Graft-versus-Host disease Physiopathology

Gérard Socié, MD PhD
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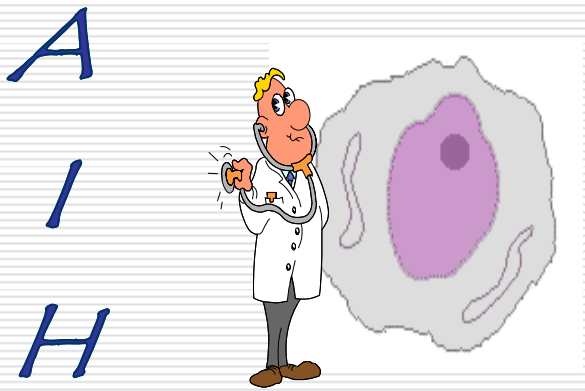

Translating experimental into clinical knowledge

Acute Graft-versus-Host Disease

Graft-versus-Host disease Physiopathology

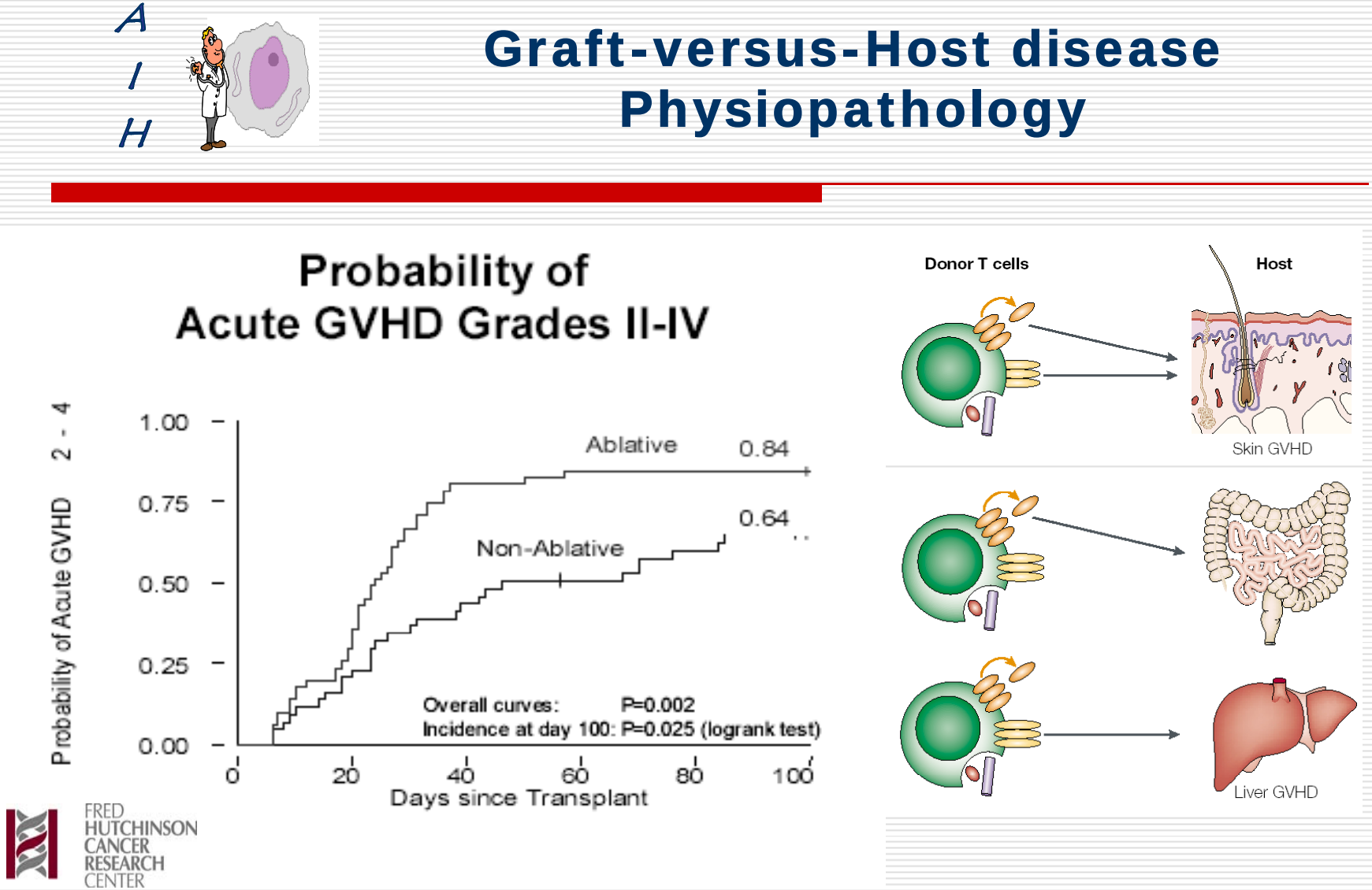

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Table 1. *The Revised Billingham Criteria for the Development of GVHD, with Revision for Homing*

(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

Billingham; ***Nature*** 1966

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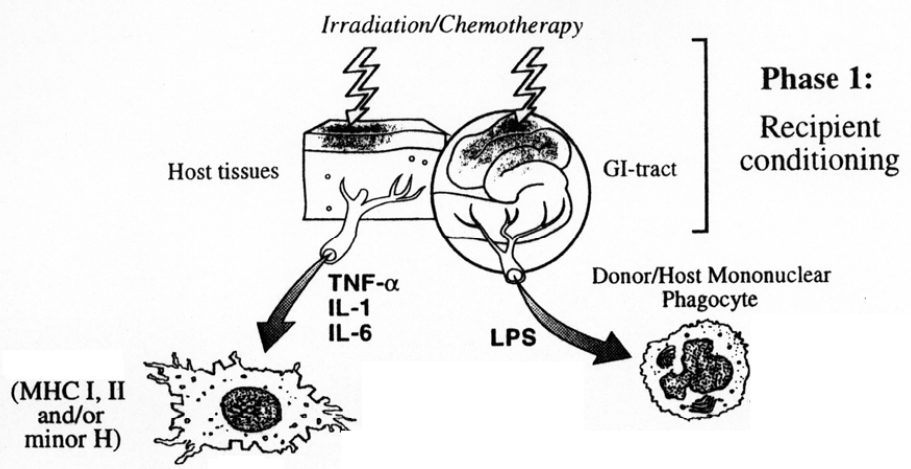

Cytokines increased expression of MHC antigens and adhesion molecules enhance the recognition of MHC / minor Ag by mature donor T-cells

<u>Phase I</u>. Induction of inflammatory cytokines & damage + activation of host tissue during conditioning

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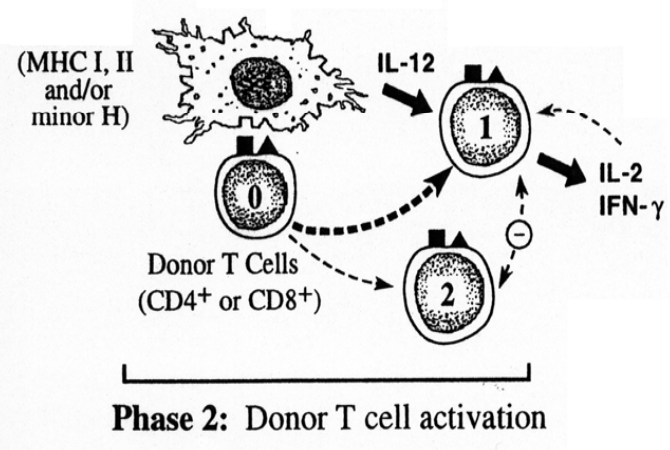
Phase 2: Donor T-cell activation



Phase 2: Donor T cell activation

- **Proliferation of Th1 T cells and secretion of IL-2 & IFNγ.**
- **IL-2 & IFNγ :**
  - ❖ **induce further T-cell expansion,**
  - ❖ **induce CTL and NK responses**
  - ❖ **Prime macrophages to produce IL-1 and TNFα**

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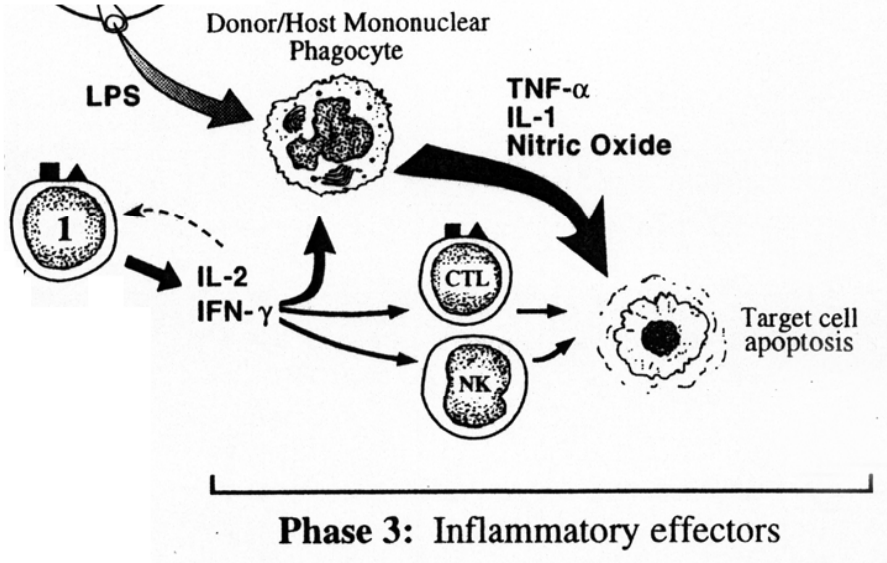
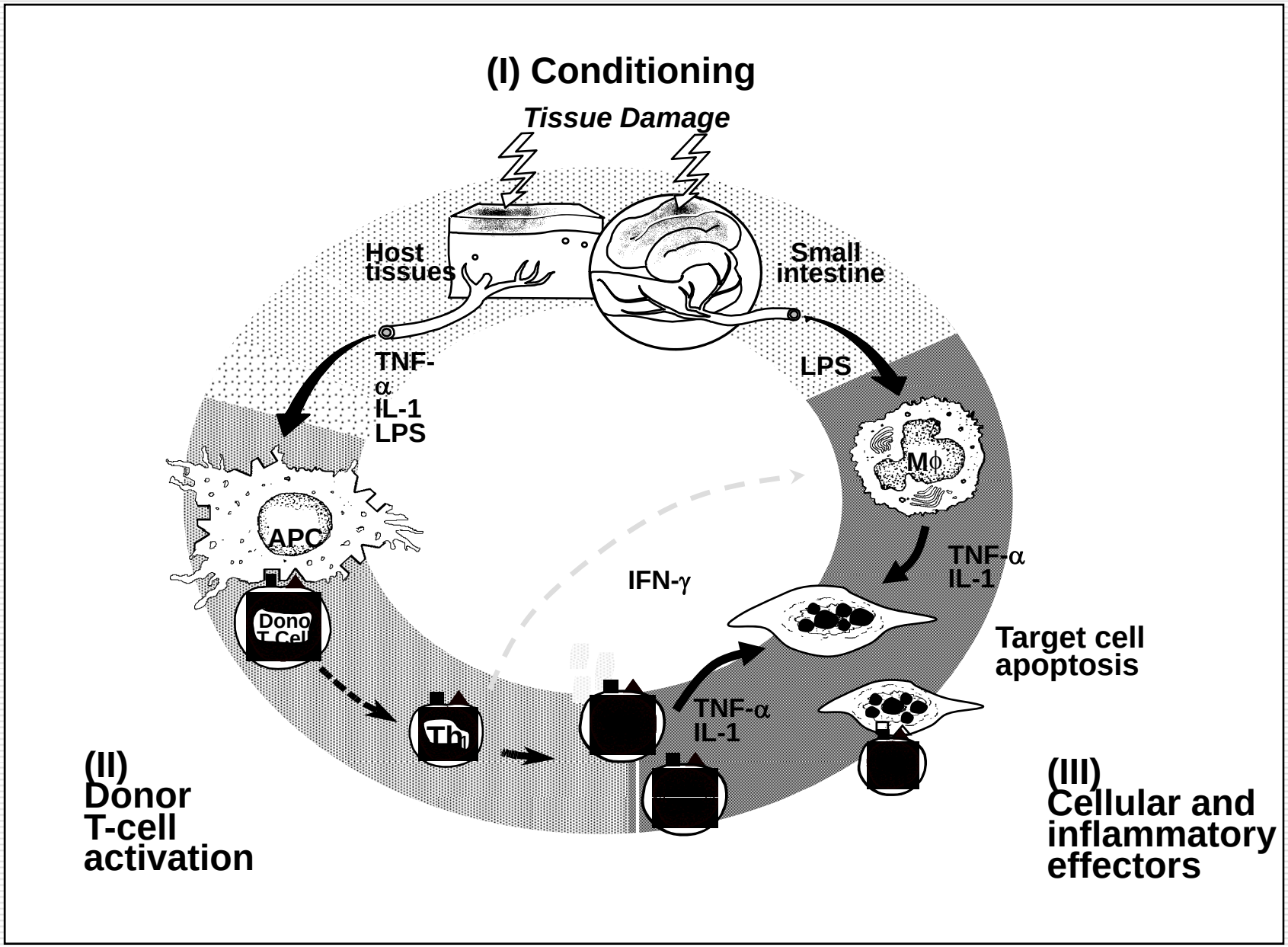
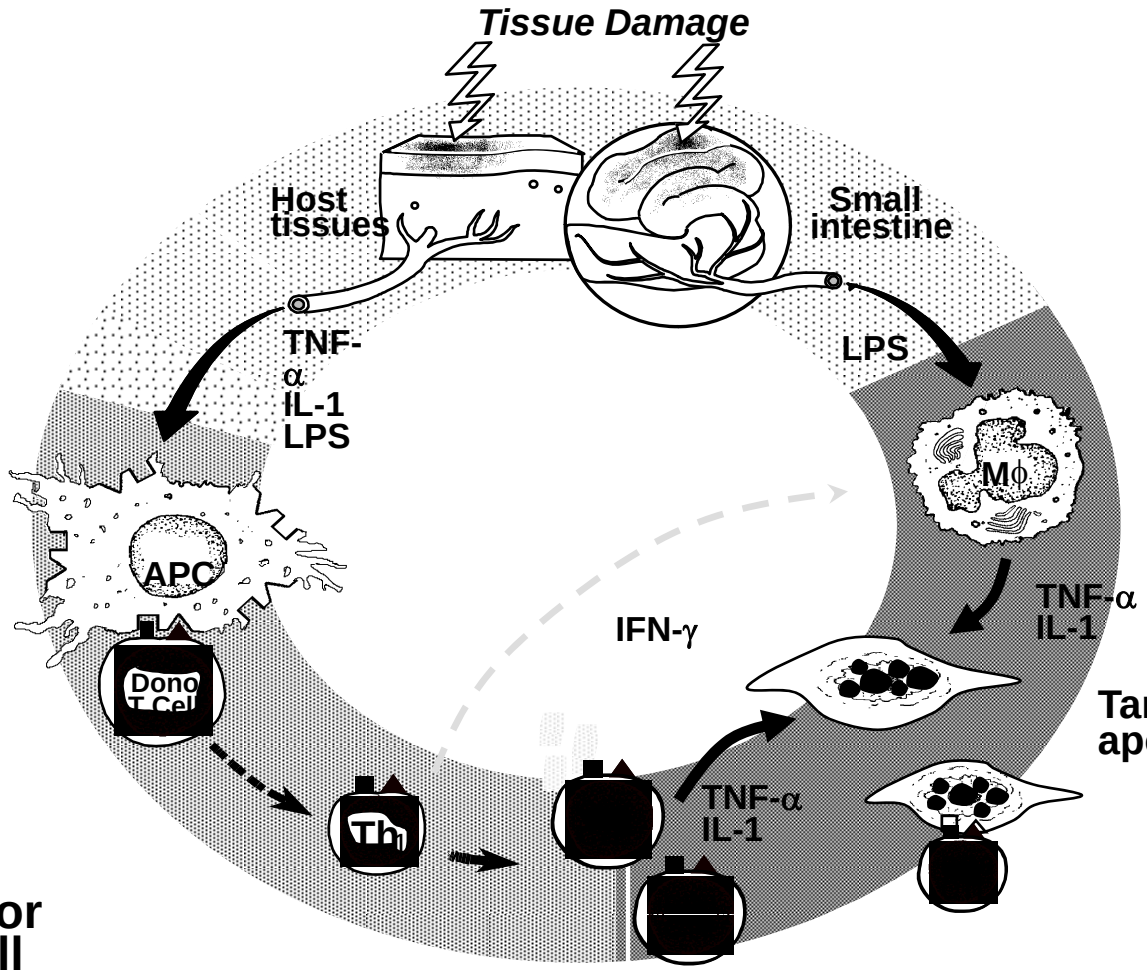
Phase 3: Inflammatory effector mechanisms

Effector functions of macrophages are triggered via a 2nd signal (LPS) LPS can stimulate tissue-associated Ly and macrophage leading to amplification of local tissue injury




(I) Conditioning
Tissue Damage
Host tissues
Small intestine
TNF-α
IL-1
LPS
LPS
Mϕ
TNF-α
IL-1
APC
IFN-γ
Target cell apoptosis
TNF-α
IL-1
(II) Donor T-cell activation
(III) Cellular and inflammatory effectors

I: Role of conditioning



(II) Donor T-cell activation

(III) Cellular and inflammatory effectors

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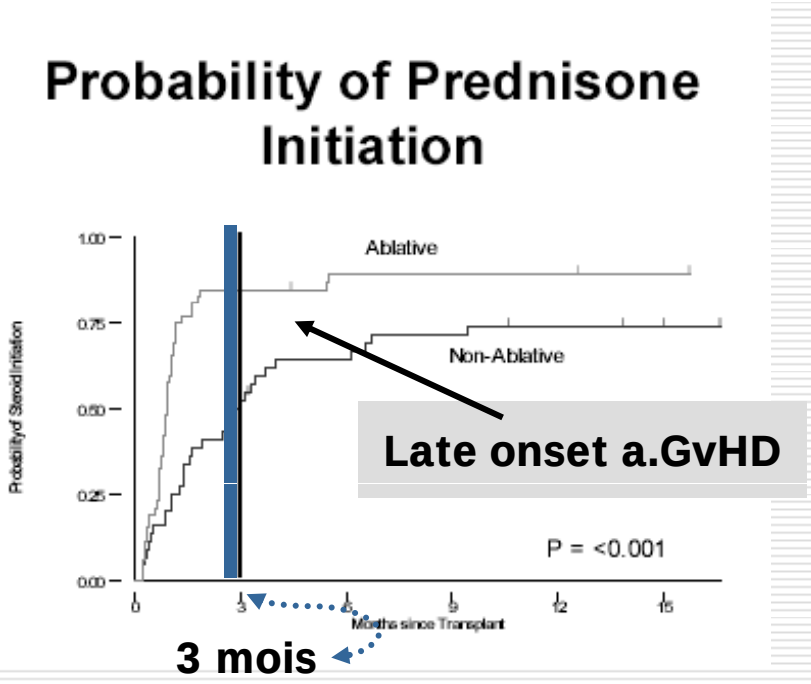
Cytokine (TNF alpha) release during conditioning results in higher GvHD and TRM
(Holler 1990)

Age and dose of TBI as major risk factors of GvHD
(Tseng et al., Blood 1999; 94:2911)



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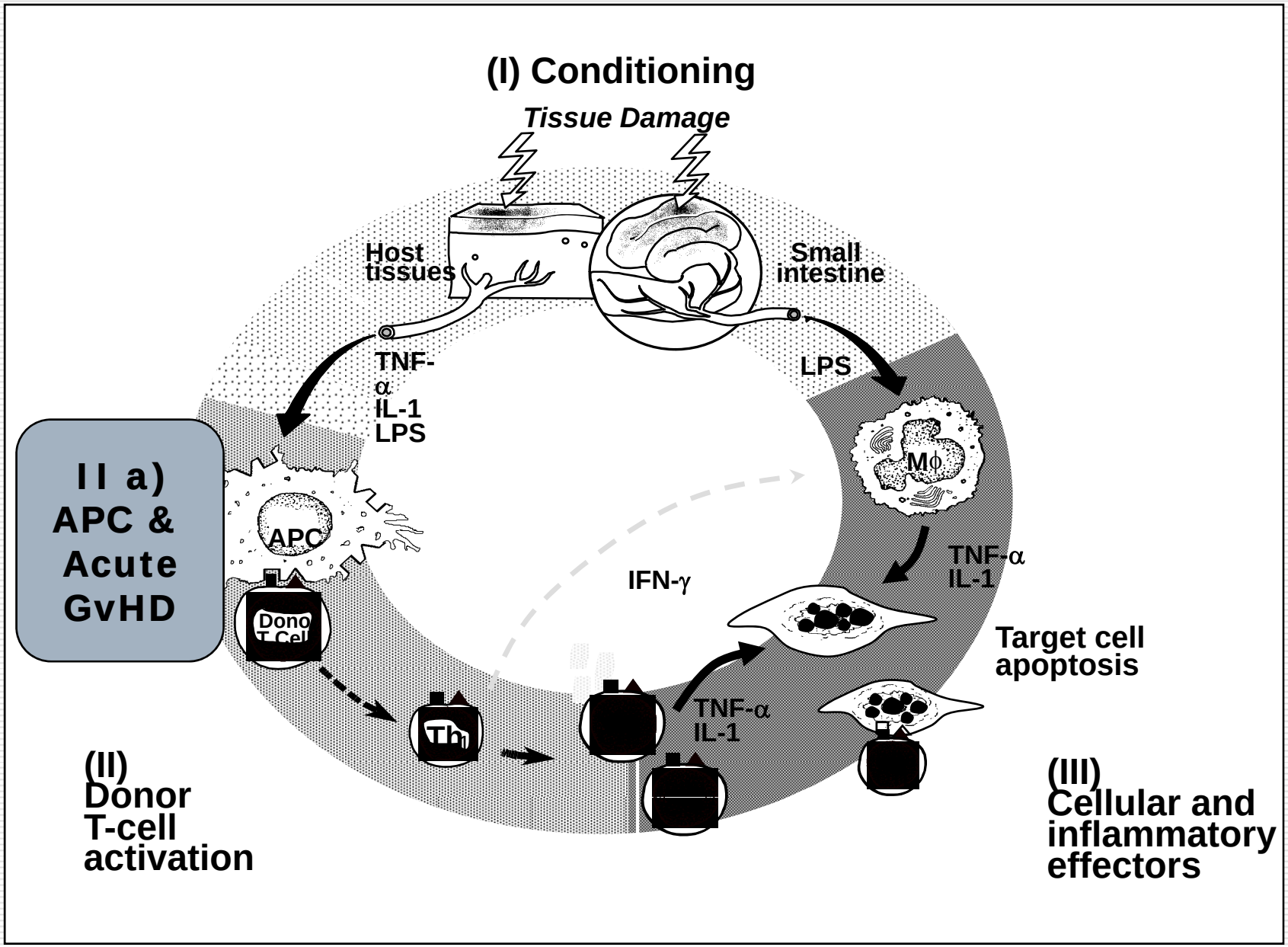
(I) Conditioning
Tissue Damage
Host tissues
Small intestine
TNF-α
IL-1
LPS
LPS
Mϕ
II a) APC & Acute GvHD
APC
TNF-α
IL-1
IFN-γ
Target cell apoptosis
TNF-α
IL-1
(II) Donor T-cell activation
(III) Cellular and inflammatory effectors

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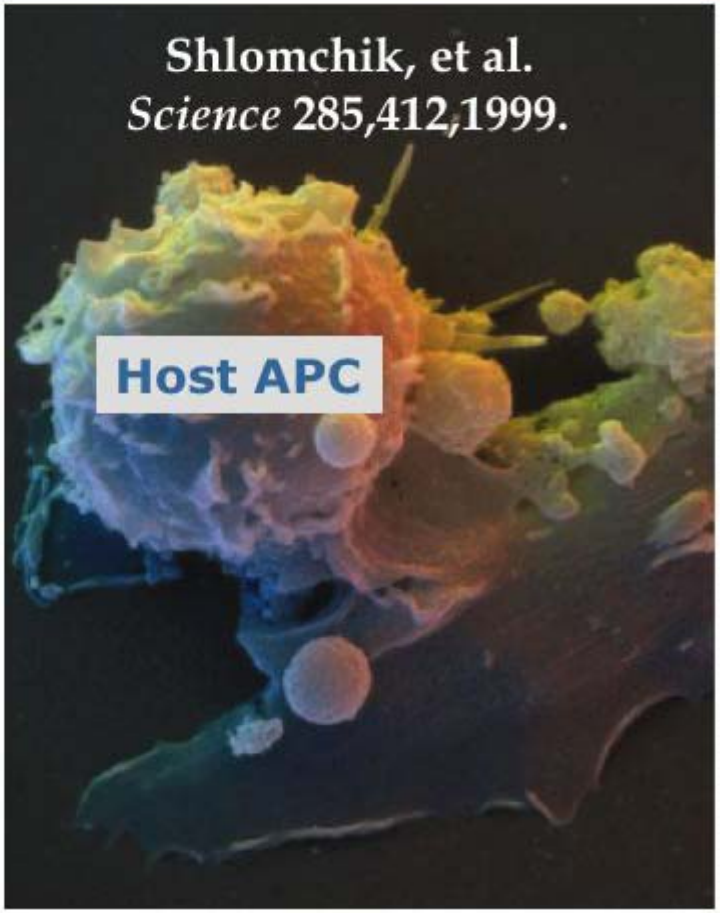

DC in GvHD

S. Emerson
Science 1999; 285: 412
JCI 2002; 109: 1335
J. Ferrara
Nat Med 2002; 8: 575
JCI 2002; 109: 1249
S. Strober
Nat Med 2004; 10: 510

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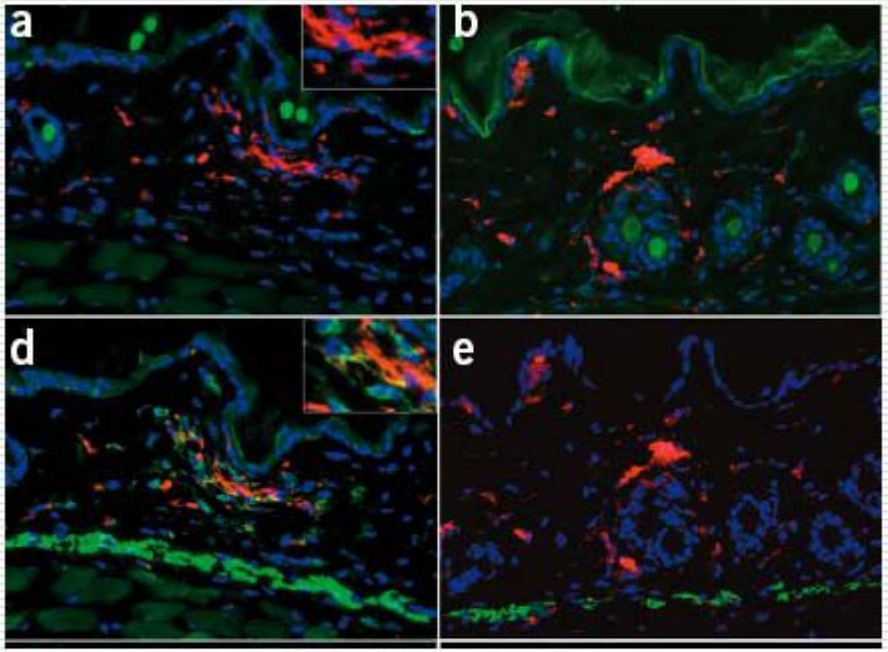
UV B-induced
Langerhans cell depletion

Merad et al,
Nature Medicine 2004

Donor-derived APC
cross-priming alloreactive CD8



Matte et al,
Nature Medicine 2004

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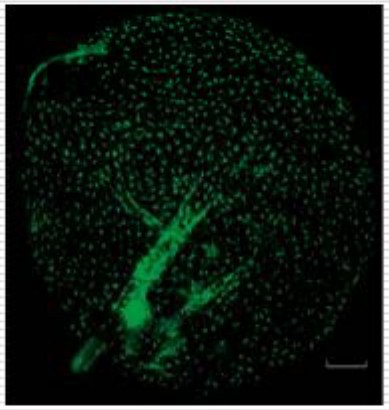
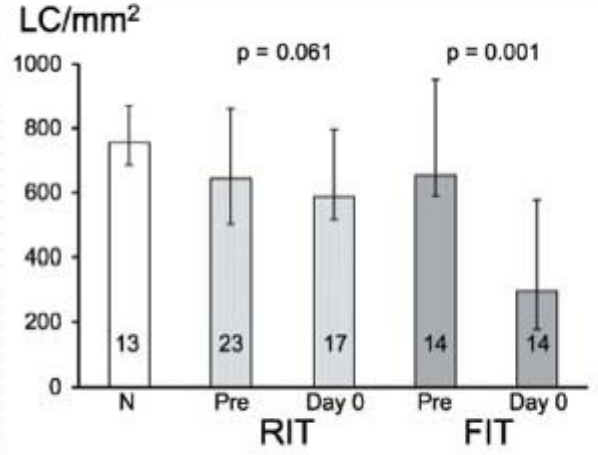
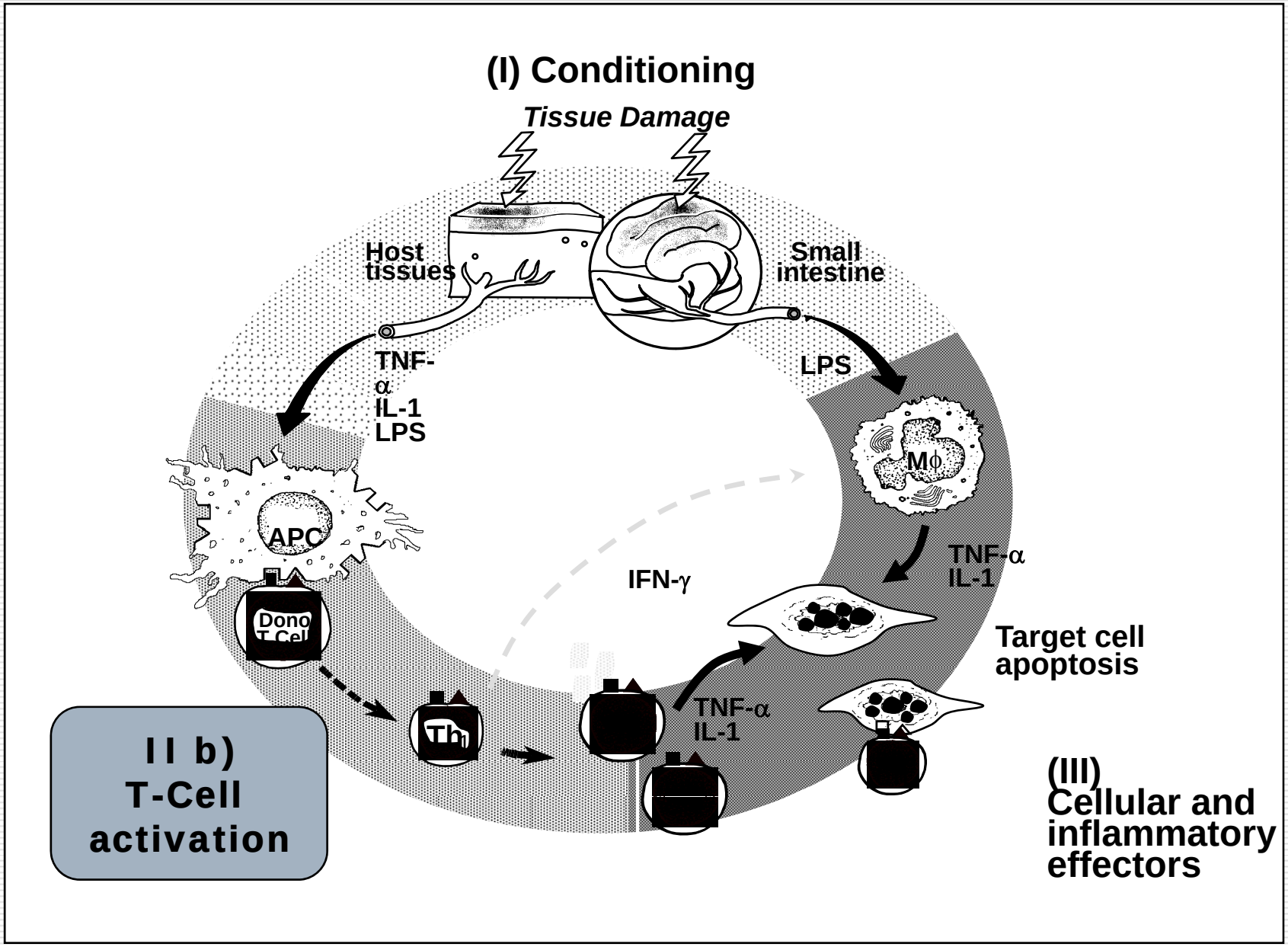
The fate of human Langerhans cells in hematopoietic stem cell transplantation

- ✓Myeloablative depletes LC more rapidly than RIC
- ✓Recovery occurs within 40 d in the absence of acute GVHD
- ✓Donor chimerism; MA (97%) /RIC (36%)
- ✓Donor chimerism is associated with prior acute GvHD





Collin et al, JEM 2006


(I) Conditioning
Tissue Damage
Host tissues
Small intestine
TNF-α
IL-1
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LPS
Mϕ
APC
TNF-α
IL-1
IFN-γ
Target cell apoptosis
TNF-α
IL-1
II b) T-Cell activation
(III) Cellular and inflammatory effectors

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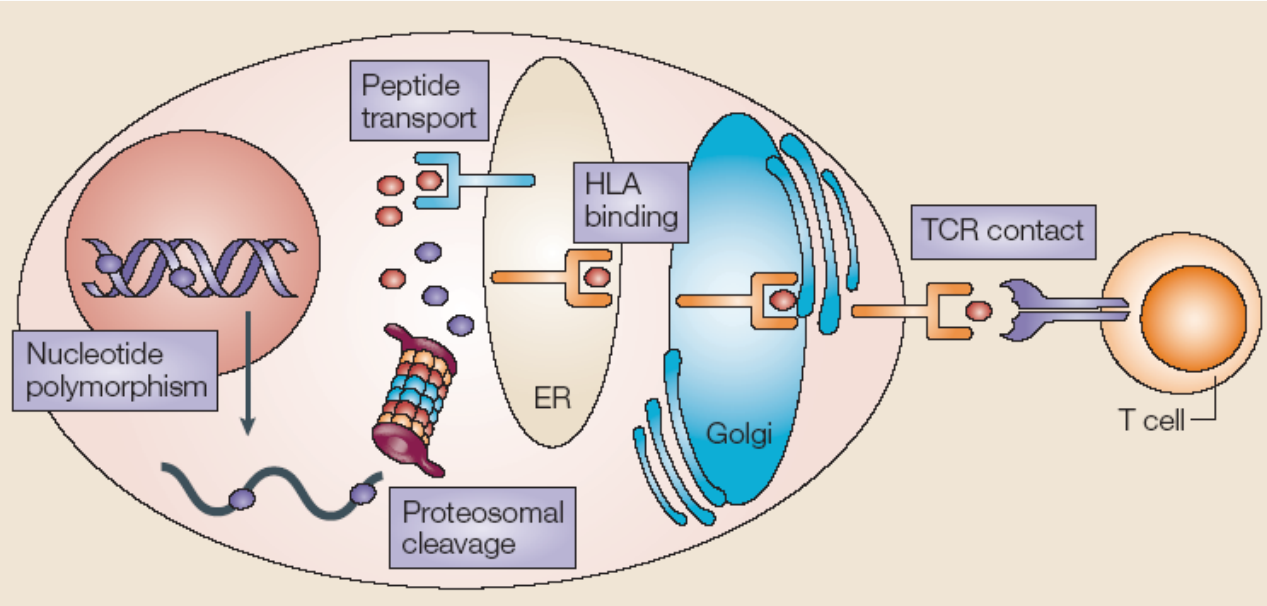
Histoincompatibility between **donor and host**:

- ✓ GvHD increases with the number of ***major MHC*** mismatches
- ✓ ***minor antigen*** mismatches in HLA-identical sibling BMT



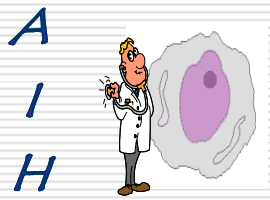


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Table 1 | **Human minor histocompatibility antigens**

Minor histocompatibility antigen	HLA restriction	Gene/chromosome	Peptide sequence	Tissue distribution	Identification technique	References
HA-1	HLA A201	*KIAA0223*/19p13	VLHDDLLEA	Haematopoietic	HPLC with mass spectometry	25
HA-1	HLA B60	*KIAA0223*/19p13	KECVLHDDL	Haematopoietic	Polymorphic-peptide screening	26
HA-2	HLA A201	*MYOG1/7*	YIGEVLSV	Haematopoietic	HPLC with mass spectometry	27,28
HA-3	HLA A1	*LBC*/15q24-25	VTEPGTAQY	Ubiquitous	HPLC with mass spectometry	29
HA-8	HLA A201	*KIAA0020*/9	RTLDKVLEV	Ubiquitous	HPLC with mass spectometry	30
HB-1	HLA B44	5q32	EEKRGSLHVW	Haematopoietic, especially B-cell leukaemias	cDNA-expression cloning	31,32
UGT2B17	HLA 2902	*UGT2B17*/4q13	AELLNIPFLY	Ubiquitous	cDNA expression cloning	33
BCL2A1	HLA A24	*BCL2A1*/15q24.3	DYLQYVKQI	Haematopoietic	Genetic-linkage analysis	34
BCL2A1	HLA B4403	*BCL2A1*/15q24.3	KEFEDDIINW	Haematopoietic	Genetic-linkage analysis	34
HY B7	HLA B702	*SMCY*	SPSVDKARAEL	Ubiquitous	HPLC with mass spectometry	35
HY A2	HLA A201	*SMCY*	FIDSYICQV	Ubiquitous	HPLC with mass spectometry	36
HY A1	HLA A101	*DFFRY*	IVDCLTEMY	Ubiquitous	HPLC with mass spectometry	37
HY B60	HLA B60	*UTY*	RESEESVSL	Ubiquitous	cDNA-expression cloning	38
HY B8	HLA B8	*UTY*	LPHNHTDL	Ubiquitous	cDNA-expression cloning	39
HY DQ5	HLA DQ5	*DBY*	HIENFSDIDMGE	Ubiquitous	cDNA-expression cloning	40
HY DRB3	HLA DRB3	*RPS4Y*	VIKVNDTVQI	Not reported	cDNA-expression cloning	41

HLA, human leukocyte antigen; HPLC, high-performance liquid chromatography.

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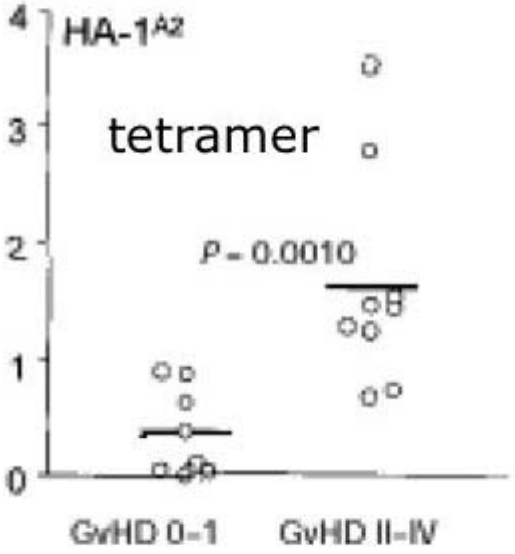
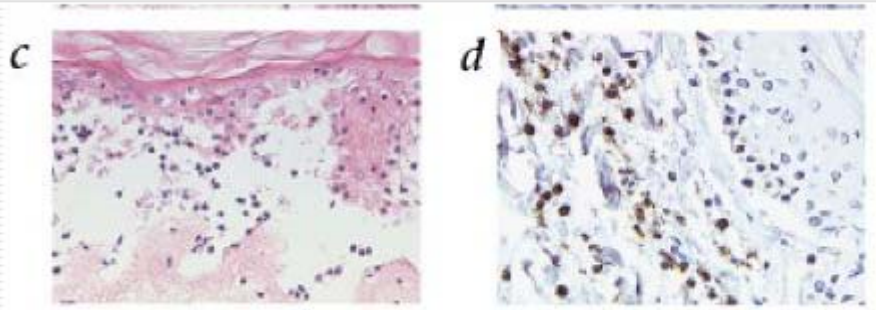
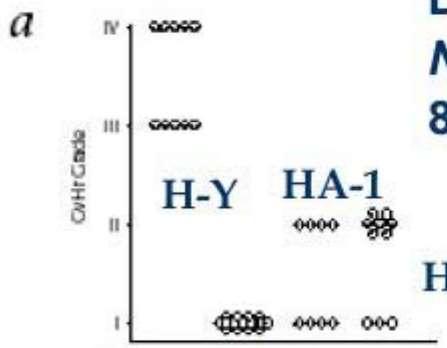


Mutis, T. *et al.*
Nature Med. 5, 839–842, 1999.





CTLs H-Y
Skin Control

Dickinson. *et al.*
Nature Med.
8, 410, 2002.

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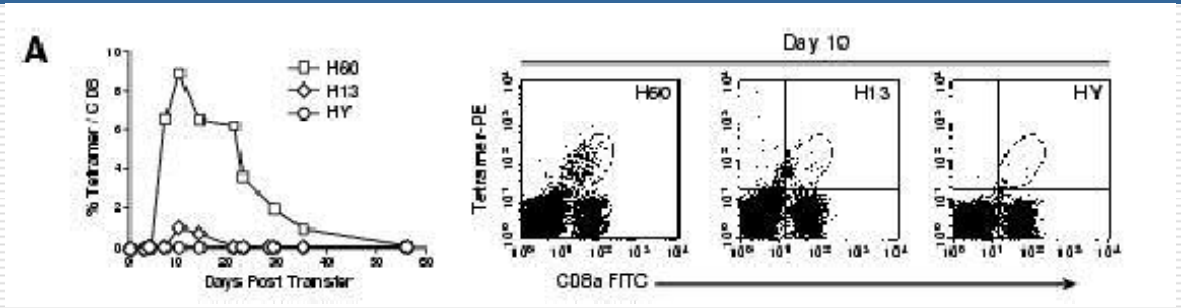
Major /minor antigens in mice

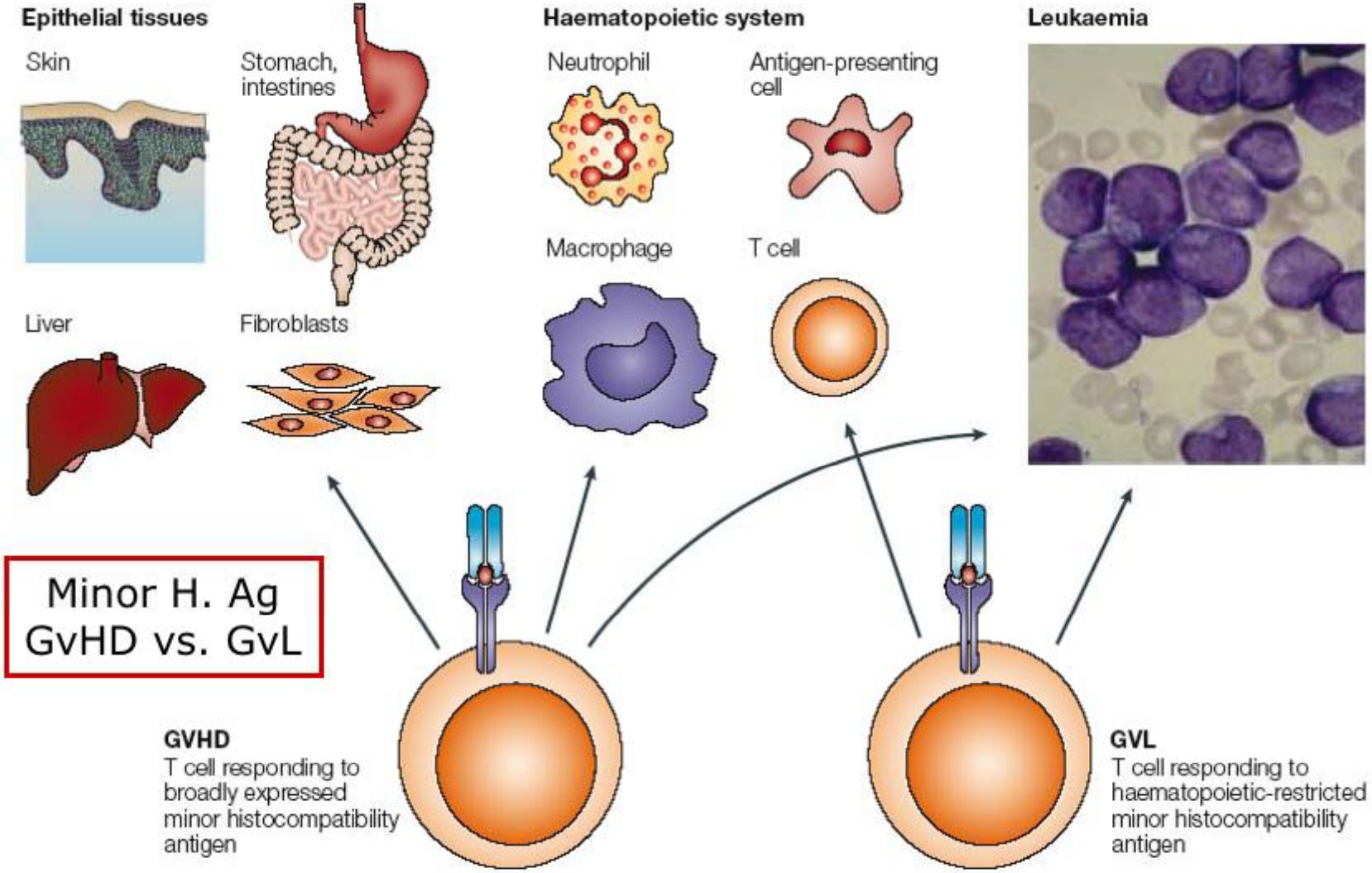
- B6 Dom **(Nature Medicine; 7: 789, 2001)**

Adoptive transfer of minor histocompatibility antigen-specific T lymphocytes eradicates leukemia cells without causing graft-versus-host disease

- H60 ++ **(Immunity; 17: 593, 2002 / Blood; 100: 4255, 2002)**

Real-time T cell Profiling Identifies H60 As a Major Minor Histocompatibility Antigen in Murine Graft-vs-Host Disease




Epithelial tissues
Skin
Stomach, intestines
Liver
Fibroblasts
Haematopoietic system
Neutrophil
Antigen-presenting cell
Macrophage
T cell
Leukaemia
Minor H. Ag
GvHD vs. GvL
GVHD
T cell responding to broadly expressed minor histocompatibility antigen
GVL
T cell responding to haematopoietic-restricted minor histocompatibility antigen

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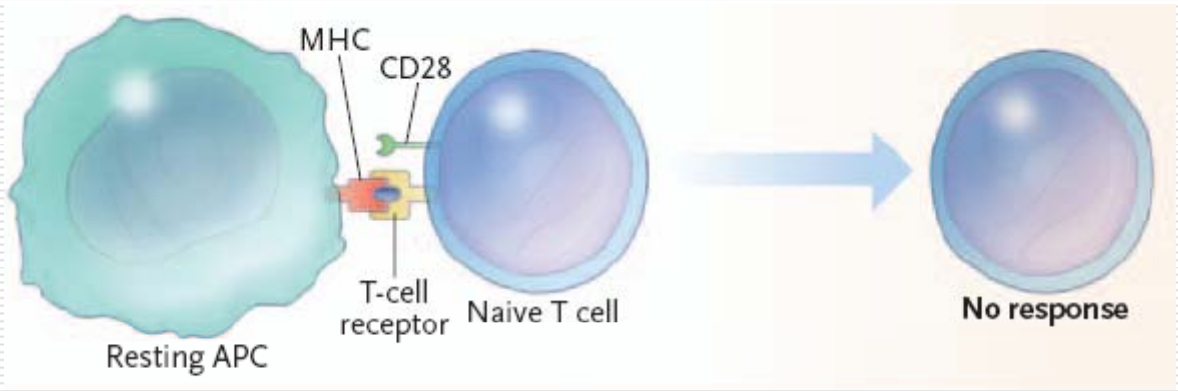

Co-stimulation & acute GvHD (mice)

CD 80/86
CTLA4-Ig
CD 40/40L
LFA1/ICAM
ICOS
.....

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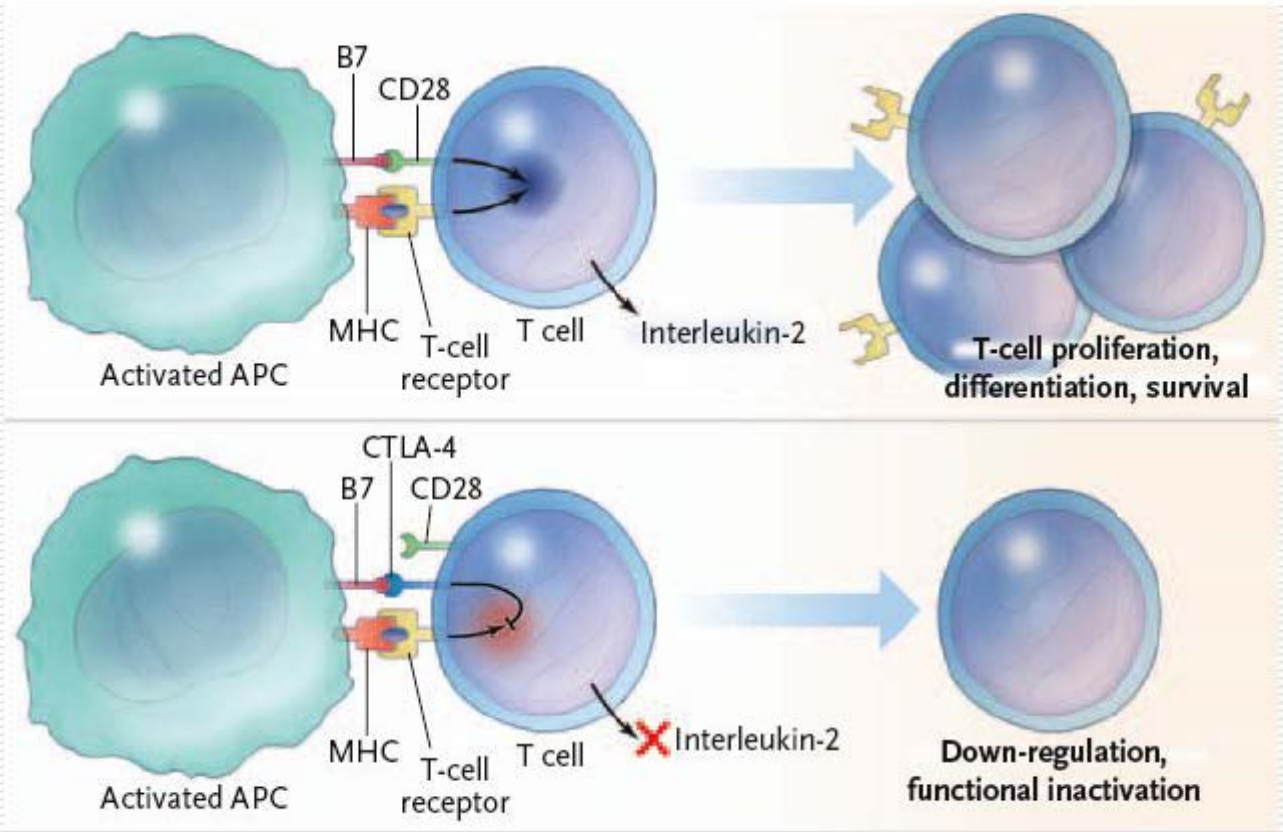

CTLA4 Ig. ++
Anti CD28 !!
See NEJM
Sept 6th 2006

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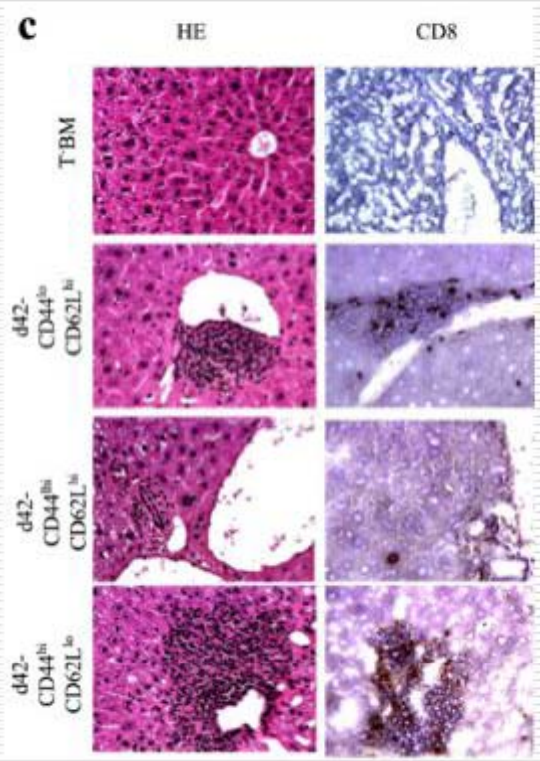

CD44loCD62LhiCD8+

generate and sustain all allogeneic T cell subsets in GVHD reactions

including central memory, effector memory, and effector CD8+ T cells, while self-renewing.

Sca-1+, IL-2/15 receptor-β, and bcl-2, and induce GVHD upon transfer into secondary recipients.

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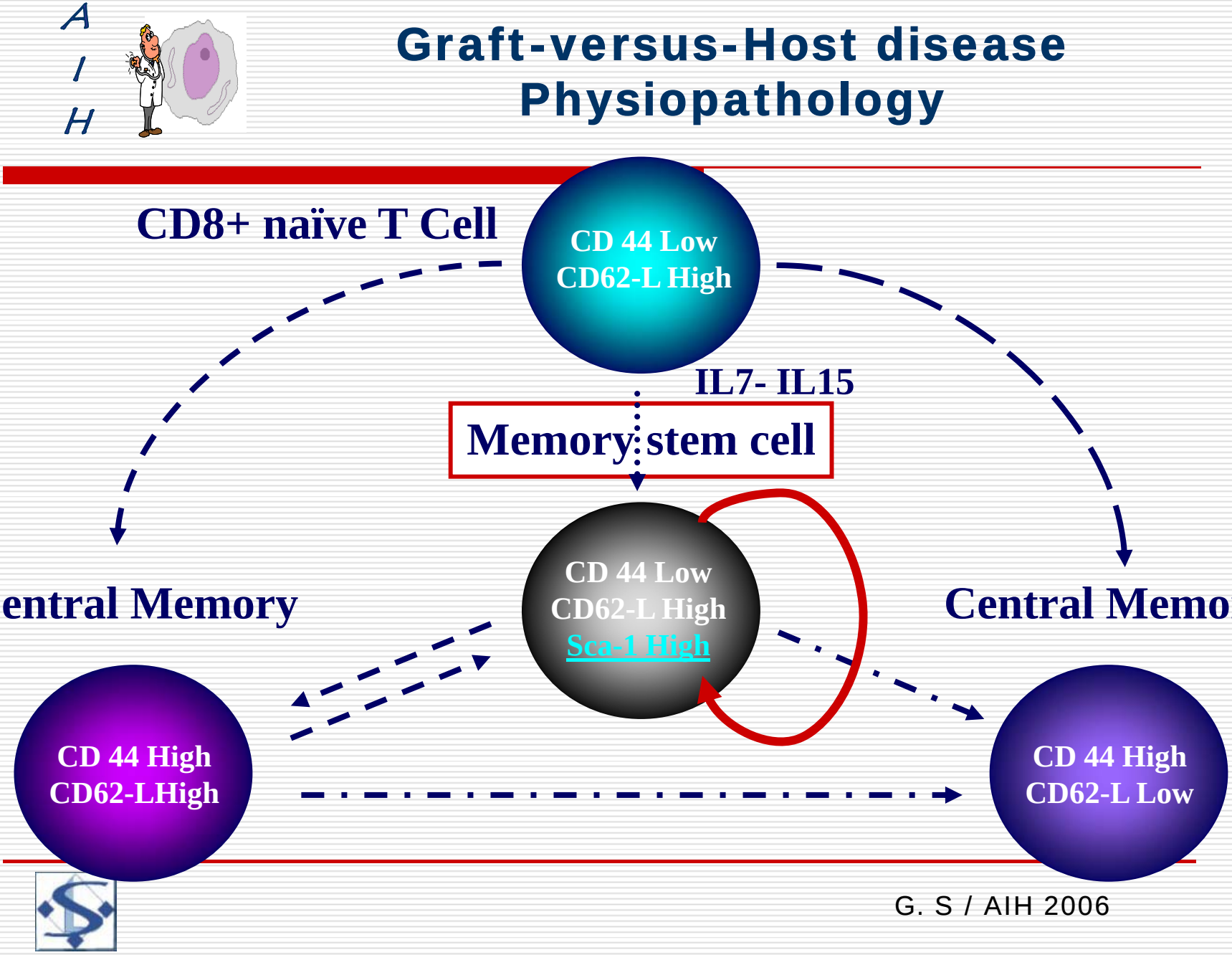

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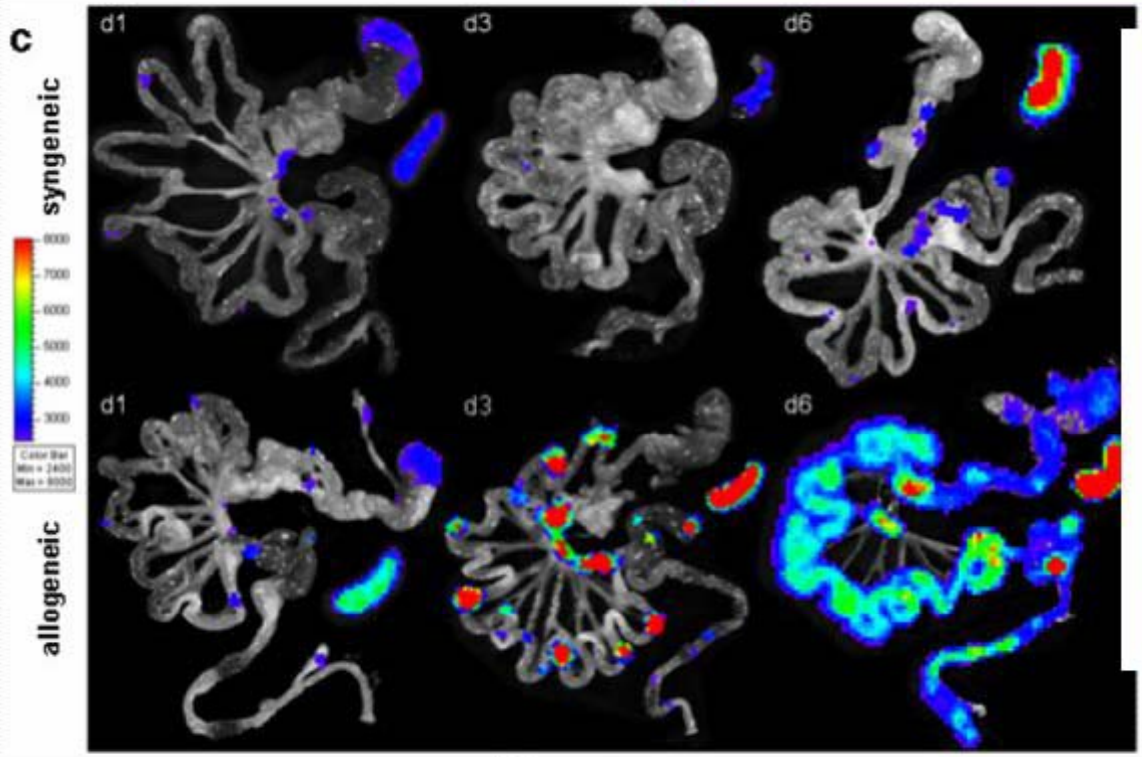
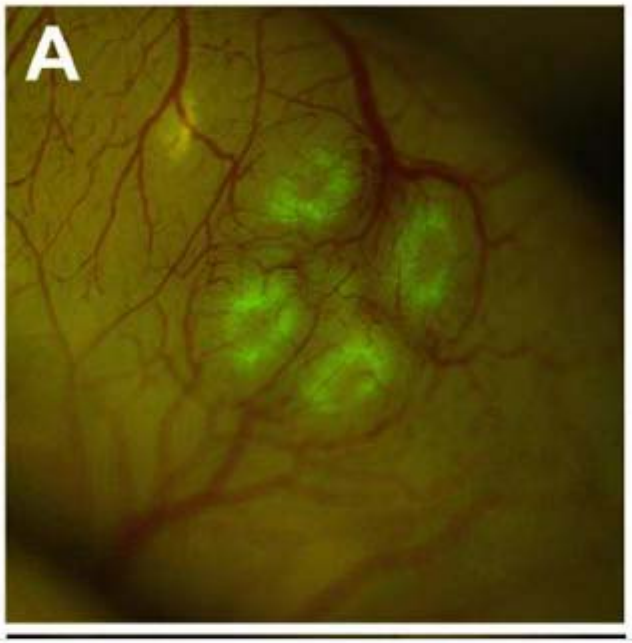
GVHD: *in vivo VERITAS*





Hours!

1 AUGUST 2005 | VOLUME 106, NUMBER 3 blood

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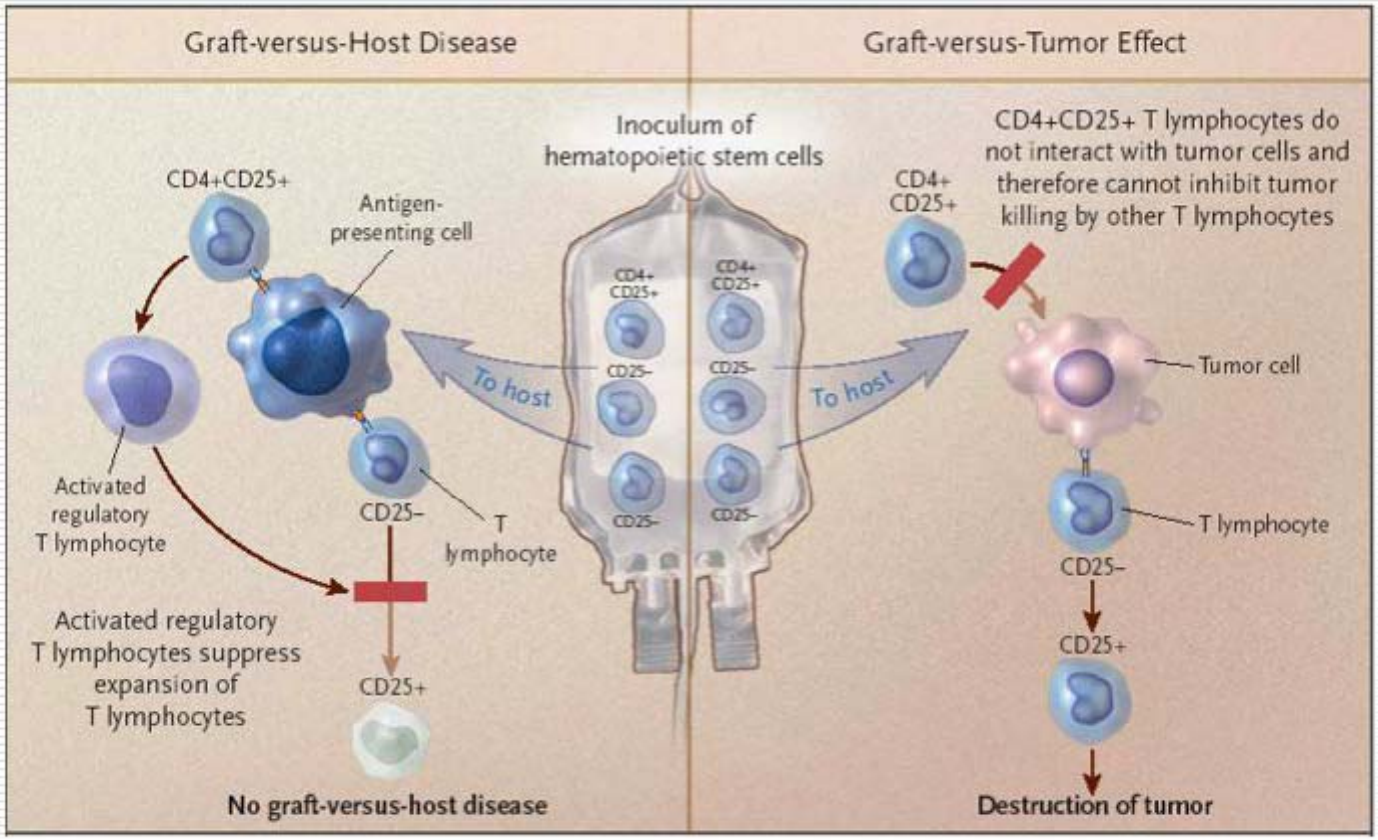

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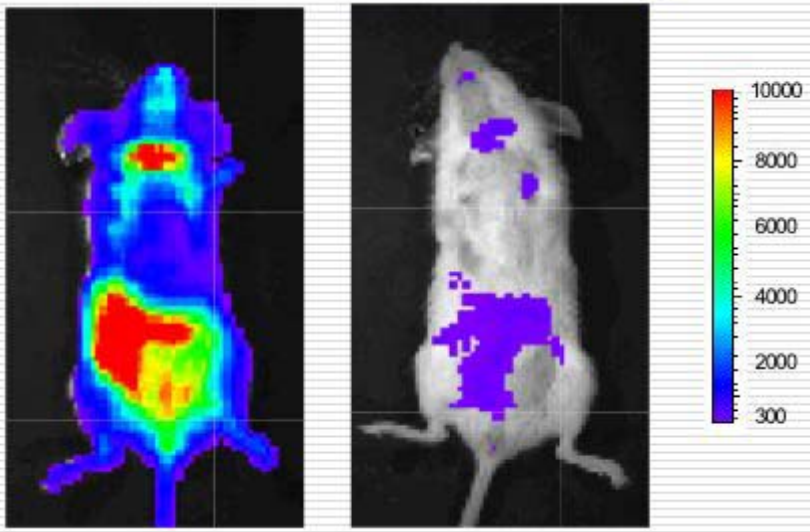
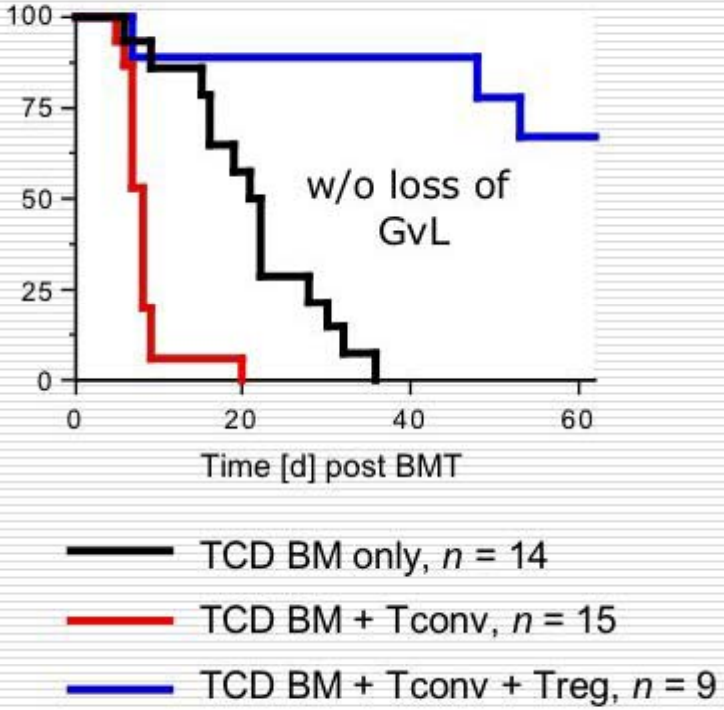
TCD BM + Tconv^{luc}

TCD BM + Tconv^{luc} + Treg



Day 7 post Transplantation



Edinger et al (2003), *Nat Med*, 9(9): 1144–50.

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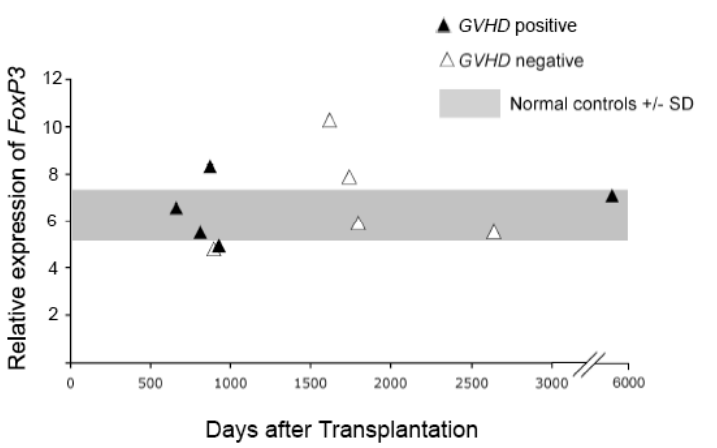

Figure 3: *FoxP3* relative expression in $CD25^{high}CD4^{+}$ T cells according to the delay from the graft

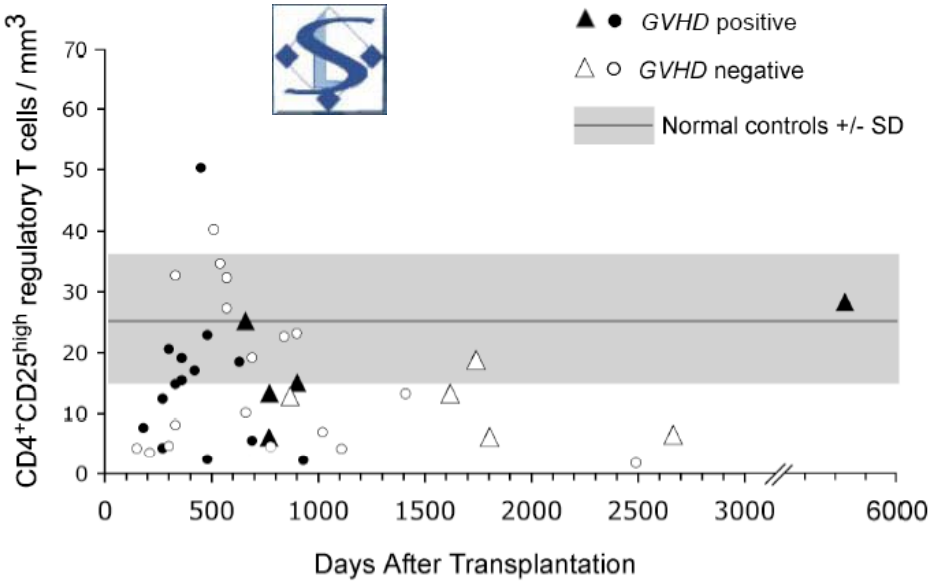

Figure 4: Recovery of $CD4^{+}CD25^{high}$ T cells following Allogeneic Stem Cell Transplantation.

Experimental Hematology 33 (2005) 894–900

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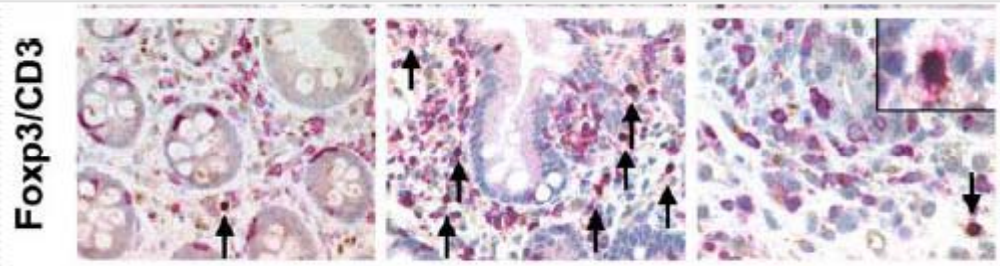
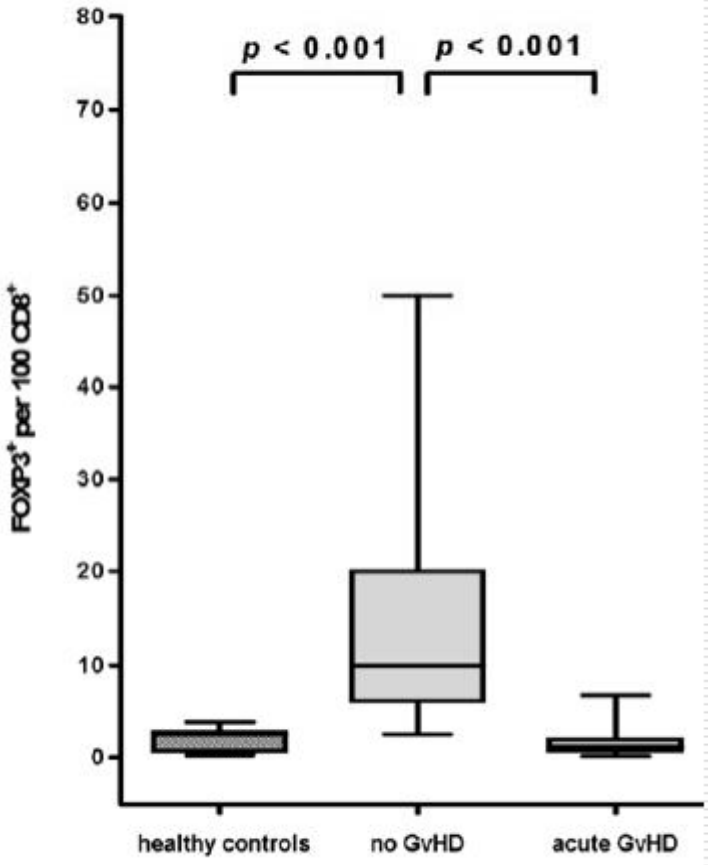


Mucosal Foxp3 & human GvHD
Blood. 2006;107:1717-1723



Non HLA Gene Polymorphisms

•TNFα (d3/d3)		Middleton et al.	Blood 1998
•IL-10^{-1064} (11-15)		Cavet et al.	Blood 1999
•IL-1; TNFα, IFNγ	Patient/donor	Hill et al.	Blood 1999
•IL-6	acute/chronic	Cavet et al.	Blood 2001
•IL-10	GvHD	Socié et al.	Transplantation 2001
•IL-6			
•IL1-Ra		Cullup et al.	Brit J Haem 2001
•TNFα; IL-10	(CBT) No association	Kögler et al.	Transplantation 2002
•Vit D receptor	aGvHD and survival	Middleton et al.	BMT 2002
•Estrogen receptor		Midleton et al	BMT 2003
•TNRII		Stark et al.	Transplantation 2003
•Mannose Binding Lectin (MBL)	Infectious complications	Mulligan et al.	Blood 2002
•FcγRIIa	Infectious complications	Rocha et al.	Blood 2002

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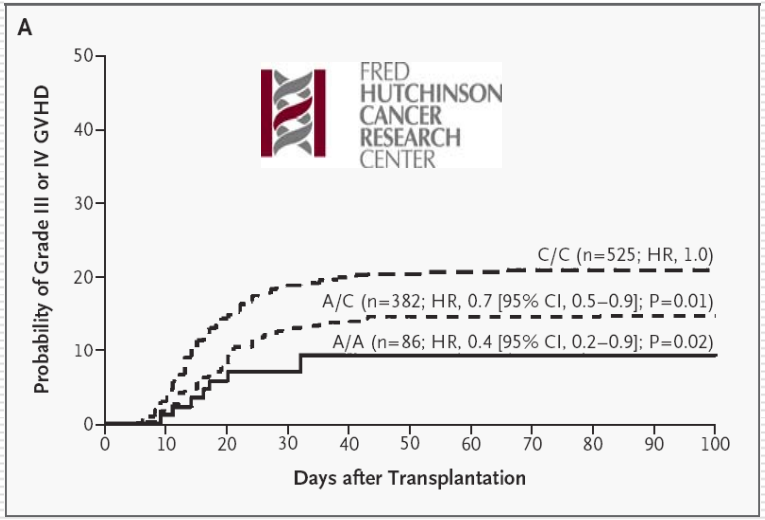
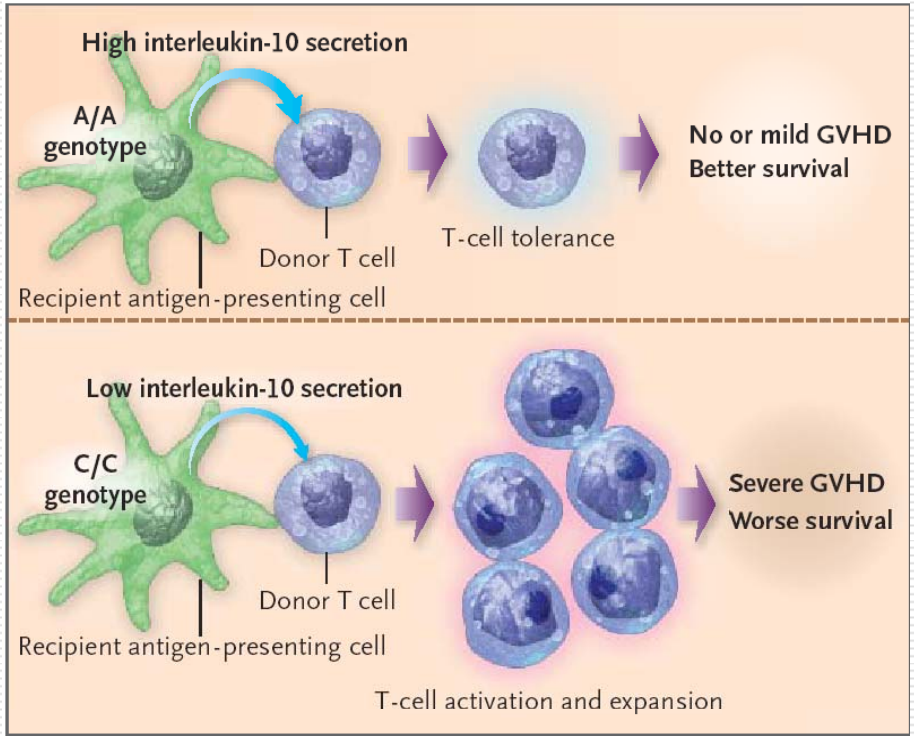


N. Engl. J. Med. 2003;349:2201-10.



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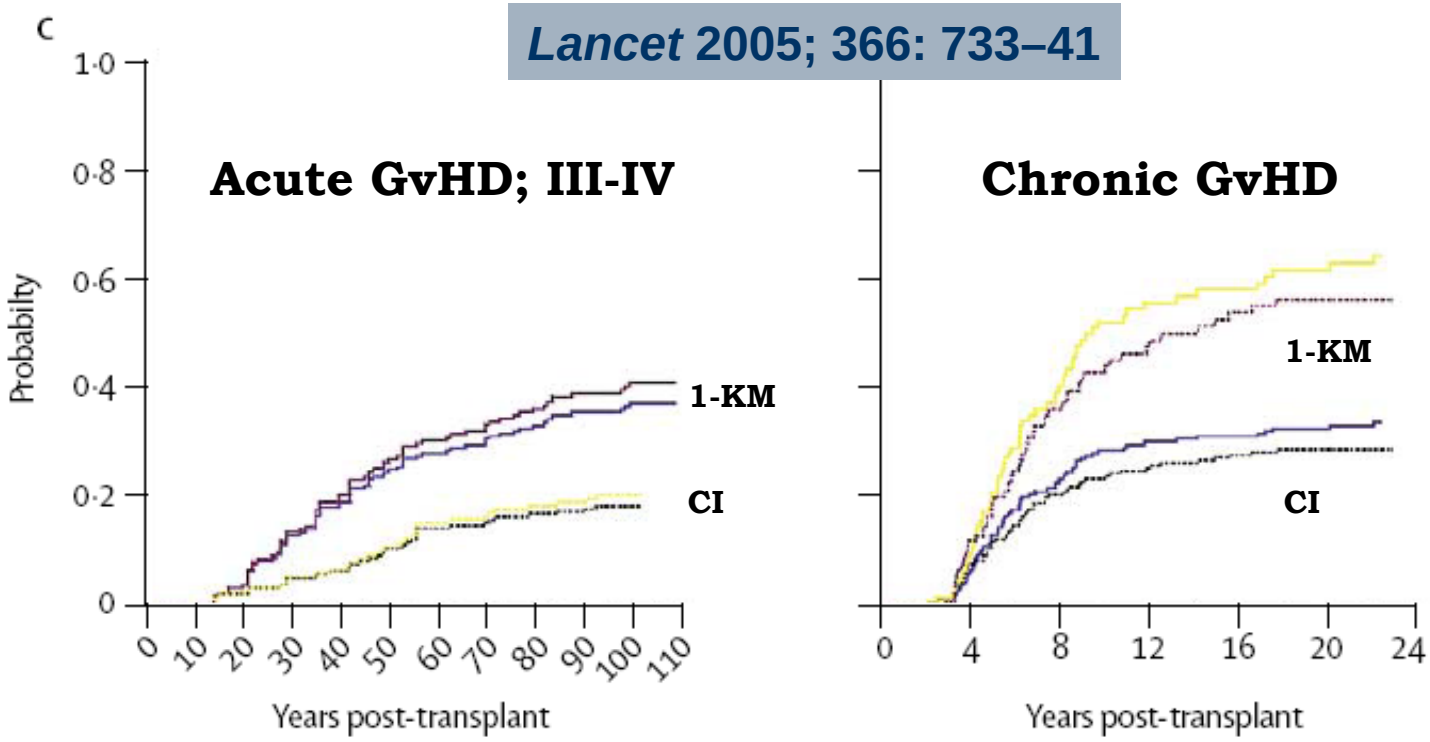
T-cell numbers and human GvHD

Lancet 2005; 366: 733–41



Effect of GvHD prophylaxis on 3-year disease-free survival in recipients of unrelated donor bone marrow

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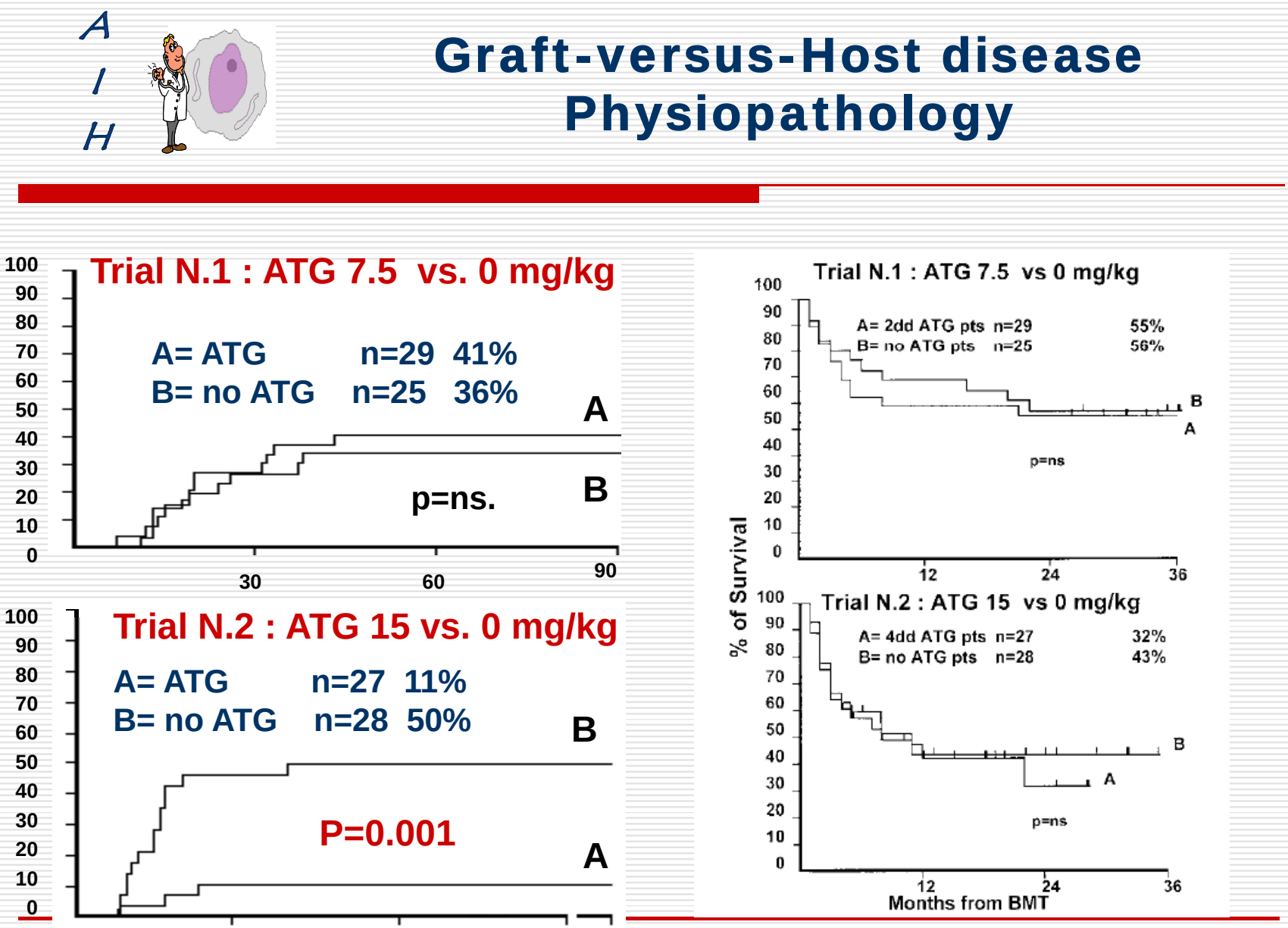

***Bacigalupo et al. Blood*. 2001;98:2942-2947**