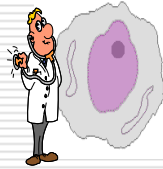


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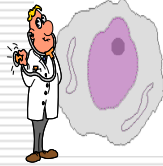
Graft-versus-Host disease Physiopathology

Table 1. *The Revised Billingham Criteria for the Development of GVHD, with Revision for Homing*

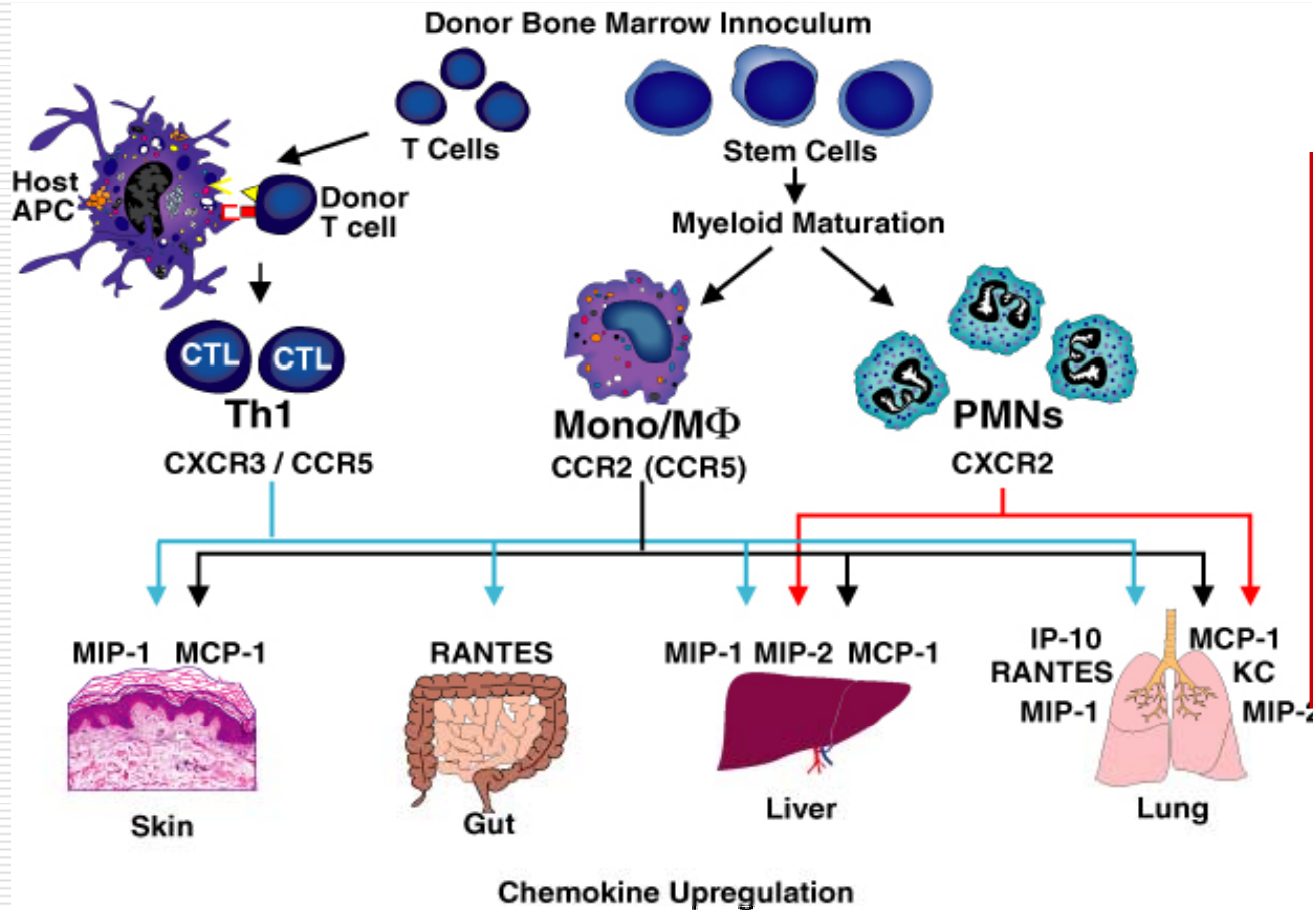
- (1) The host must be incapable of rejecting the graft**
 - (2) The graft must contain immunocompetent cells**
 - (3) There must be incompatibilities in transplantation antigens between donor and host**
 - (4) The effector cells must migrate to the target tissues**
-



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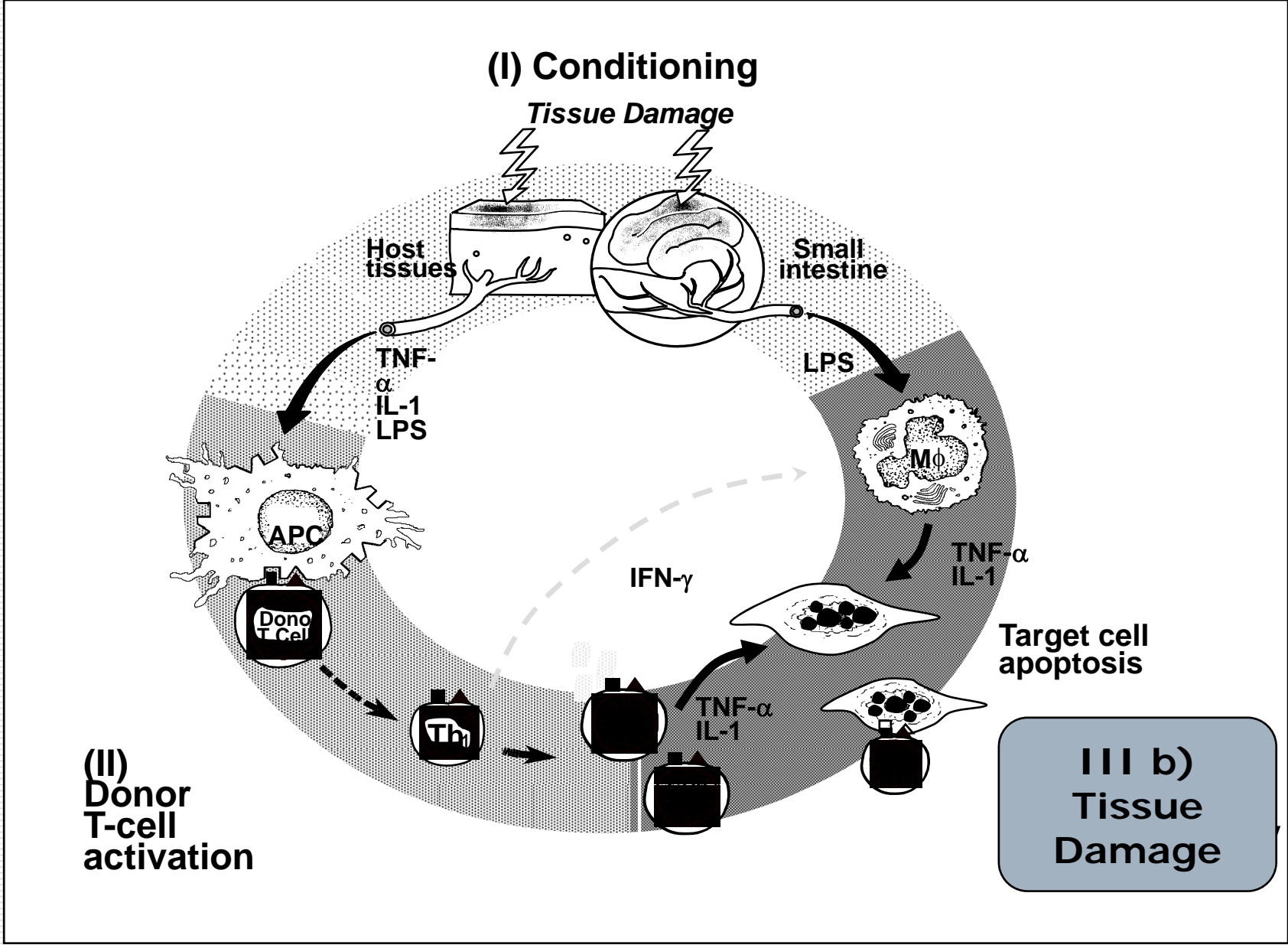
Graft-versus-Host disease Physiopathology



Tissue-tropic
effector T cells:
generation and
targeting
Opportunities

Nature Review
Immunology
September 2006







Graft-versus-Host disease Physiopathology

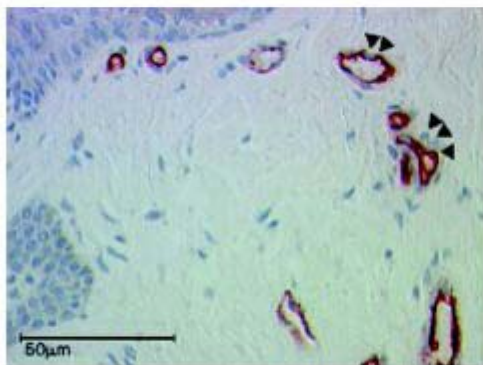
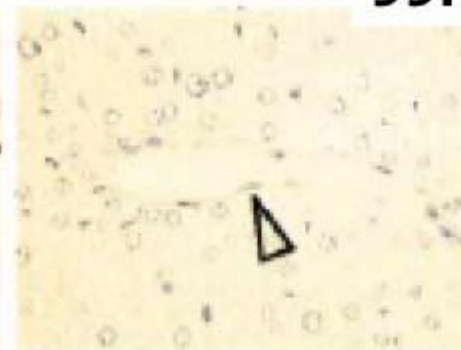
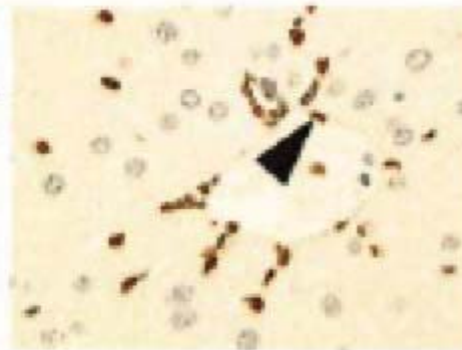
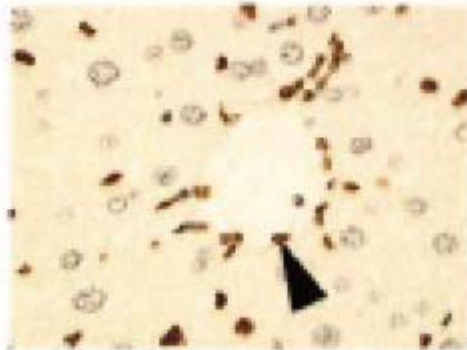
Endothelial cells
WT

LPR

GLD

Mice
Blood 2002;
99: 2240-7

Liver



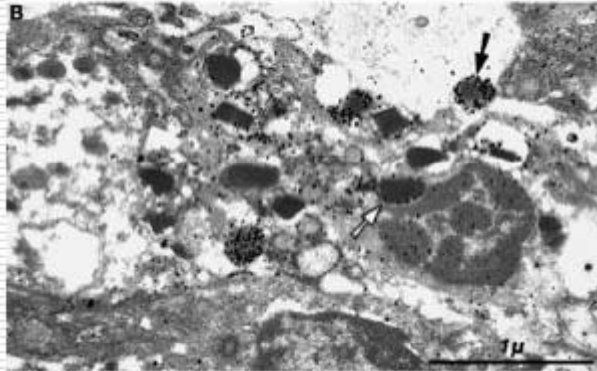
Human
Lancet 2002; 359: 2078-83



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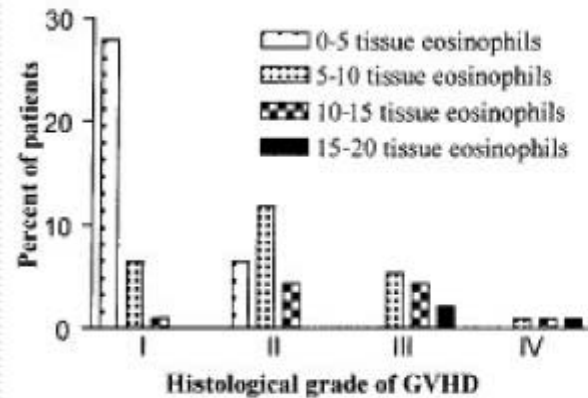
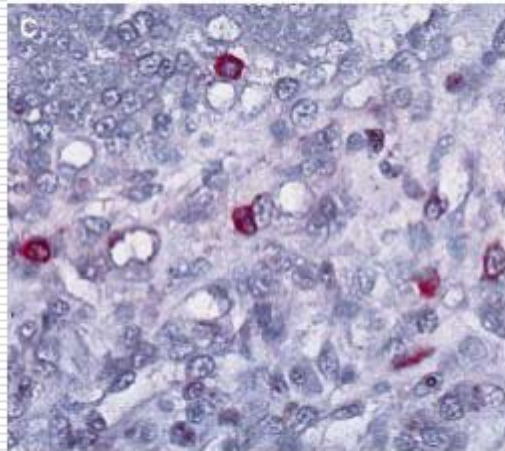


Graft-versus-Host disease Physiopathology



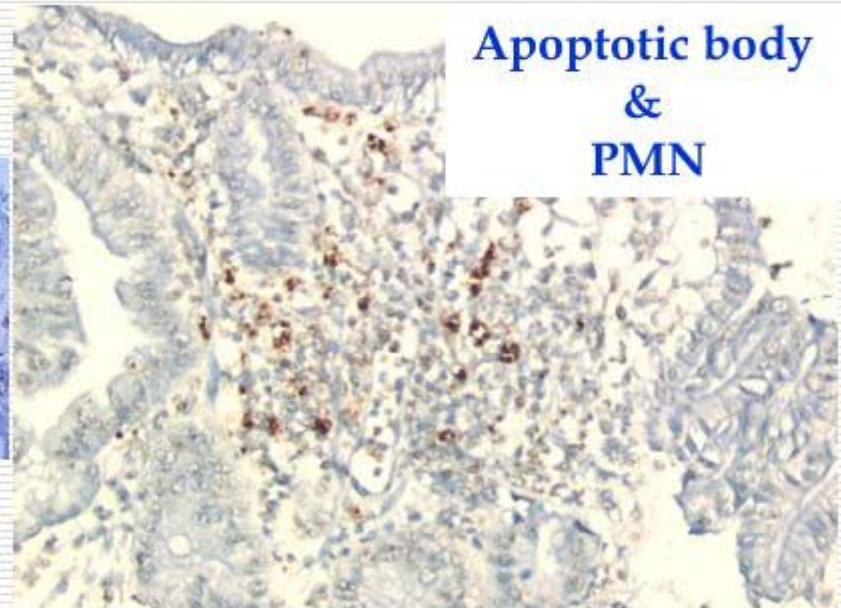
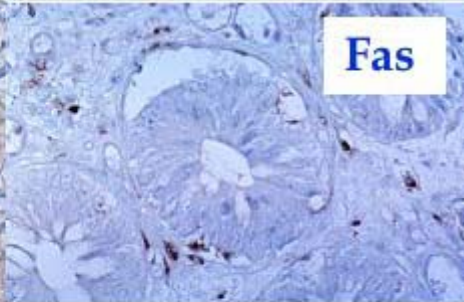
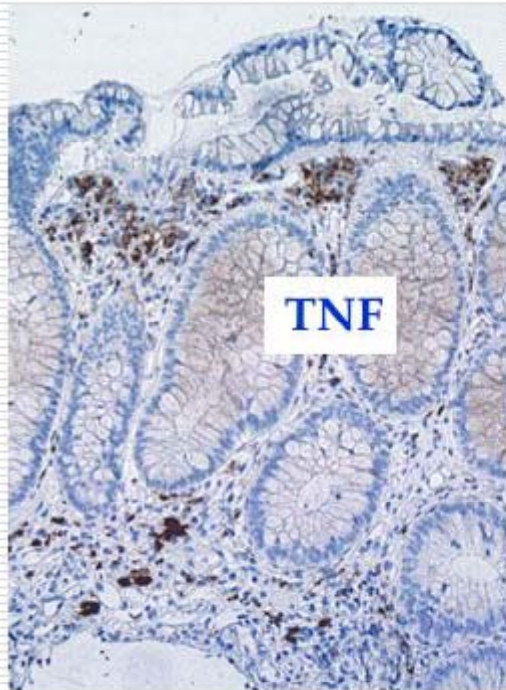
INSERM ERM 0220
Blood 2002; 99: 3033
Human GI GvHD

Eosinophils
&
GvHD





Graft-versus-Host disease Physiopathology

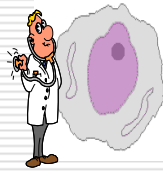


INSERM ERM 0220

Blood 2004; 103: 50-7

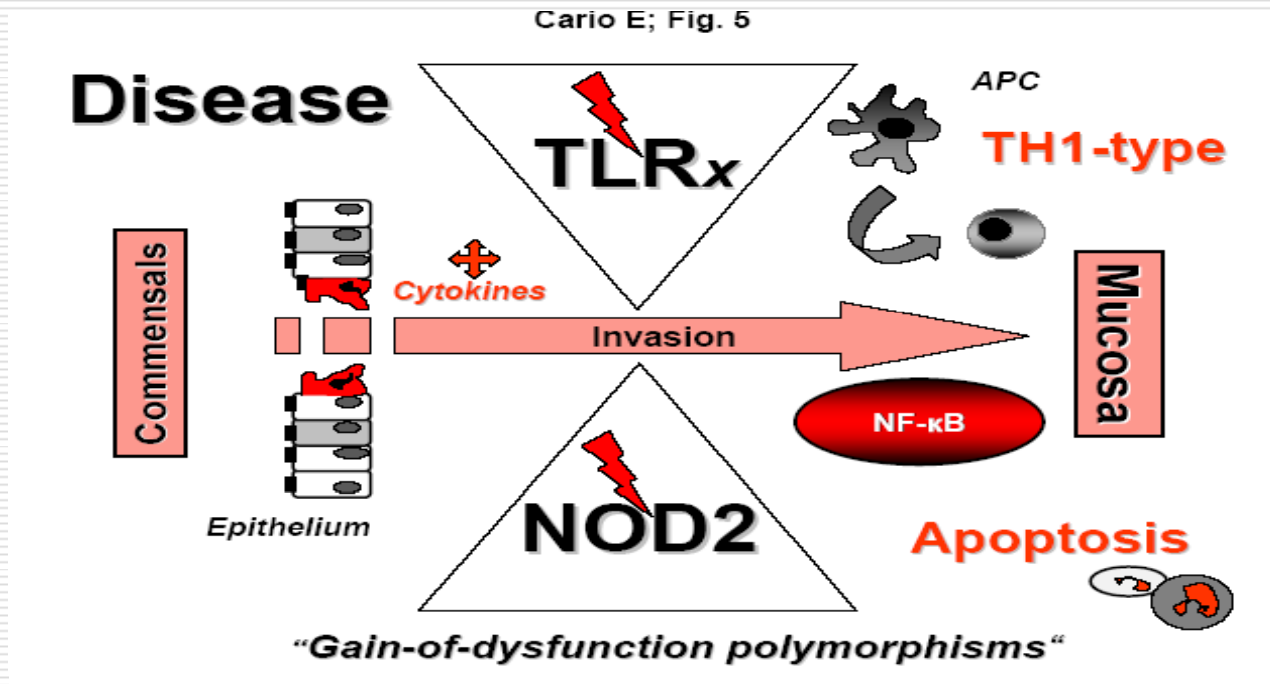
Human GI GvHD



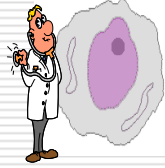


Graft-versus-Host disease Physiopathology

Inflammatory bowel diseases:
Mucosa associated receptors (PRM) decide on
tolerance versus activation

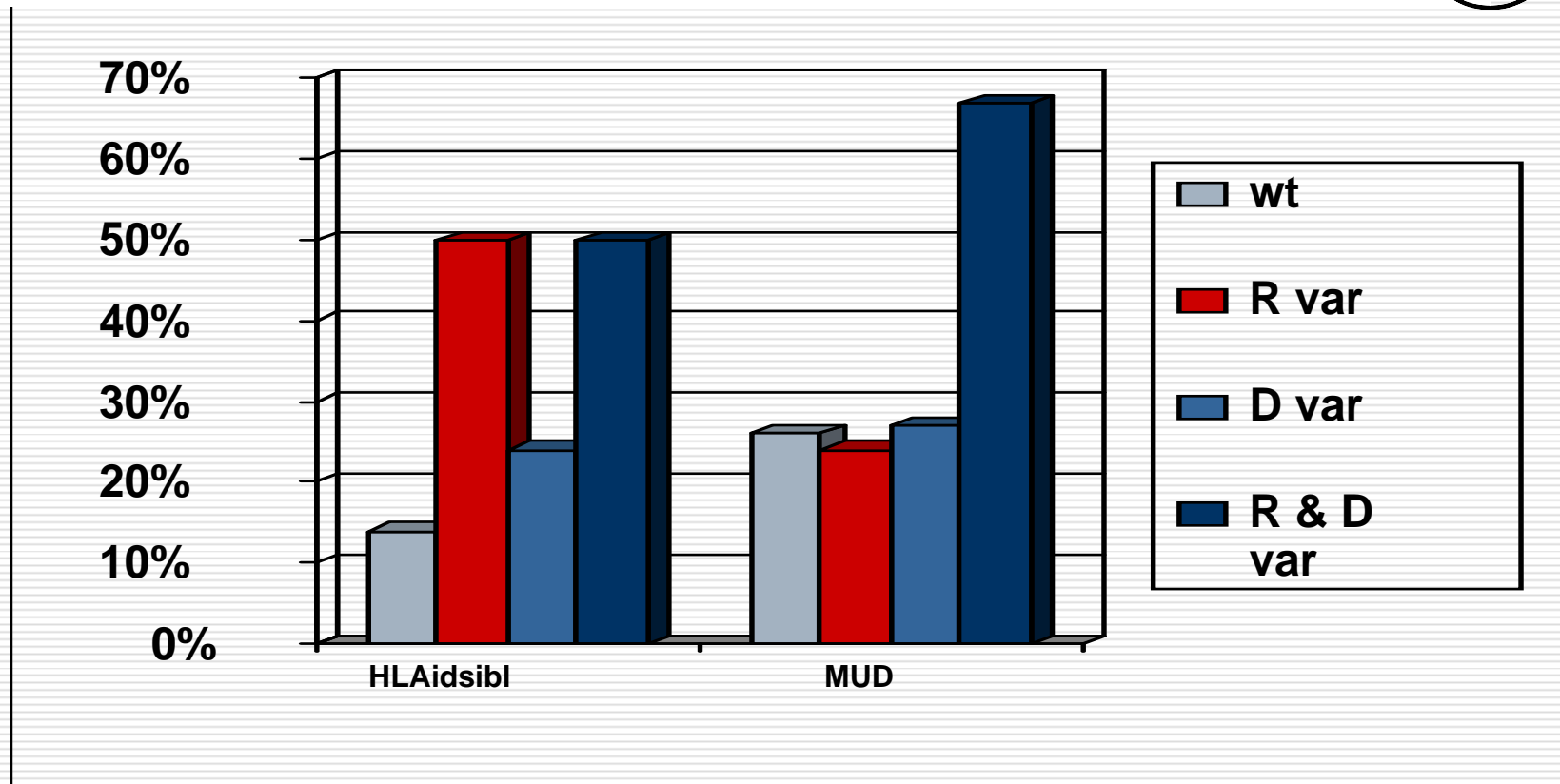
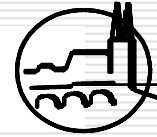


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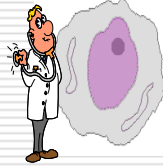


Graft-versus-Host disease Physiopathology

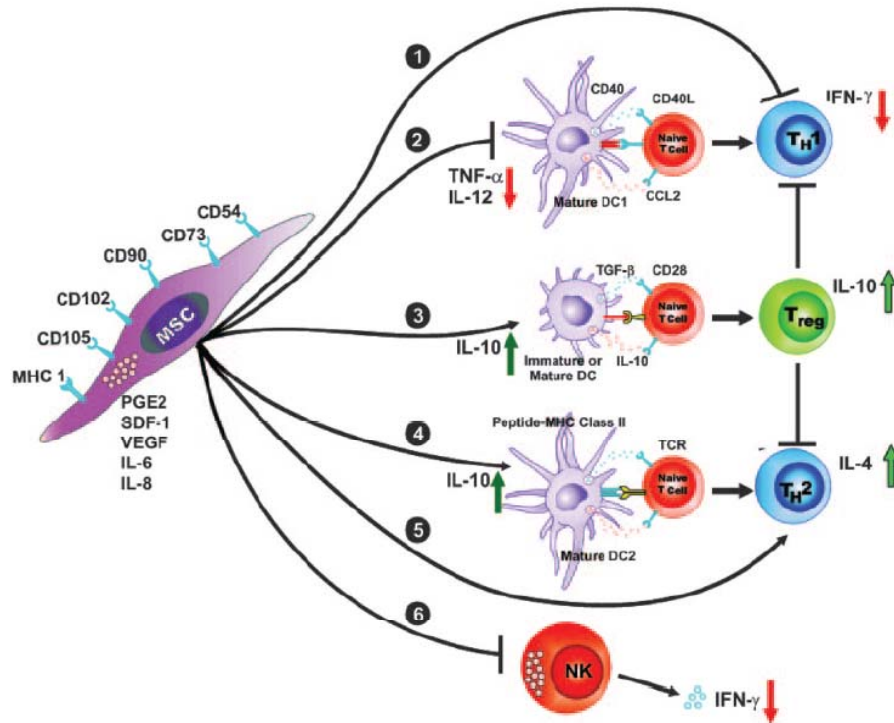
NOD2/CARD15 variants associate with severe GvHD



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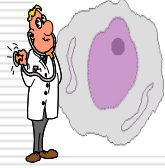
Graft-versus-Host disease Physiopathology



Mesenchymal
Stem Cells
And
GvHD?



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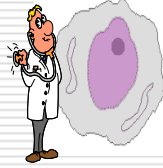


Graft-versus-Host disease Physiopathology

Chronic Graft-versus-Host Disease

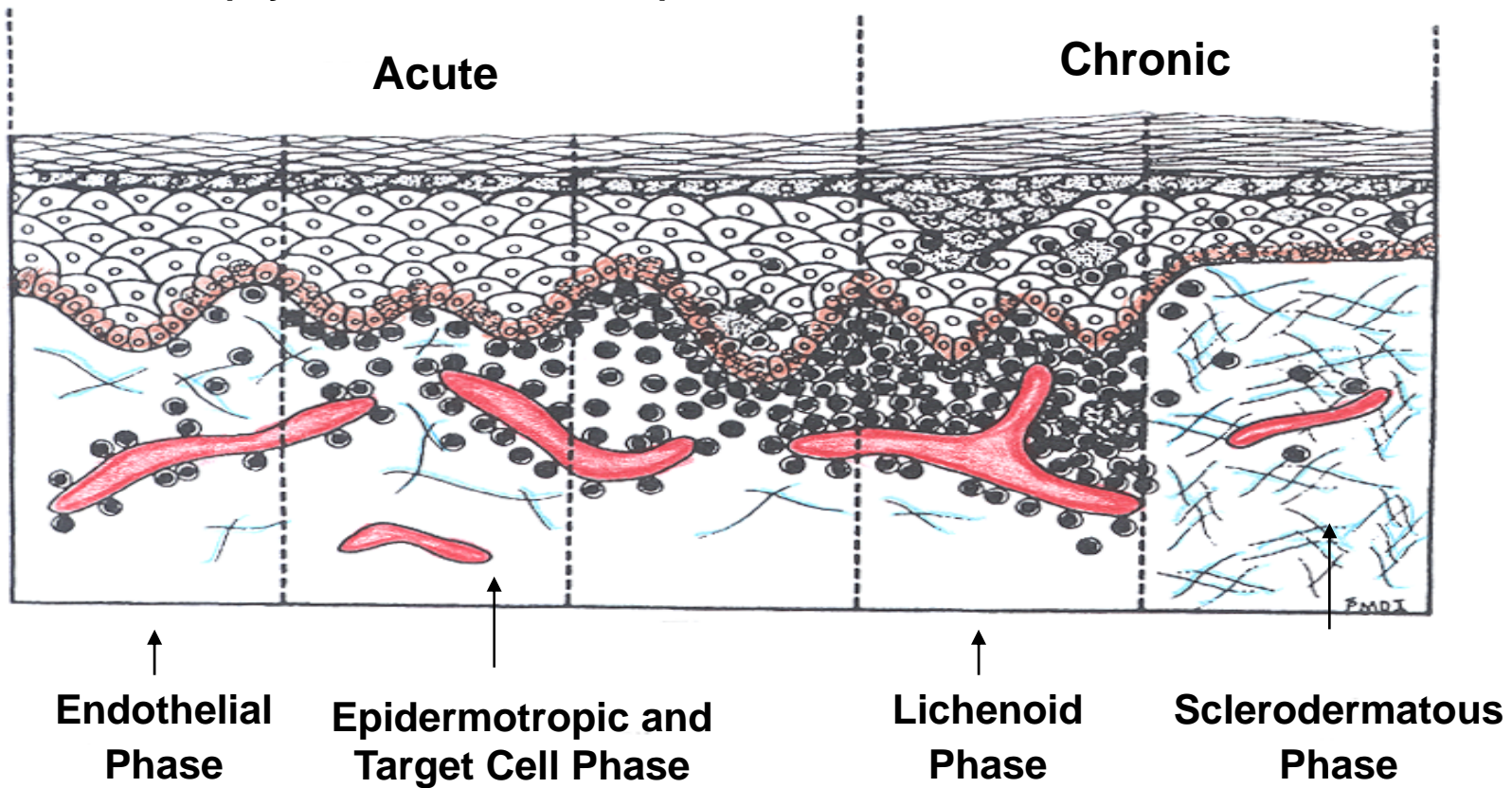


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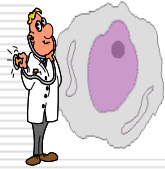


Graft-versus-Host disease Physiopathology

Gilliam and Murphy, GVHD 2nd ed., 1997, p. 299



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Graft-versus-Host disease Physiopathology

1) Haploidentical P → F1 (MHC I, II, minor H)

- B6 → B6D2F1: acute GVHD
- D2 → B6D2F1: chronic GVHD
- D2: ↓ CD8+, ↓ IFN γ

More CD8s convert to acute GVHD

2) B10.D2 → Balb (minor H)

- Skin disease, immunodeficiency
- Sub-lethal radiation (600 day)

Lethal radiation → acute GVHD

(mixed chimerism needed for chronic?)



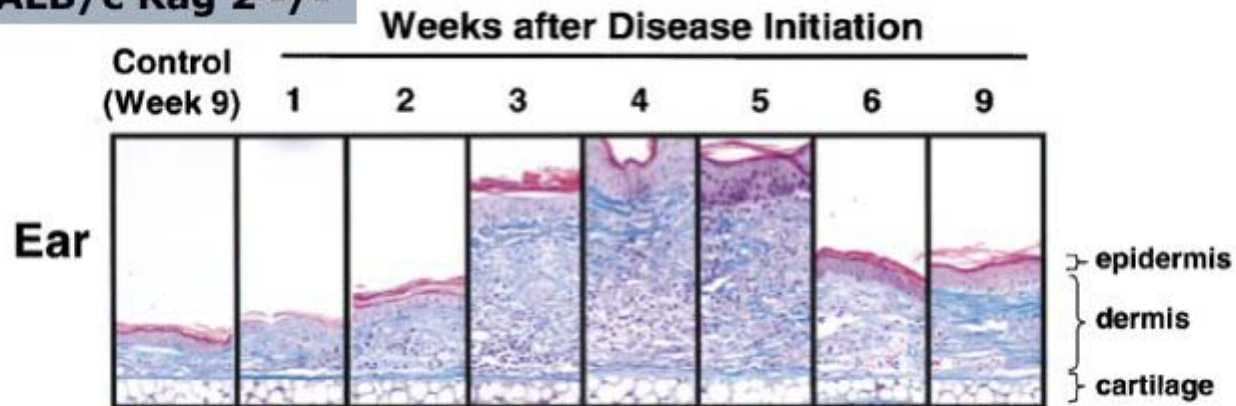


Graft-versus-Host disease Physiopathology

ARTHRITIS & RHEUMATISM 2004;5: 1319–1331

A Modified Model of Graft-Versus-Host–Induced Systemic Sclerosis (Scleroderma) Exhibits All Major Aspects of the Human Disease

B10.D2 > BALB/c Rag 2 -/-



CD4-mediated; required CD40/ Cd80/86 donor APC
Blood 2005;105: 2227–2234



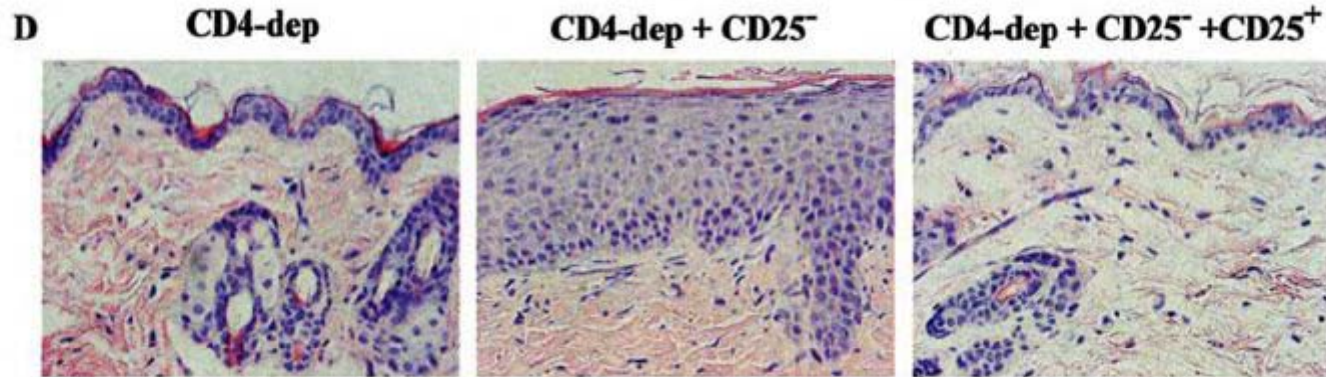


Graft-versus-Host disease Physiopathology

Blood 2006;107: 2993–3001

Donor CD4⁺ T and B Cells in Transplants Induce
Chronic Graft versus Host Disease with Autoimmune Manifestations

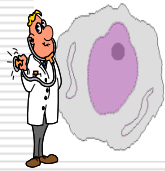
**DBA/2 (H-2d) spleen cells into minor mismatched
sub-lethally irradiated BALB/c (H-2d)**



Required both donor CD25-CD4⁺ T and B cells
Donor T-reg cells prevented the disease induction.

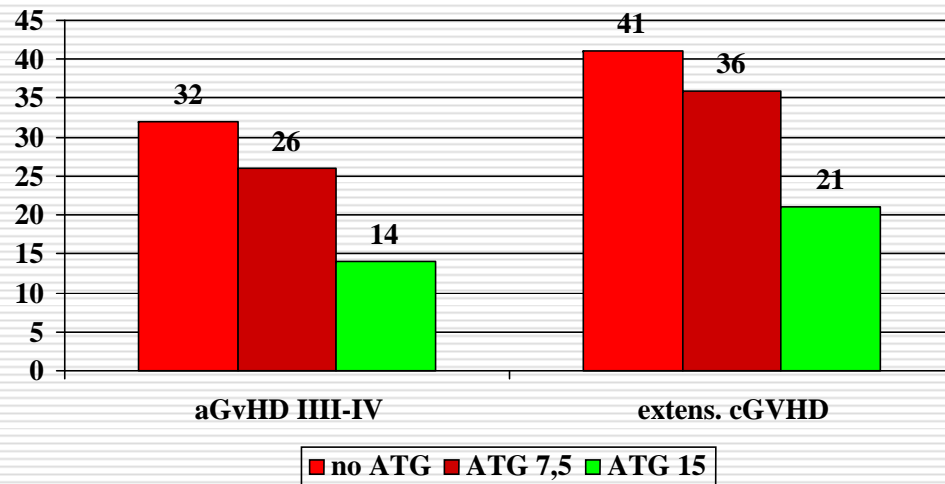


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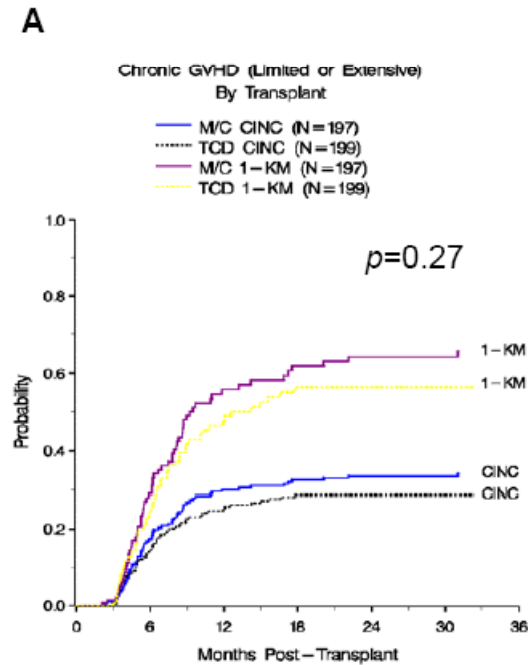


Graft-versus-Host disease Physiopathology

Is T-cell depletion associated with less chronic GVHD ?

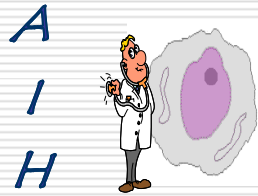


BB & MT 8:656-661 (2002)



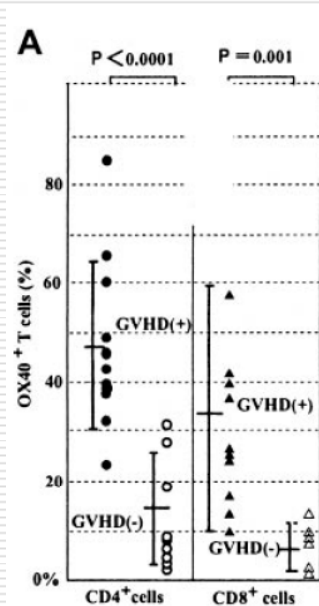
Blood. 2005;106:3308-3313





Graft-versus-Host disease Physiopathology

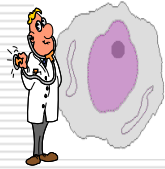
- ✓ Amplified clonal T-cell & c.GvHD. *BMT* 2002; 30: 509-15
- ✓ OX40 (CD134) CD4+ CD8+ T-cell & c.GvHD. *Blood* 2001; 98: 3162-64



**both OX40+ CD4+ and
OX40+ CD8+ T cells were
higher in patients with c.GVHD
than those without (P < .0001
and P < .001, respectively)**



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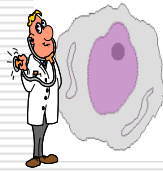


Graft-versus-Host disease Physiopathology

- ✓ High levels of **IL-1**, **IL-6**, **IFN**, and **TNF** are associated with more severe chronic GVHD
- ✓ High serum **TGF** also was associated with chronic GVHD independent of platelet and white blood cell counts
- ✓ Patients with chronic GVHD have low levels of **IL-10** (anti-inflammatory) and Ig production

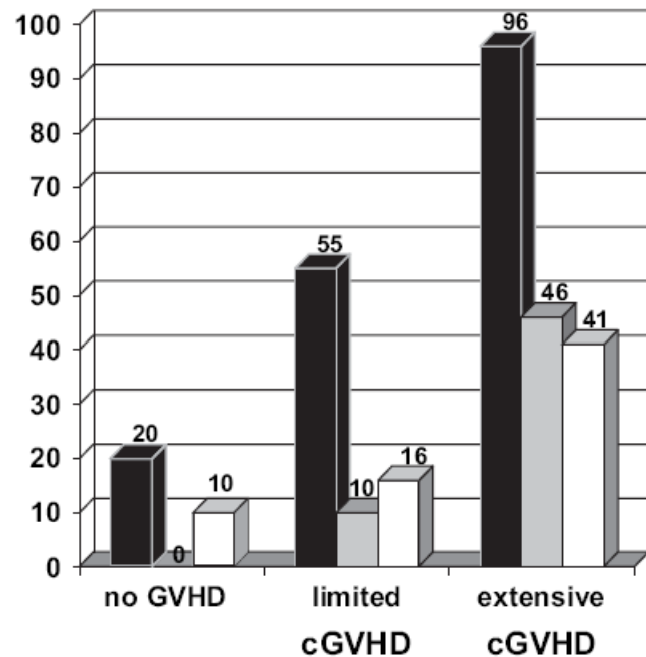


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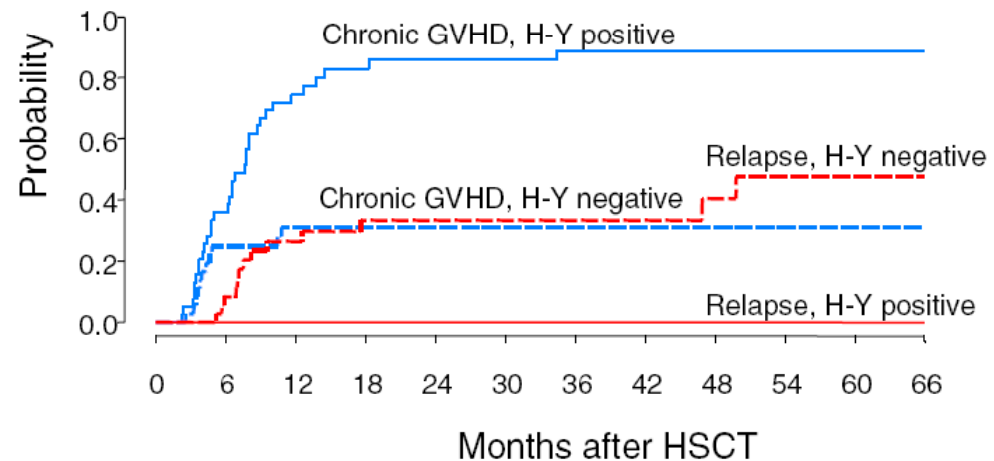
Graft-versus-Host disease Physiopathology

Transplantation. 1988;46:238–240.
Experimental Hematology 34 (2006) 389–396

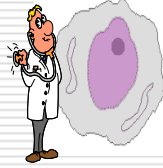


Blood. 2005;105:2973-2978

DBY; UTY; ZFY; RPS4Y; EIF1AY

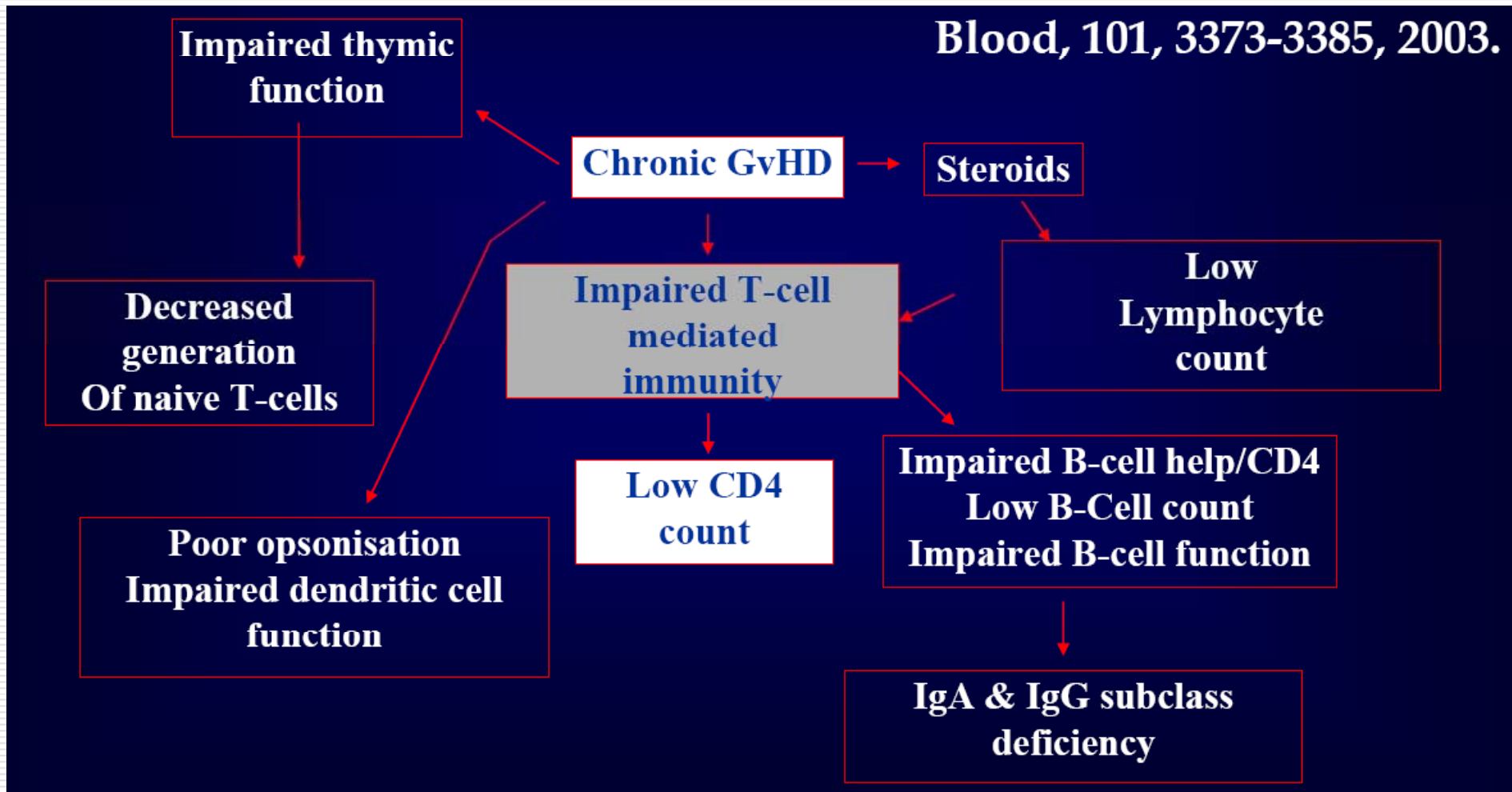


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Graft-versus-Host disease Physiopathology

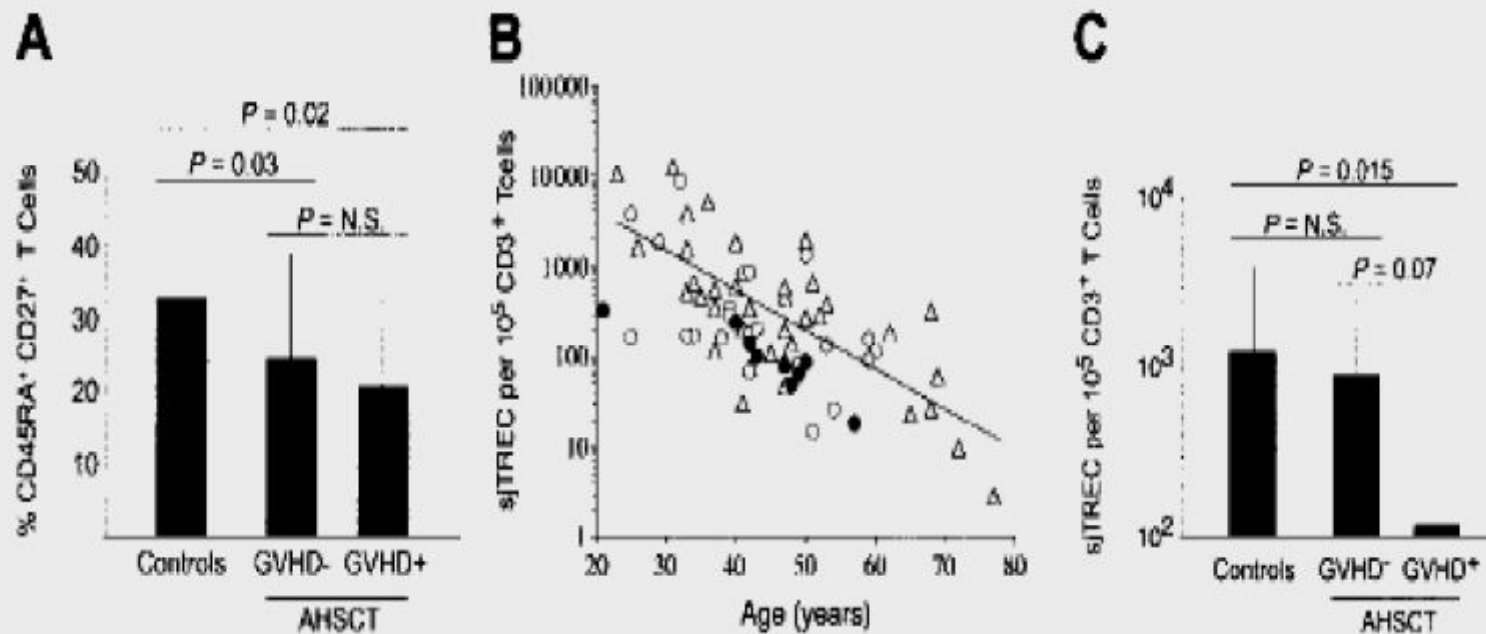
Blood, 101, 3373-3385, 2003.



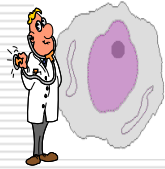


Graft-versus-Host disease Physiopathology

Reduced TREC associate with cGVHD



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Graft-versus-Host disease Physiopathology

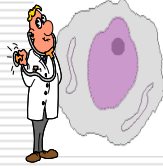
Prognostic factor	aHR (95%CI)*	P
Extensive chronic GvHD within 1 yr	2.94 (1.26-6.88)	0.013
TBI or TAI	3.11 (1.24-7.83)	0.016
Negative CMV donor to positive recipient	2.53 (1.08-5.94)	0.033

1985-2000:

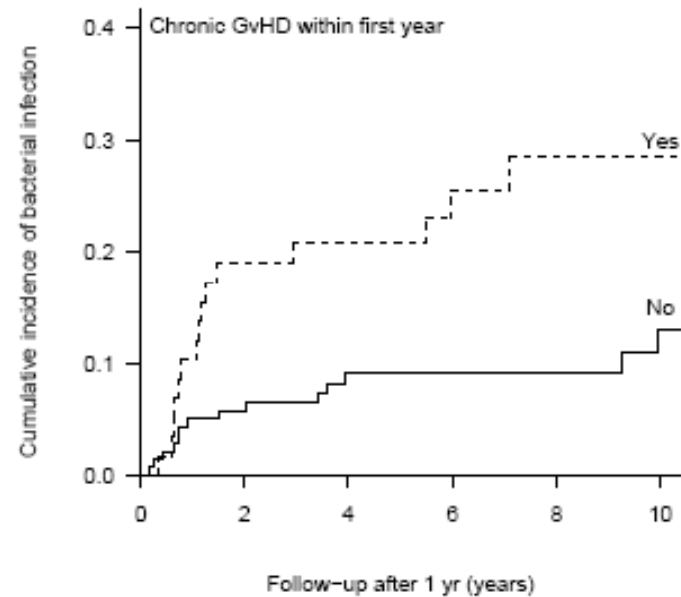
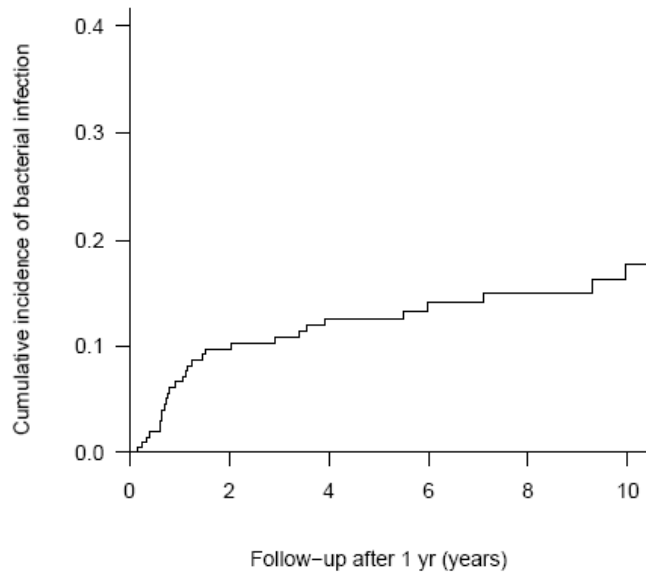
- ✓ 198 patients / HLA id. sibling D
- ✓ Good risk ; i.e. AML CR, CML 1st CP, SAA
- ✓ > 1year without relapse



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Graft-versus-Host disease Physiopathology

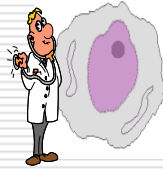


1985-2000:



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EDITORIALS



Graft-versus-Host Disease — From the Bench to the Bedside?

Gérard Socié, M.D., Ph.D.

***N. Engl. J. Med.* 353;13: September 29, 2005**

**2nd ESH EBMT
Teaching course
GvHD / GvL
2007**



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