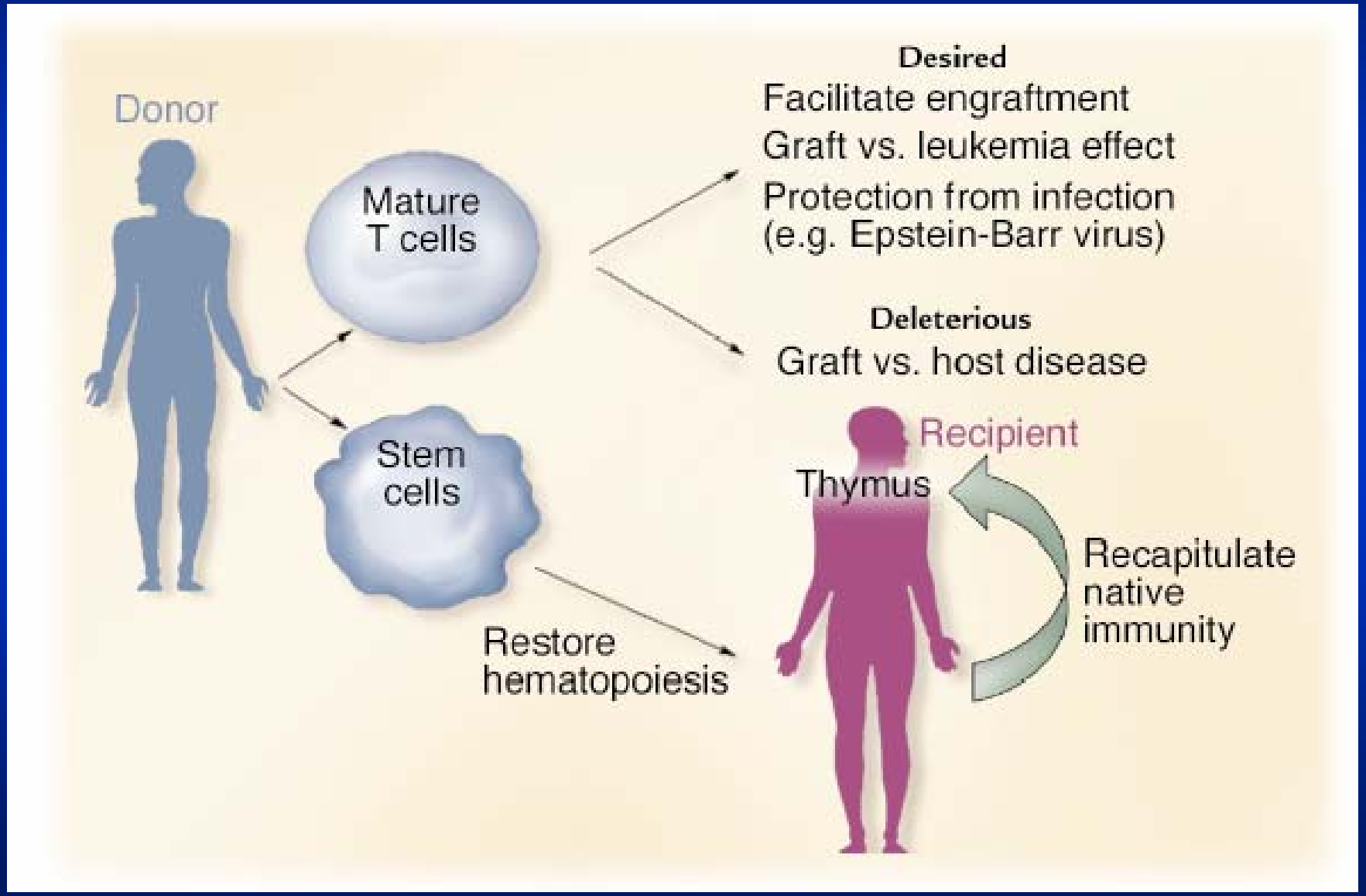


Causes of Death after Transplants Done in 1996-2000

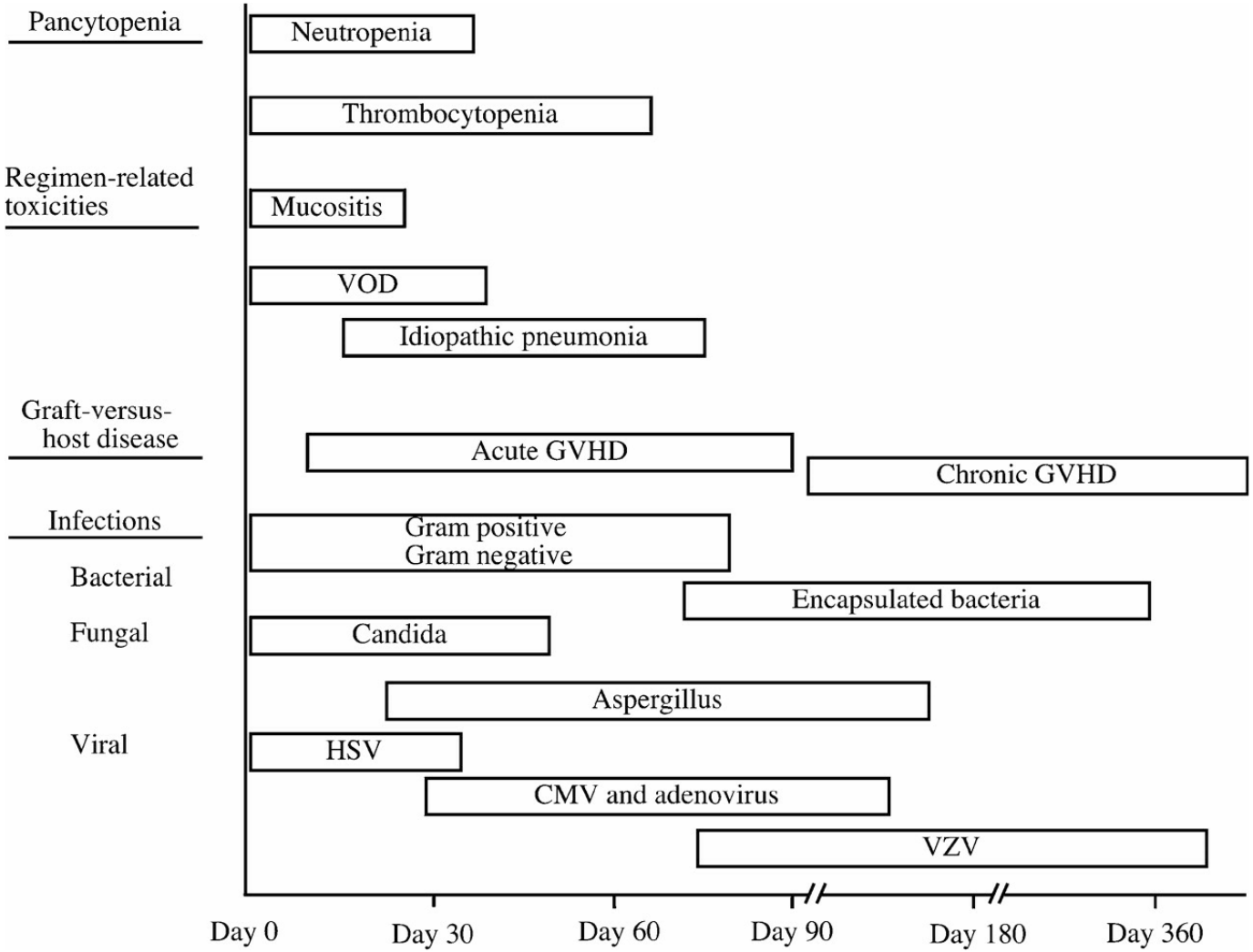


CIBMTR

El gran dilema del allo-SCT



Complicaciones del allo-SCT



Annu. Rev. Med. 2003. 54:491-512

RUTA

- Que es el GVHD?
- Patogenia
- Factores de riesgo
- Como evitar el GVHD
- Tratamiento

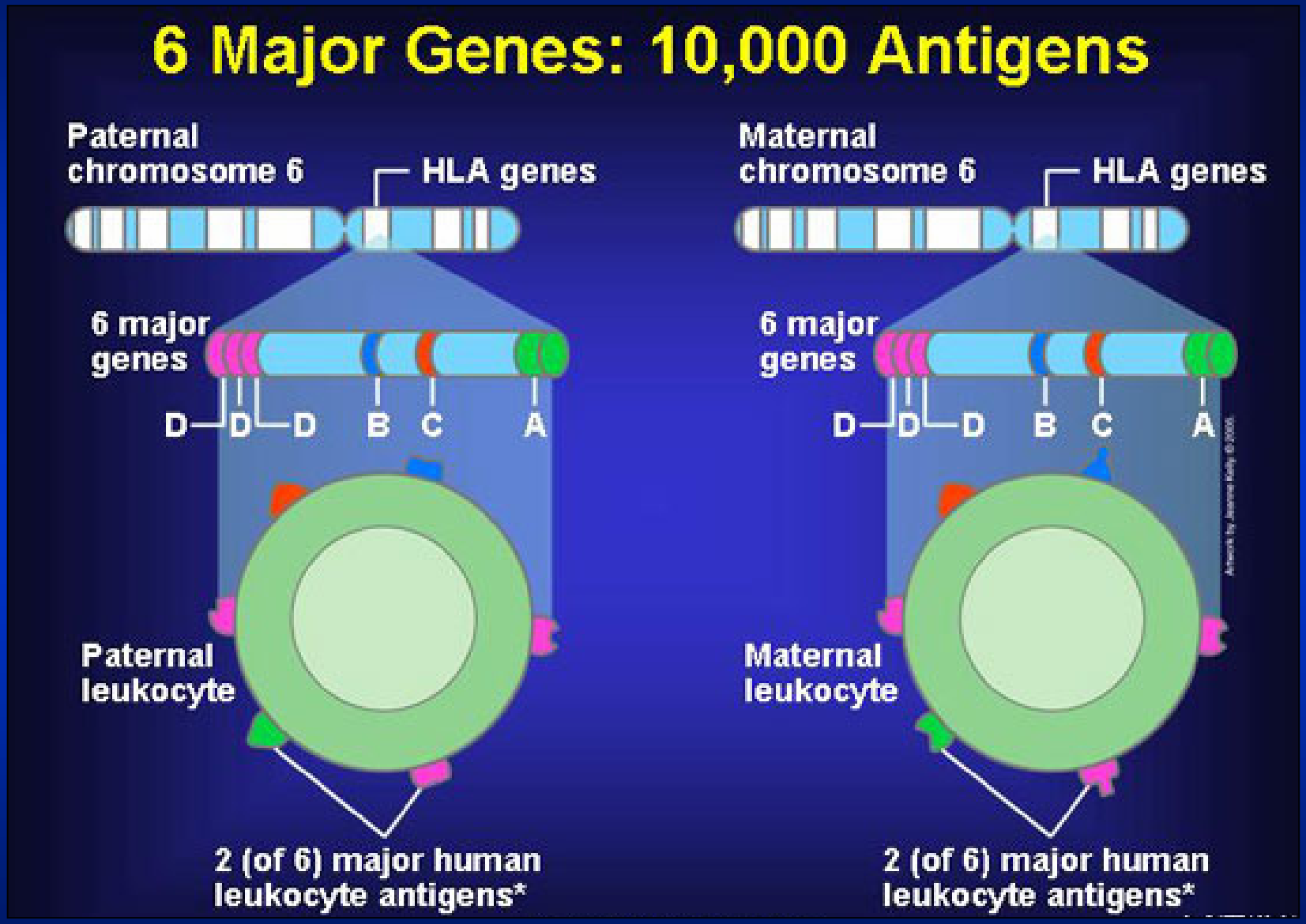
GVHD

1. Incidencia aGVHD (grado II-IV):
    a. 25-60% HLA identicos.
    b. 45-70% HLA no-relacionados

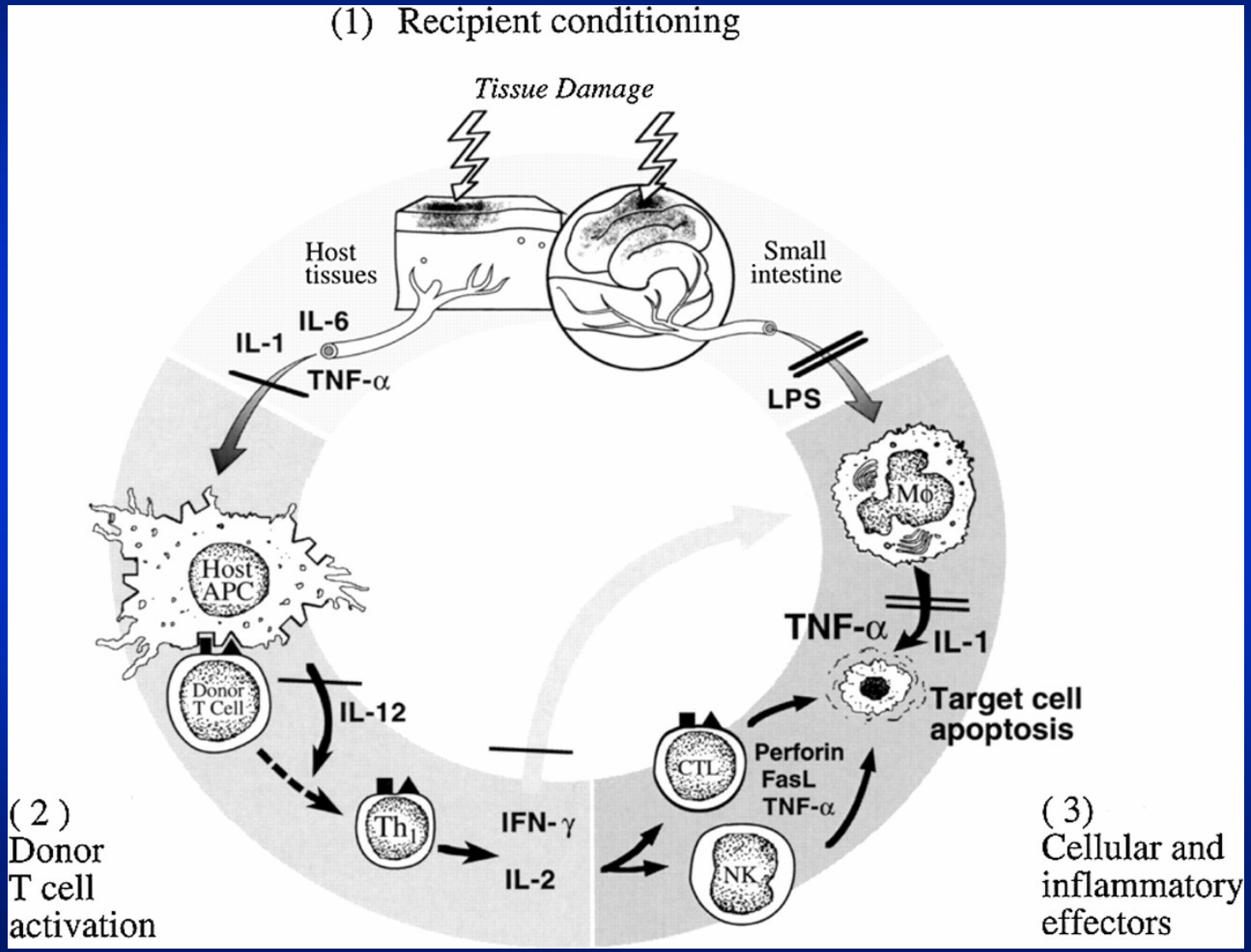
2. Linfocitos allo-T ataca tejidos blancos.

3. Si HLA OK, GVHD es por Ag menores.

4. 20%-40% de pacientes que sobreviven > 6m desarrollan cGVHD.


6 Major Genes: 10,000 Antigens
Paternal chromosome 6
HLA genes
6 major genes
D D D B C A
Paternal leukocyte
2 (of 6) major human leukocyte antigens*
Maternal chromosome 6
HLA genes
6 major genes
D D D B C A
Maternal leukocyte
2 (of 6) major human leukocyte antigens*

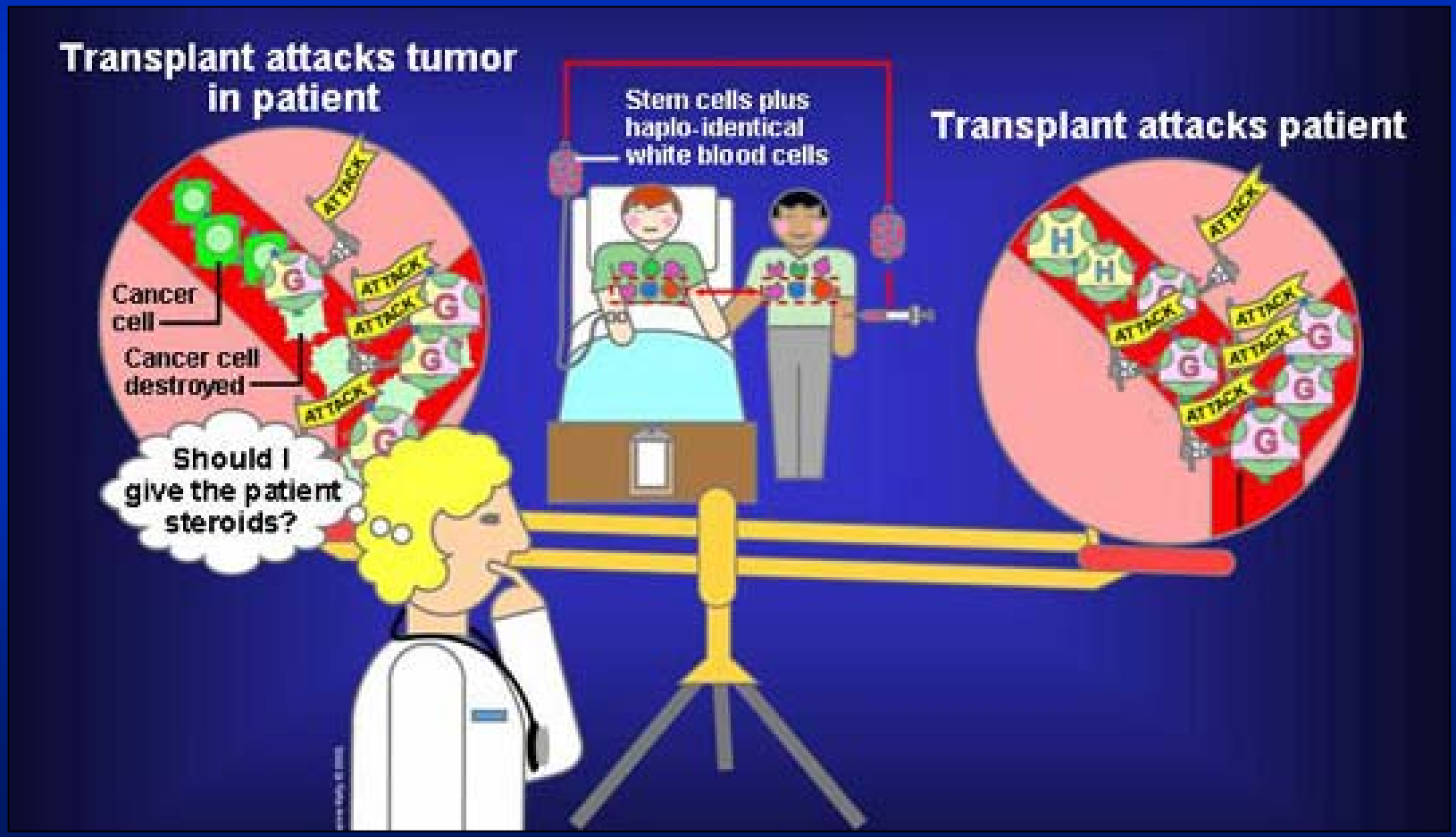
Fisiología del GVHD



Etapa GVHD

Table 52.3-2: Glucksberg Clinical Stage and Grade of Acute Graft-Versus-Host Disease			
Stage	**Skin**	**Liver**	**Intestinal Tract**
1	Maculopapular rash <25% of body surface	Bilirubin, 34–50 μmol/L	>500 mL diarrhea/d
2	Maculopapular rash 25–50% of body surface	Bilirubin, 51–102 μmol/L	>1000 mL diarrhea/d
3	Generalized erythroderma	Bilirubin, 103–225 μmol/L	>1500 mL diarrhea/d
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin >255 μmol/L	Severe abdominal pain with or without ileus
Grade	**Degree of Organ Involvement**		
I	Stage 1–2 skin rash; no gastrointestinal tract involvement; no liver involvement; no decrease in clinical performance		
II	Stage 1–3 skin rash; stage 1 gastrointestinal tract involvement or stage 1 liver involvement (or both); mild decrease in clinical performance		
III	Stage 2–3 skin rash; stage 2–3 gastrointestinal tract involvement or stage 2–4 liver involvement (or both); marked decrease in clinical performance		
IV	Similar to grade III with stage 2–4 organ involvement; extreme decrease in clinical performance		

Un balance delicado:
Injerto contra Huésped vs Huésped contra Injerto

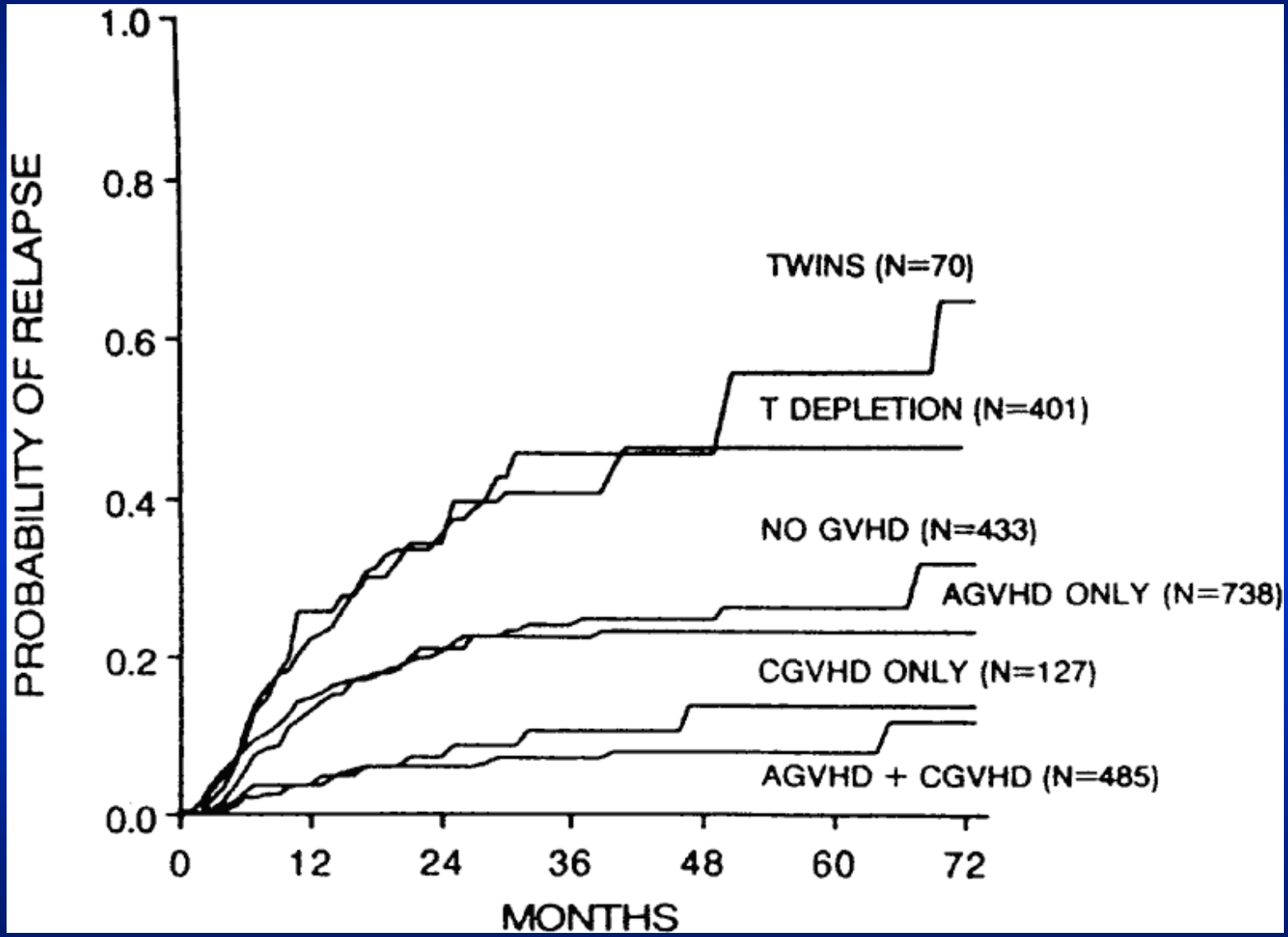


Factores que determinan la incidencia y severidad del GVHD

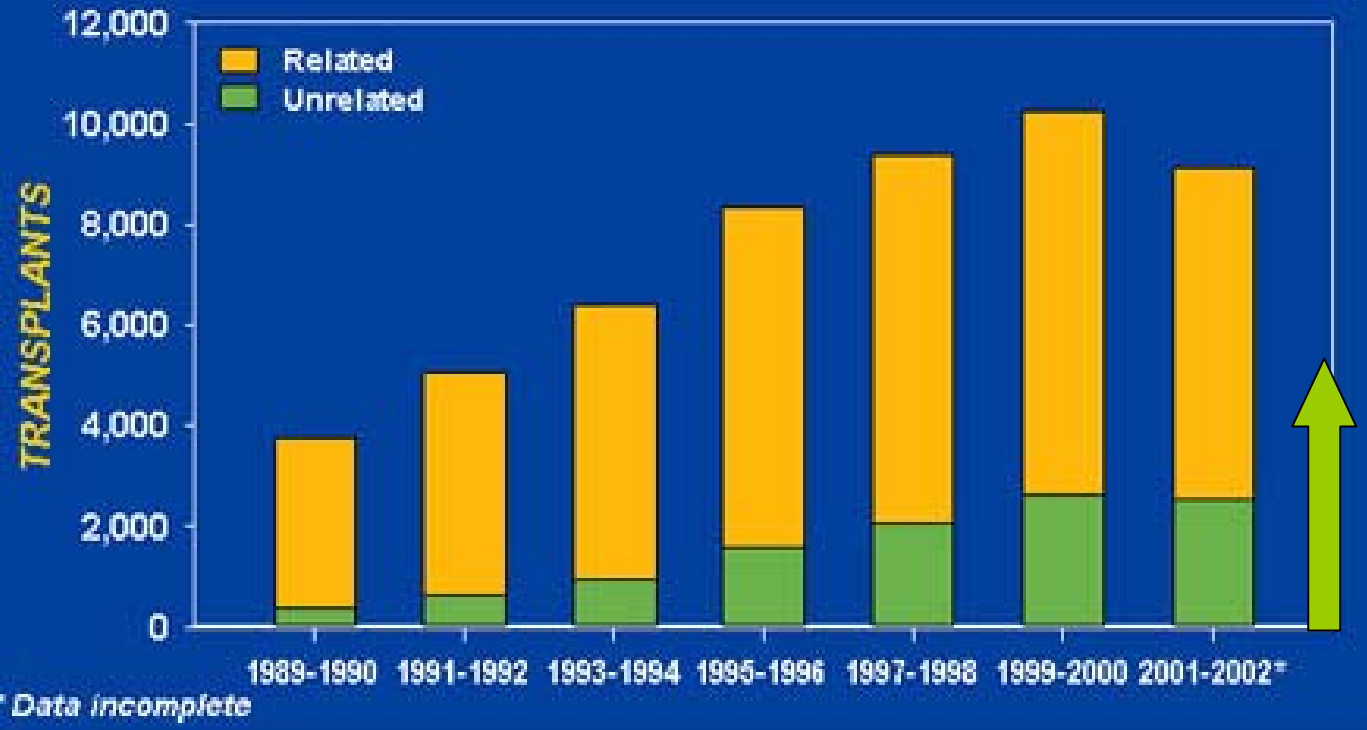
- HLA paciente/donante
- Donante relcionado/no-relacionado
- MO, PBMC, cordon
- Tipo de profilaxis GVHD
- T depletado
- Edad paciente
- Intensidad regimen quimioterapia:
  - mieloablativo
  - No-mieloablativo

Recaída post-trasplante

	auto	allo
AML CR1	35-65	10-25
AML CR2	40-70	40
ALL CR1	50	10
ALL refractory	50-80	30
CML chronic phase	NA	10
NHL/HD	45	20


PROBABILITY OF RELAPSE
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
MONTHS
TWINS (N=70)
T DEPLETION (N=401)
NO GVHD (N=433)
AGVHD ONLY (N=738)
CGVHD ONLY (N=127)
AGVHD + CGVHD (N=485)

Allogeneic Transplants in Patients >20 yrs Registered with CIBMTR, 1989–2002 – by donor type



** Data incomplete*

CIBMTR

Origen de CD34 influye en riego de GVHD

Hematopoietic Cell Sources for Allogeneic Transplant			
Characteristic	**Marrow**	**PBSC**	**Umbilical Cord Blood**
HLA matching requirements	**5/6 6/6**	**5/6 6/6**	**4/6 5/6 6/6**
aGVHD	**UCB < (BM ~ PBMC)**		
cGVHD	**UCB < BM < PBSC**		

The NEW ENGLAND JOURNAL of MEDICINE

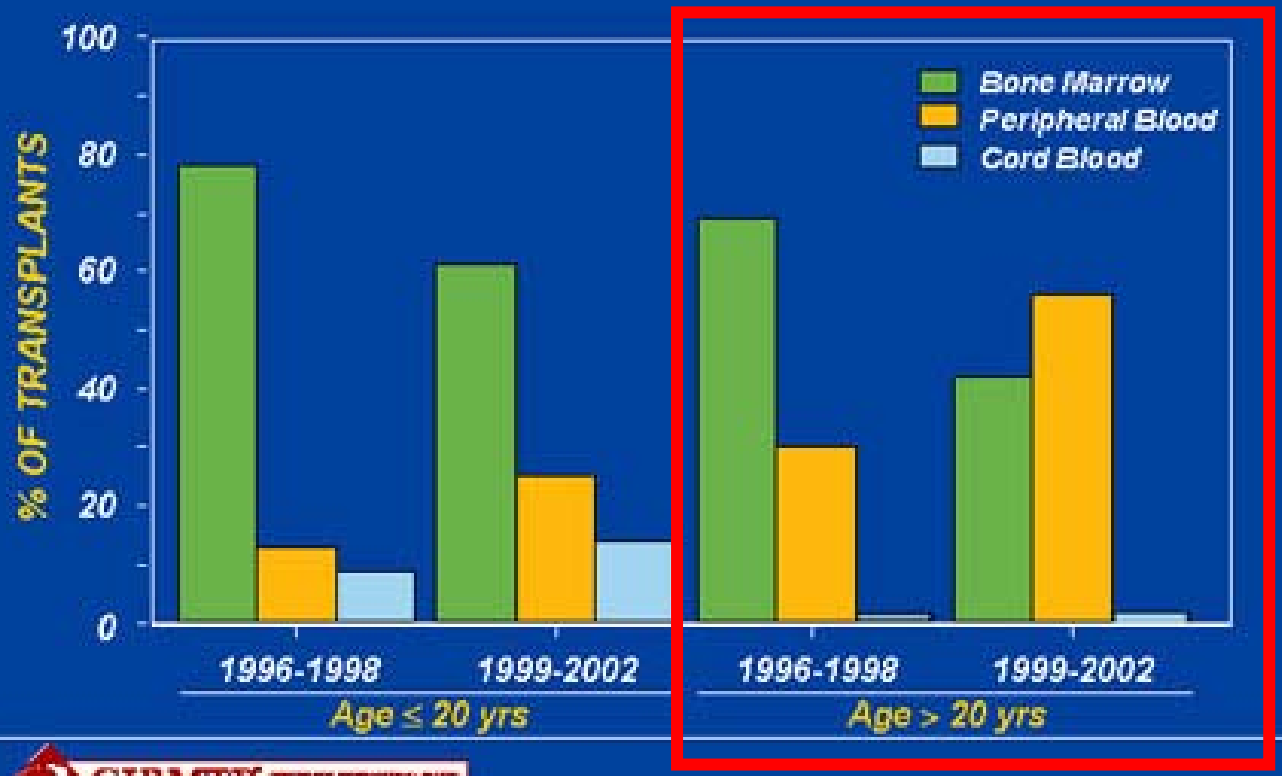
Table 4. Causes of Death after Transplantation of Unrelated Cord Blood or Unrelated Bone Marrow.

Mortality*	Unrelated Cord-Blood Transplant (N=62)	Unrelated Bone Marrow Transplant (N=320)
Related to relapse or progression — no. (%)	19 (31)	118 (37)
Related to transplantation — no. (%)	43 (69)	202 (63)
GVHD†	5 (12)	63 (31)
Toxicity‡	15 (35)	13 (6)
Graft failure or hemorrhage	4 (9)	10 (5)
Infections§	18 (42)	82 (41)
Other or unknown	1 (2)	34 (17)

* The P value for overall causes of death is <0.001 and was determined by Fisher's exact test.
† GVHD denotes graft-versus-host disease.
‡ Death from toxicity in the cord-blood group included cardiac toxicity (three patients), acute respiratory distress syndrome or interstitial pneumonitis (six), and multiorgan failure (six).
§ Infections in the cord-blood group were bacterial (three patients), viral (five), fungal (seven), parasitic (one), and not determined (three).

Rocha V et al. N Engl J Med 2004;351:2276-2285

Allogeneic Stem Cell Sources by Recipient Age, 1996-2002



CIBMTR

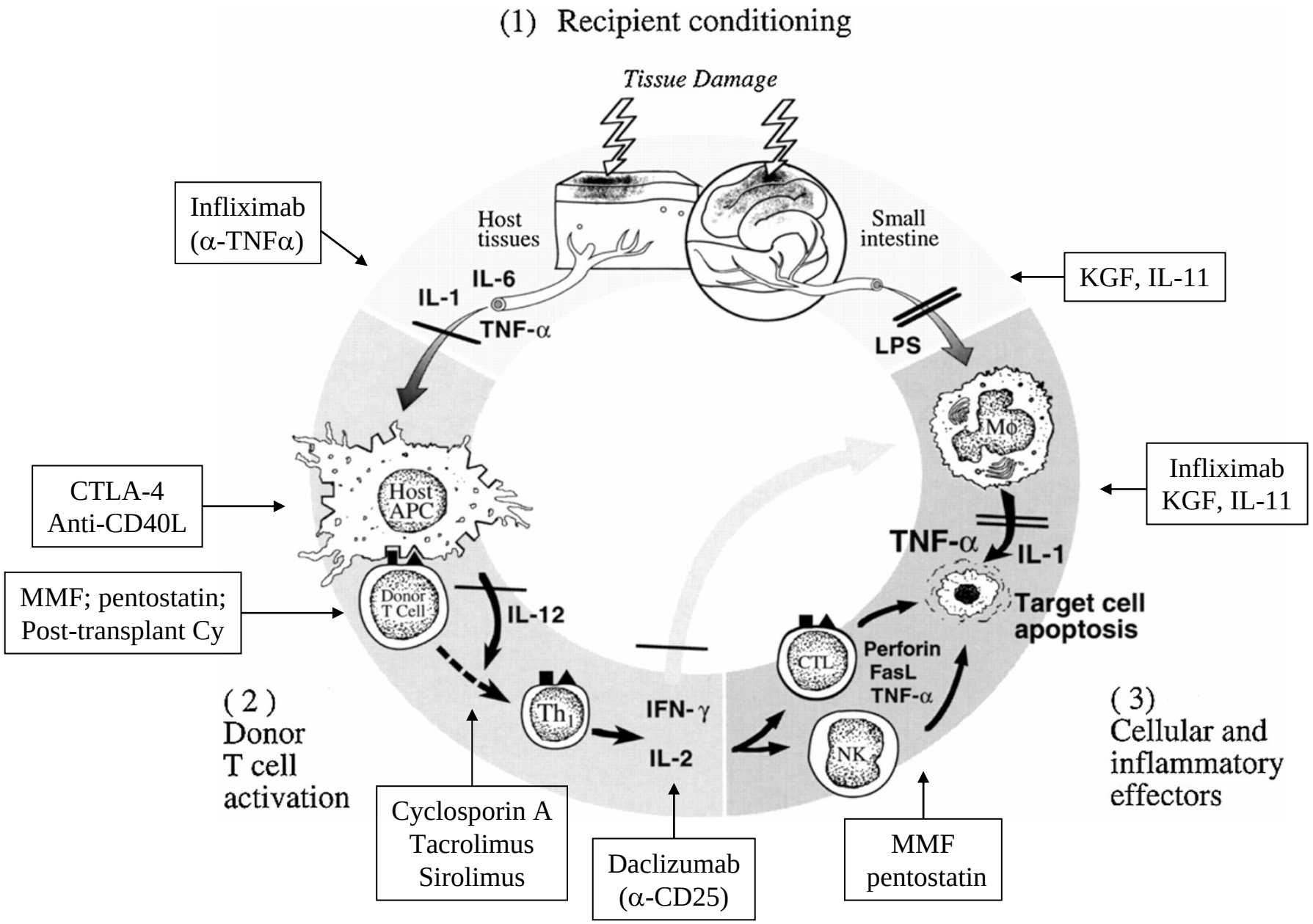
Profilaxis GVHD

Efficacy of Drug Prophylaxis for Acute Graft-Versus-Host Disease†

Drug(s)	GVHD, percent
None	52-100
Methotrexate	56-70
Cyclosporine	33-54
ATG-methotrexate-prednisone	21
Cyclosporine-methotrexate	15-33
Cyclosporine-prednisone	12-21
Cyclosporine-methotrexate-prednisone	9-32

†None of these regimens improve disease-free survival

Fisiología del GVHD



aGVHD

- John Hopkins,blood 2004, n=54, no mieloabl
  - Flu/Cy/TBI; Tac/Micofenolato
  - Ciclofosfamida 50mg/k d3 vs d3-4
  - GVHD IV: 43 vs 78%, GVHD III 20 vs 53% a dia 200
- Mayer, BMT 2005. a o cGVHD
  - Ciclofosfamida 1gr/m2
  - 100% respuesta en piel, 70% en higado, 100% oral, pogre en GI

aGVHD

- Yanada, BMT 2004, aGVHD, Tacrolimus vs ciclosporina
  - N=1935 relacionados, n=777 no relacionados
  - No relac: mejor tacrolimus; relac: no hay diferencia
  - cGVHD III-IV mas raro en Tac
- Lazarus, Blood 2005
  - Fase I aGVHD refractario, n=46
  - Stem cells mesenquimaticas expandidas ex vivo en d0
  - aGVHD II-IV 28%, cGVHD 61%, recaida 24%
- John Hopkins,blood 2004, n=54, no mieloabl
  - Flu/Cy/TBI; Tac/Micofenolato
  - Ciclofosfamida 50mg/k d3 vs d3-4
  - GVHD IV: 43 vs 78%, GVHD III 20 vs 53% a dia 200
- Bortezomib, SAHA (inh deacetilasa de histonas), inh JAK3, IL-7, IL-10, anti-citokinas

Therapy for chronic GVHD: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone

Koc S. Blood 2002

→ Corticoides

→ Corticoides + Ciclosporina

Seguimiento 1.6 a

54% logro suspender tratamiento a 5ª

Micofenolato

- Segunda línea para cGVHD
- 46-76% respuesta en refractarios a corticoides
- No se miden niveles plasmáticos

Sirolimus

- Inhibidor de rapamicina
- 15/16 cGVHD refractarios a corticoides respondieron
- Aumenta mucho toxicidad si se administra junto con tacrolimus y corticoides
- Rango terapéutico 3-12 ng/ml

Talidomida

Kulcarni et al. BMT 2003

- cGVHD refractario a corticoides
- 500-1200 mg/d
- 22% CR

Randomized clinical trial of thalidomide, cyclosporine, and prednisone versus cyclosporine and prednisone as initial therapy for cGVHD
Arora M, et al. Biol Blood Marrow Transplant 2001

→ thalidomide, cyclosporine, and prednisone
→ cyclosporine, and prednisone
No hay diferencia

Rituximab

- 375 mg/m2/semana x 4
- 18/24 respondieron, serie mas grande Dana Farber. Biol BMT 2002

KGF

- Factor de crecimiento de keratinocitos
- Efecto *in vivo* e *in vitro.*
- Induce proliferation de queratinocitos, neumocitos II, hepatocitos y epitelio GI

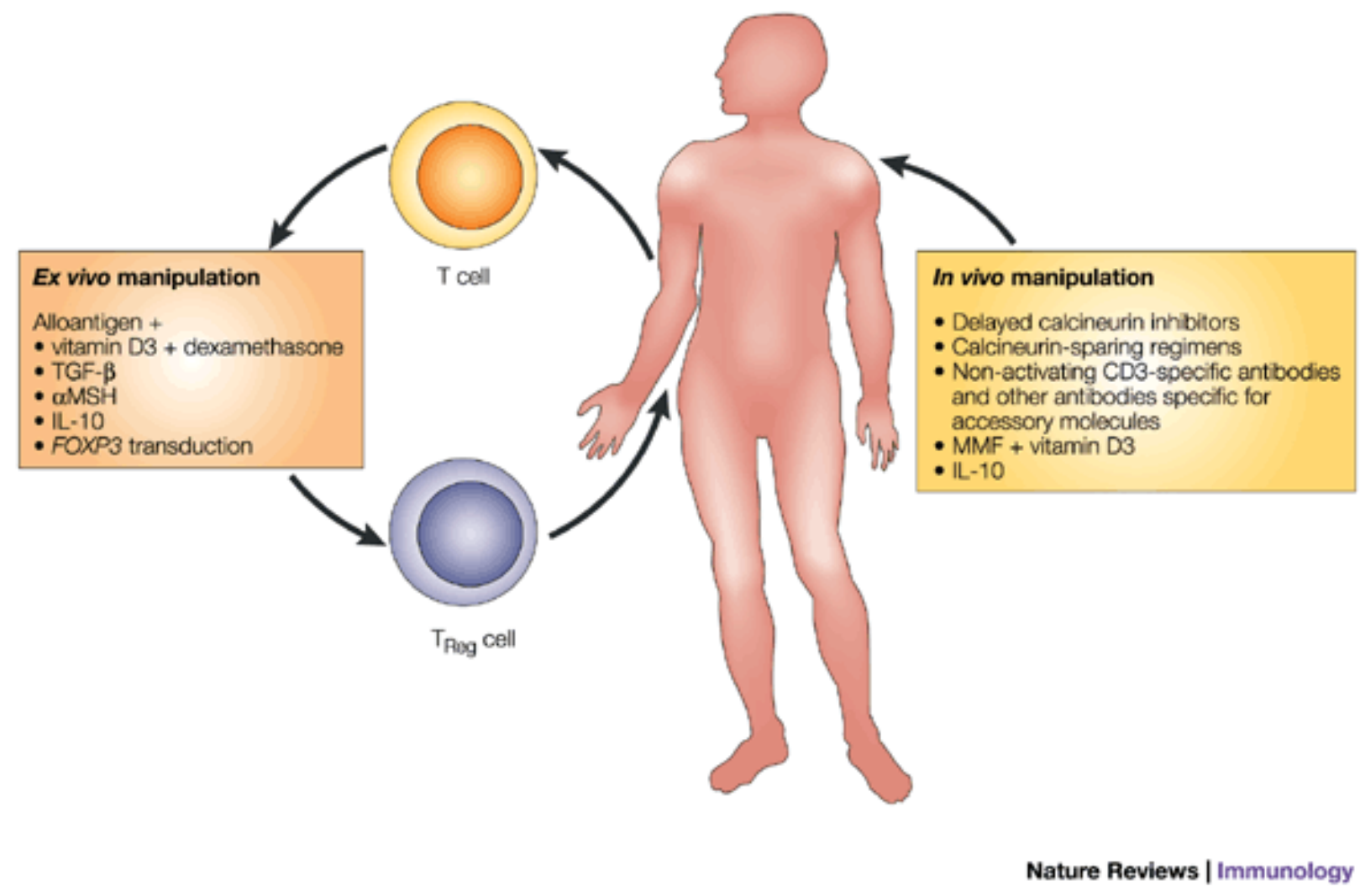
Otros

- Ciclofosfamida
- Hidroxicloroquina
- Pulsos alta dosis corticoiodes
- Fotoforesis extracorporea

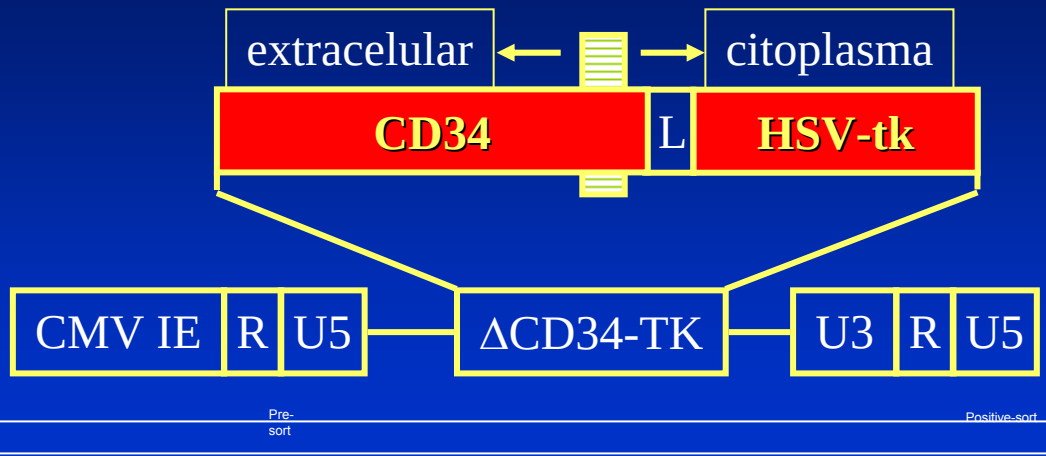
Se puede separar GVHD de GVL??

- Pacientes con GVHD tienen menos recaídas
- Trasplantes singeneicos tienen menos GVHD y mas recaídas
- La profilaxis de GVHD ↓ GVL?
- El tratamiento del GVHD ↑ el riesgo de recaída??

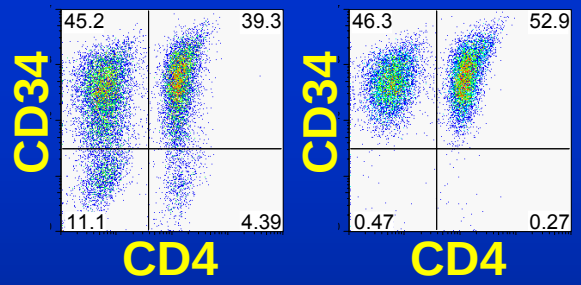
T_{Reg} y GVHD


T cell
Ex vivo manipulation
Alloantigen +
• vitamin D3 + dexamethasone
• TGF-β
• αMSH
• IL-10
• FOXP3 transduction
In vivo manipulation
• Delayed calcineurin inhibitors
• Calcineurin-sparing regimens
• Non-activating CD3-specific antibodies and other antibodies specific for accessory molecules
• MMF + vitamin D3
• IL-10
TReg cell
Nature Reviews | Immunology

Gen suicida



Protocolo de activacion y transduccion



huPBMC
anti-CD3/CD28 beads
IL-2

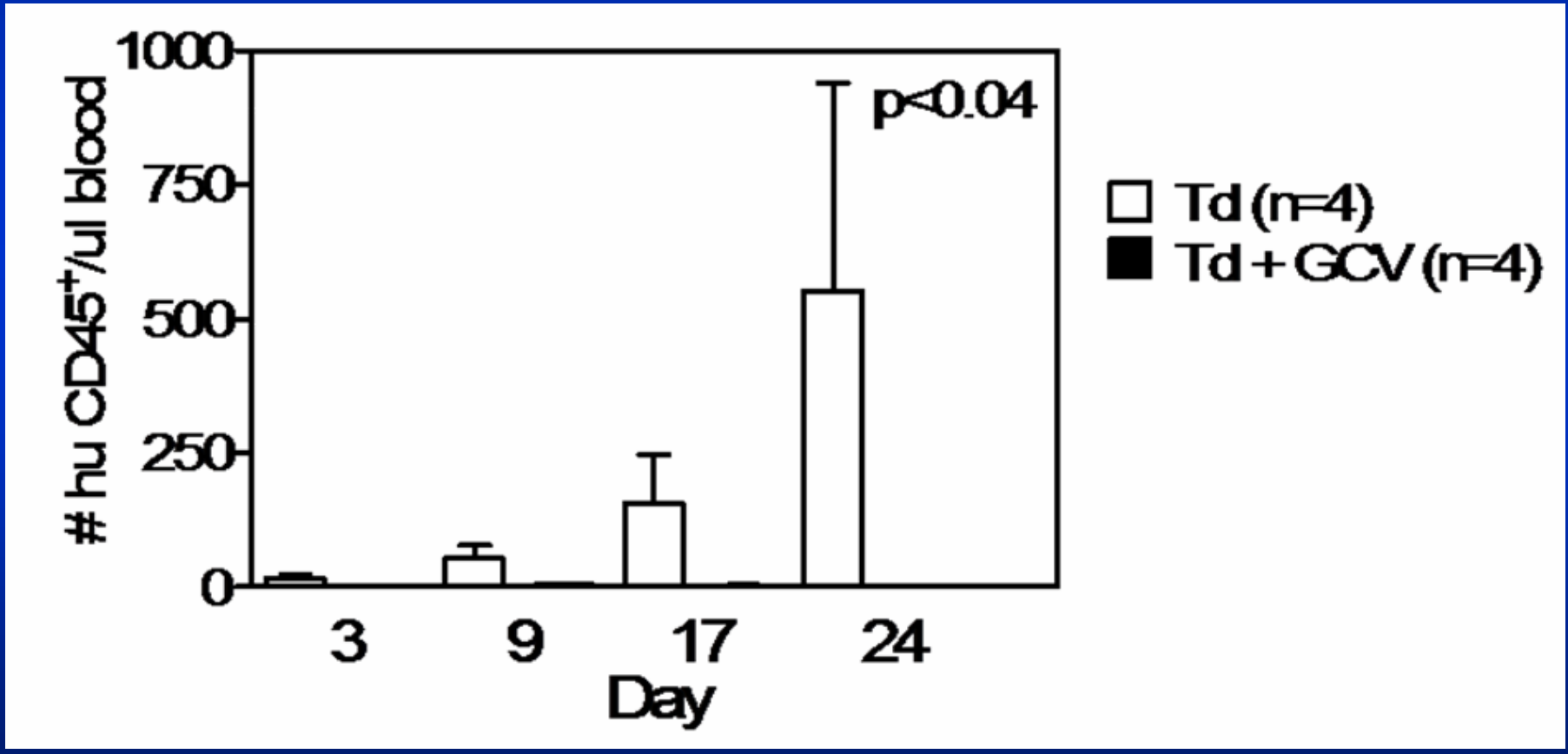
VSV-G pseudotyped
MLV-based retrovirus
CD34-tk

CD34 MACS
99% pureza

Activacion	Infeccion	Expansion	Aislamiento

0 48 56 96 hours

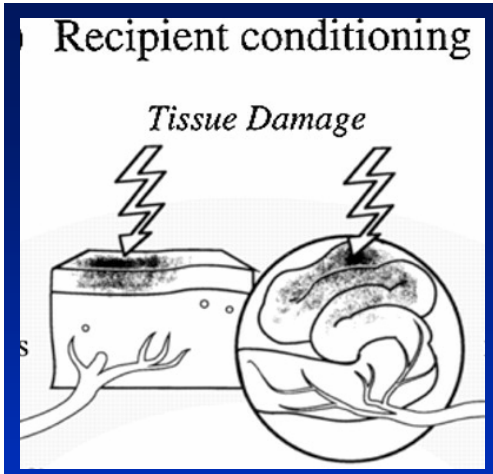
Terapia genica suicida para controlar GVHD



Prevencion de GVHD usando terapia genica suicida (ΔCD34-TK/GCV)

No Ganciclovir

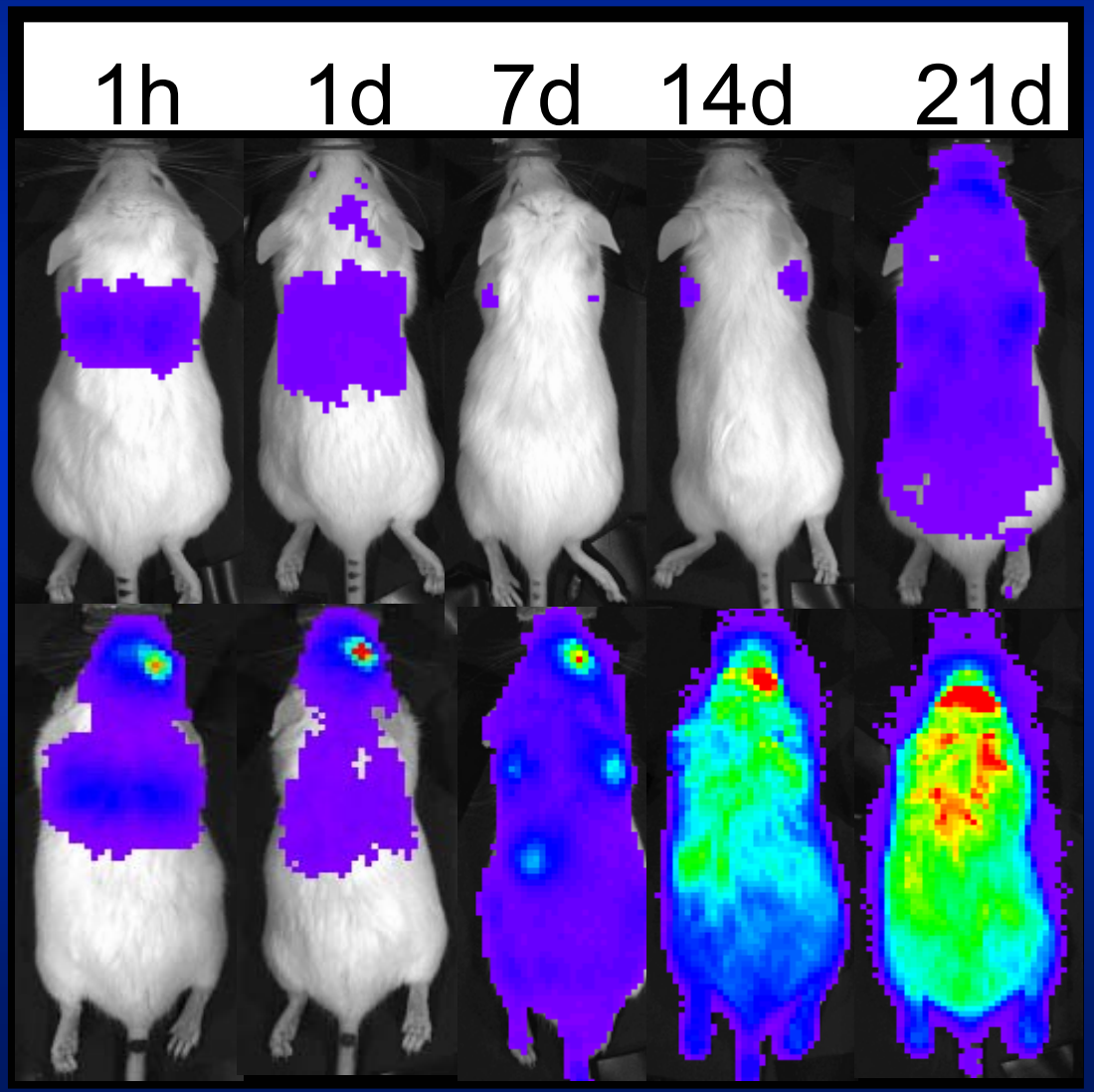
Ganciclovir dias 1-7



1. Distanciar condicionamiento de infusión HSC
2. ↓ intensidad condicionamiento
3. radiacion nodal total

Inyección vena de la cola

Inyección retro-orbital



CONCLUSIONES

1. Aun sabemos poco de GVHD
2. Hay que estudiar los mecanismos para encontrar mejores tratamientos
3. Lo mas importante en trasplante es la inmunomodulacion
4. No abandonar a los GVHD refractarios a corticoides, aun quedan cosas que hacer