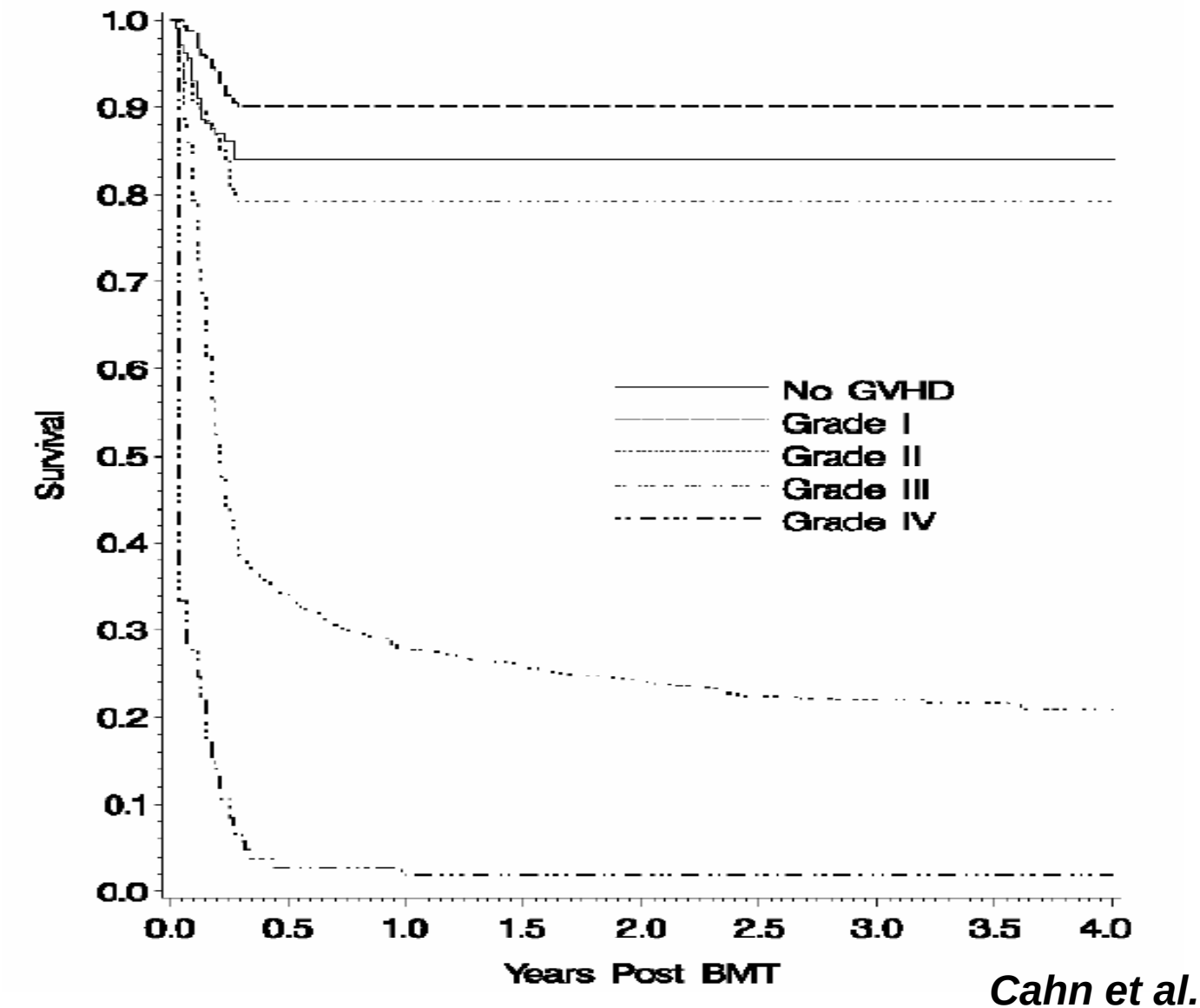
Immunosuppressive therapy for graft-versus-host disease

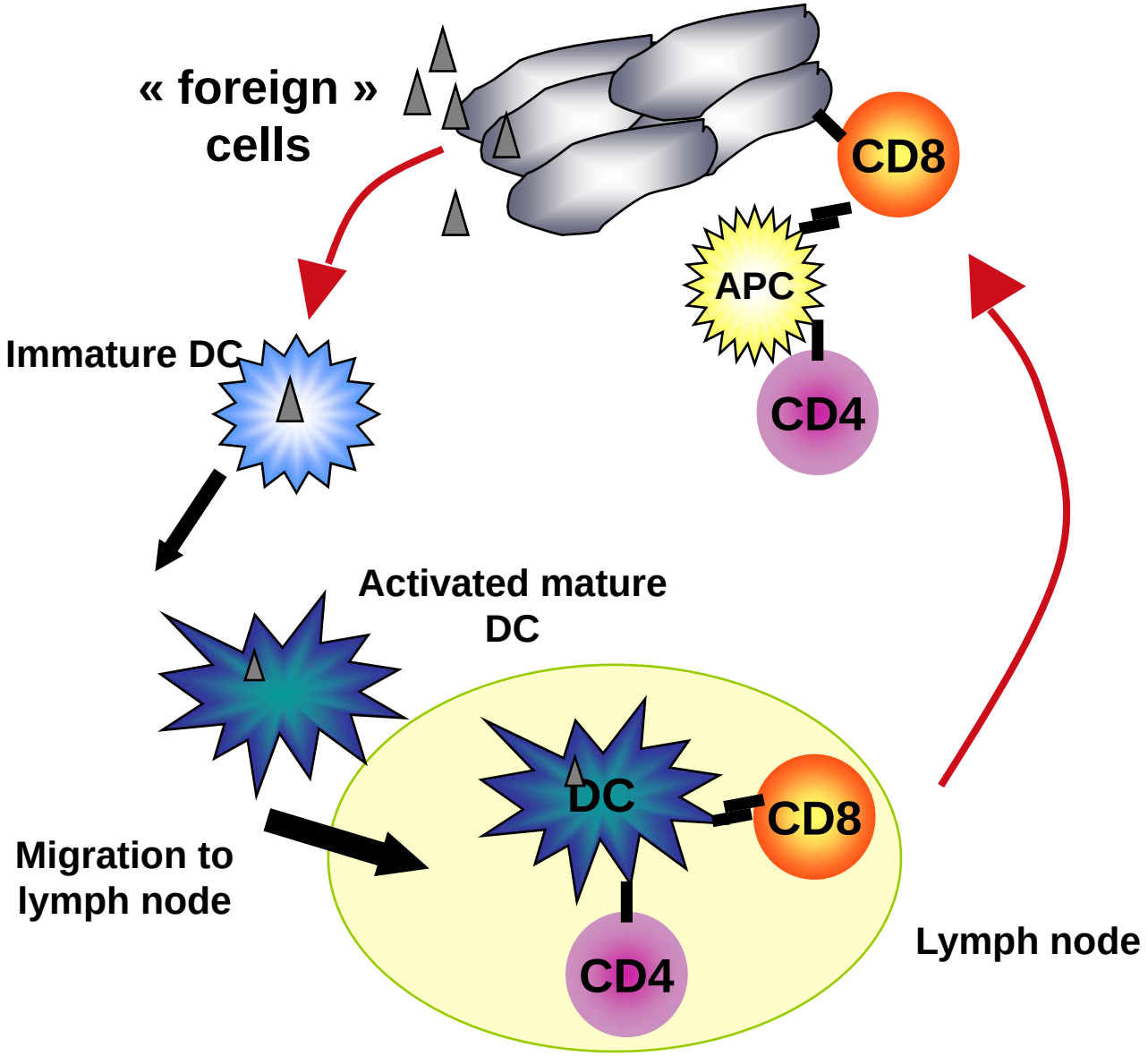
Mohamad Mohty
Institut Paoli-Calmettes, Marseille

Survival according to GVHD grade
(Joint SFGM-TC, DFCI and IBMTR data; N=607)

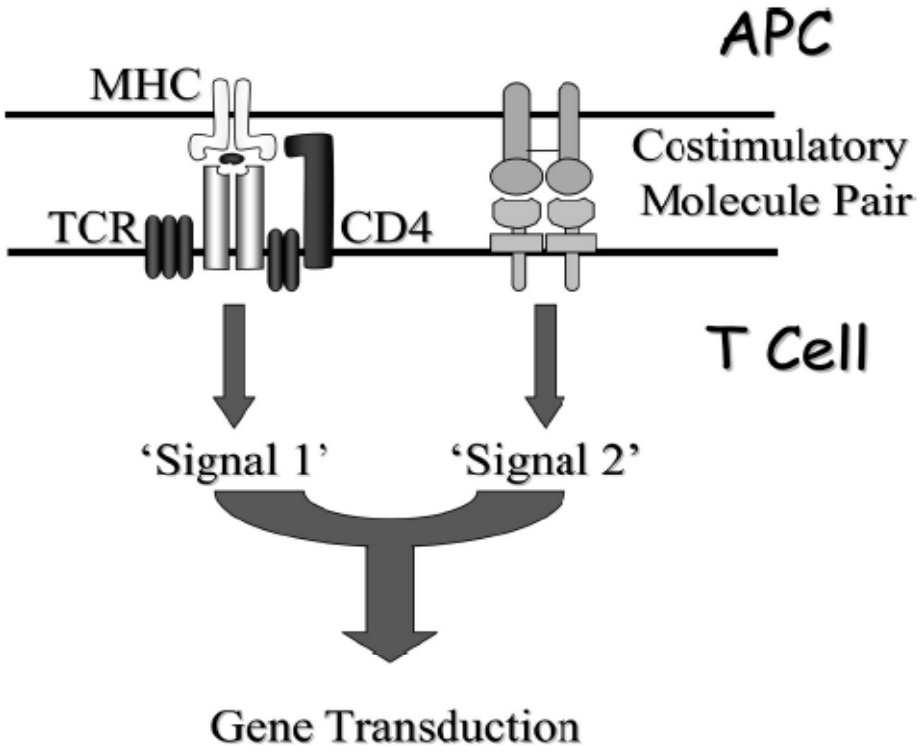


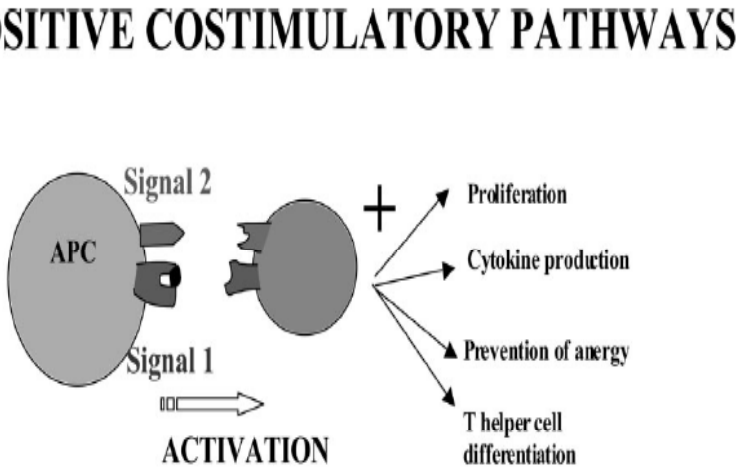
Cahn et al., Blood 2005

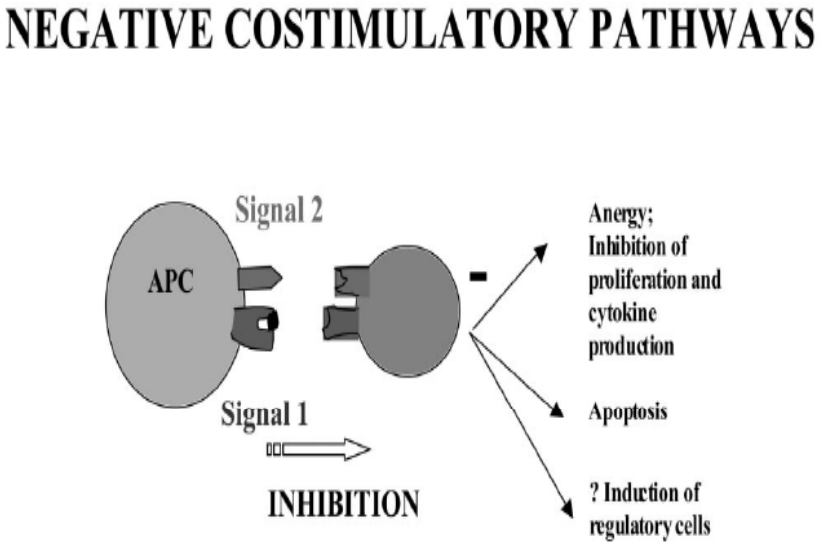
Immune response to a «foreign» antigen



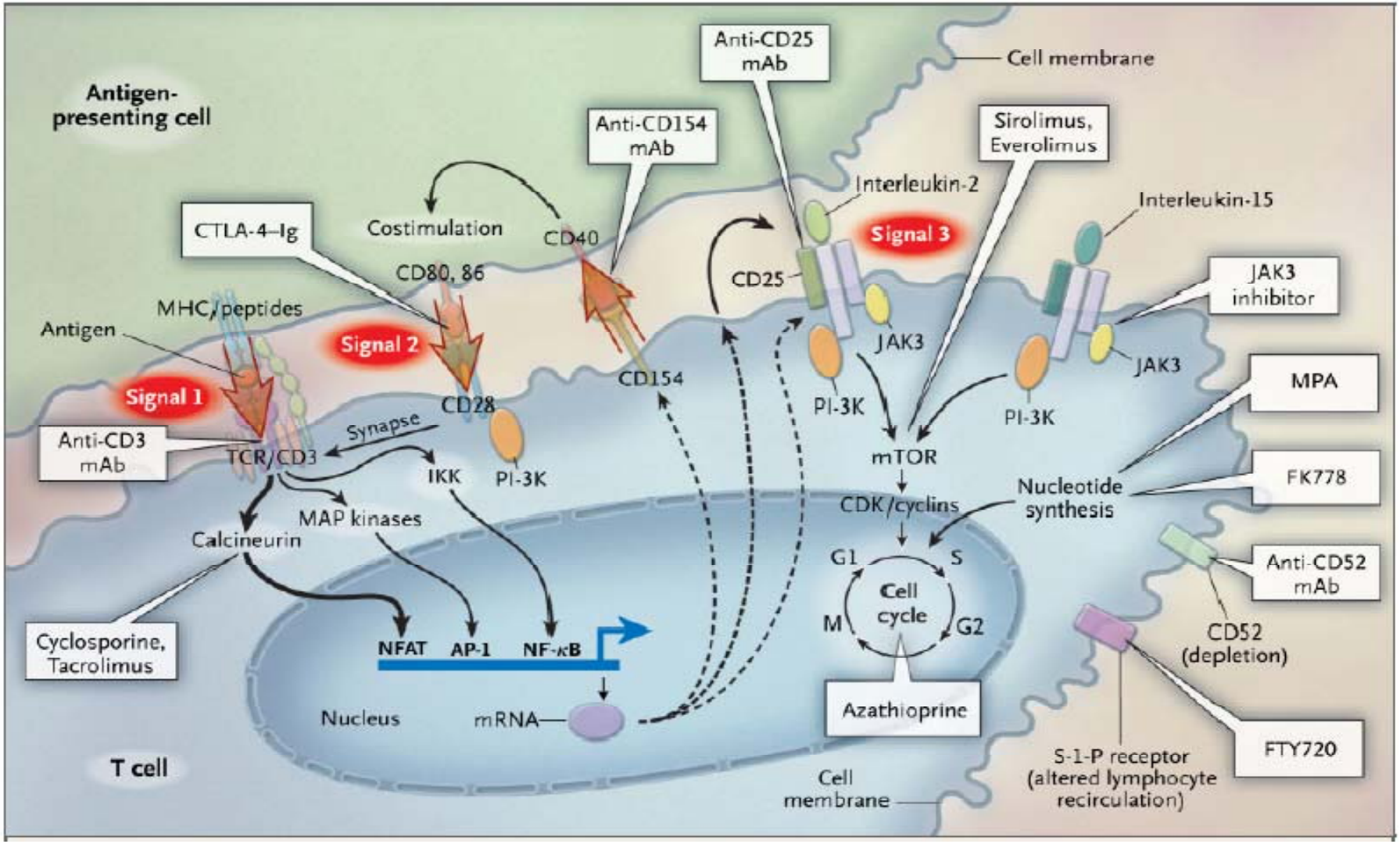
The “Two/Three-Signal” Paradigm of Costimulation





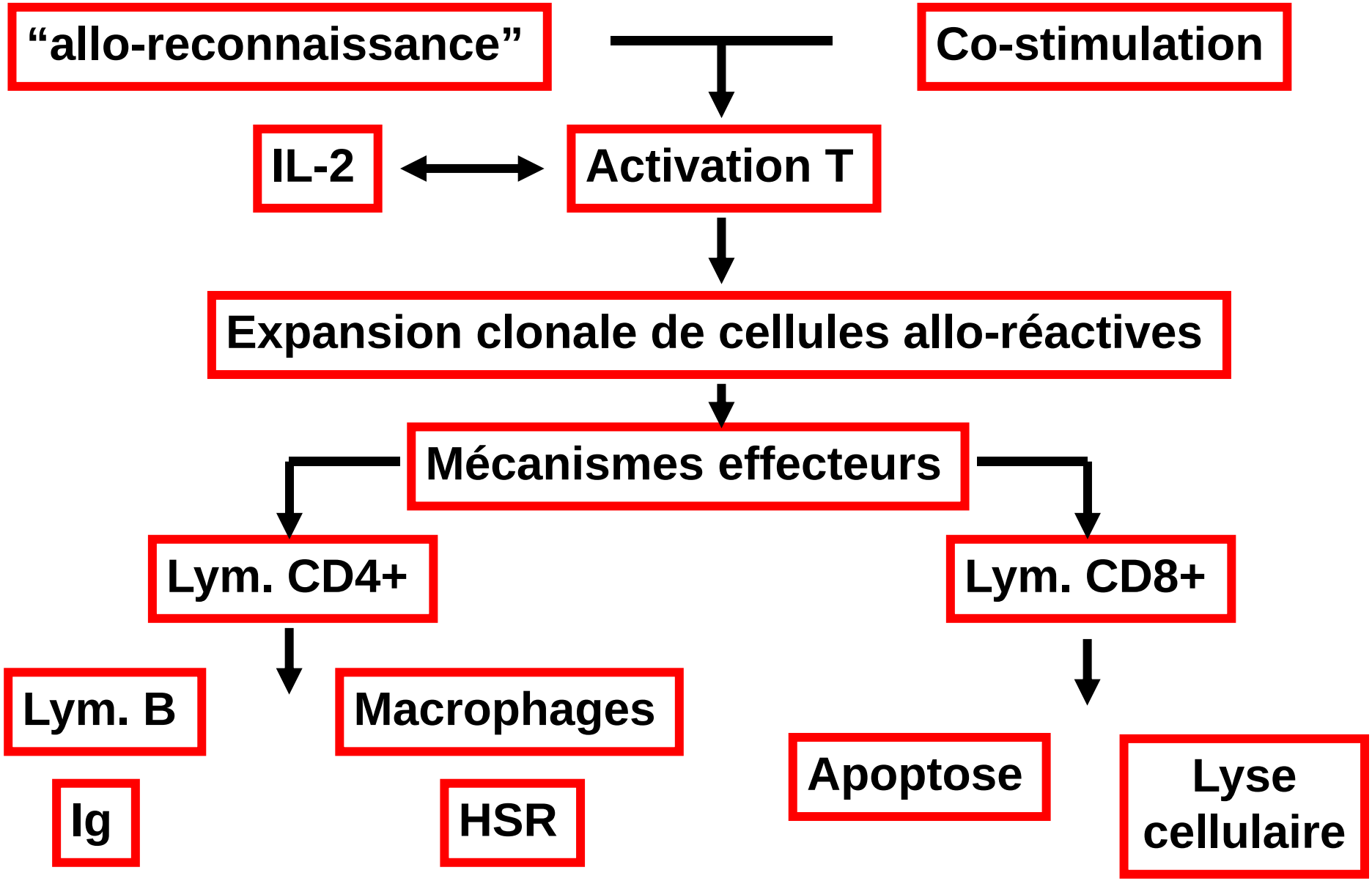


Immunosuppressive Drugs and Sites of Action in the Three-Signal Model



Halloran, N Engl J Med 2004

La réponse “allo-immune”



Evolution of Immunosuppression: the Pre-Cyclosporine Era

- Total lymphoid irradiation
- Lymphocytes depletion
- Donor-specific transfusions
- 1962 – Azathioprine (AZA)
- 1963 - AZA + Steroids
- 1966 - “Home brew” anti-lymphocyte sera
- 1970 - Cyclophosphamide

Evolution of Immunosuppression: the Cyclosporine Era

- 1978 - Cyclosporine
- 1983 - OKT3
- 1994 - Tacrolimus
- 1995 - Neoral
- 1995 – Mycophenolate
- 1997 - Daclizumab
- 1998 - Basiliximab
- 1999 - Sirolimus
- 2000 - Generic CSA

Immunosuppressive Drugs

- ***Cytotoxic drugs***
  - **Destroy stimulated lymphocytes**
  - **Block DNA synthesis (Cyclophosphamide, Azathioprine, Mycophenolate (MMF), Methotrexate)**
- ***General immuno-suppressants***
  - **Anti-inflammatory, non-specific (corticosteroids)**
- ***Selective immunosuppressants***
  - **Block T-helper cells (Cyclosporine, Tacrolimus, Sirolimus)**
- ***Antibodies***
  - **Antithymocyte antibodies (Thymoglobuline)**
  - **Anti-T cell surface (CD3 or OKT3; Muromaonab)**
  - **IL-2 receptor antagonists (Basiliximab, Daclizumab)**

Immunosuppressive Drugs: Cytotoxic Agents

- **Most cytotoxic drugs act non-specifically**
- **Easier to block or attenuate primary immune response than to suppress established response**
- **Classical cytotoxic agents are anti-proliferative (overlap with chemotherapy)**
- **In general, lymphoid cells more sensitive to cytotoxic agents than normal cells; APCs relatively resistant**

Side effects of non-specific immunosuppression
(e.g. Azathioprine, Methotrexate, Cyclophosphamide)

Hemopoetic	Gastrointestinal	Genito-urinary
Bone marrow: - leucopenia - thrombocytopenia - anemia	Nausea/vomiting Diarrhea Anorexia Acute liver atrophy Hepatic toxicity	Genito-urinary toxicity Renal toxicity Reduced fertility Teratogenicity Hemorrhagic cystitis
Skin	**Other**	
Ulcerative stomatitis Hair loss Pigmentation	Pulmonary fibrosis Neurotoxicity	

Les Corticoïdes

- **Effets anti-inflammatoires non-spécifiques:**

➔ **inhibition de la migration des monocytes, diminution de la synthèse et relargage des chemokines)**

- **Effets immunosupresseurs:**

➔ **Inhibition de gènes de cytokines (IL-1, IL-2, IL-3, IL-6, TNF-a, IFN-g etc.)**

➔ **Inhibition de AP-1, NF-kB, NF-IL-6**

Cyclosporine-A

- Calcineurine blockade inhibits translocation of transcritpion factor NF-AT, leading to reduction of early genes activation (IL-2, IL-3, IL-4, GM-CSF, TNF-a, IFN-g, CD40L etc.)
- Inhibition of the activation of AP-1, NF-kB (JNK and p38 blockade)
- Inhibition of the prolactine gene: activator of several cytokine genes

➔ CD4+ cells inhibition+++ (CD8+ cells to a lesser extent)

➔ Inhibition of peripheral lymphocytes proliferation

➔ Increase of TGF-b (not tacrolimus)

Cyclosporine-A /Tacrolimus toxicity

- Renal

Reduced GFR

Hypertension

hyperuricemia

hyperkalemia and acidosis

- Liver

raised Alk Phos, bilirubin

- gum hypertrophy
- hypertrichosis
- facial brutalisation

- CNS

convulsions, depression

memory loss, anorexia

- PNS

acral dysesthiae

tremor

- Cardiac

Cardiac hypertrophy

- *glucose intolerance*
- hyperlipidaemia

Mycophenolate Mofetil (MMF)

- **Inhibition de la voie de synthèse de novo des bases puriques: effet anti-métabolite plus marqué sur les lymphocytes.**
- **Blocage de la prolifération T et B**
- **Inhibition de la sécrétion des Ig**
- **Inhibition de la génération de CTL**
- **Diminution de l'expression des molécules d'adhésion**

Risk factors of acute GVHD

- Histocompatibility
- Conditioning regimens with either TBI or high-dose chemotherapy
- Microenvironment
- Patient and donor age
- Donor: recipient gender
- Source of stem cells and graft cell composition
- State of primary donor alloimmunization
- Underlying primary disease status
- Viral infection
- Prior splenectomy
- Type of acute GVHD prophylaxis

“Standard” GVHD prevention with cyclosporin-A/methotrexate regimen

Day of transplantation	Cyclosporin-A dosage	Cyclosporin-A route
−2 to +3	5 mg/kg	IV QD by infusion over 20 hours
+4 to +14	3 mg/kg	IV QD by infusion over 20 hours
+15 to +35	3.75 mg/kg	IV QD by infusion over 20 hours
+36 to +83	5 mg/kg	po BID
+84 to +97	4 mg/kg	po BID
+98 to +119	3 mg/kg	po BID
+120 to +180	2 mg/kg	po BID

Day of transplantation	Methotrexate dosage	Methotrexate route
+1	15 mg/m^2	IV
+3	10 mg/m^2	IV
+6	10 mg/m^2	IV
+11	10 mg/m^2	IV

Combination drug prophylaxis for acute GVHD

Published trial	Diseases	Drug prophylaxis (patient numbers)	Incidence of grade II–IV Acute GVHD (p-value)
Ramsay[150], 1982	Aplastic anemia and hematologic malignancy	MTX+ATG+Pred. (32) vs MTX (35)	21% vs 48% ($p = .01$)
Storb[151], 1986	Hematologic malignancy	MTX+CsA (43) vs CsA (50)	33% vs 54% ($p = .0014$)
Santos[152], 1987	Nonmalignant and malignant disorders	CsA−MetPred. (42) vs CTX + MetPred. (40)	32% vs 68% ($p = .005$)
Forman[153], 1987	Leukemia	MTX+Pred. (53) vs CsA+Pred. (54)	47% vs 28% ($p = .05$)
Storb[154], 1989	Aplastic anemia	MTX+CsA (22) vs MTX (24)	18% vs 53% ($p = .01$)
Sullivan[155], 1989	Hematologic malignancy	Long MTX (44) vs short MTX (40) vs Long MTX+DBC (25)	25% vs 59% vs 82%
Storb[156], 1990	Nonmalignant and malignant disorders	MTX+CsA+Pred. (59) vs MTX+CsA (63)	46% vs 25% ($p = .02$)
Chao[6], 1993	Hematologic malignancy	CsA+Pred. (74) vs MTX+CsA+Pred. (75)	23% vs 9% ($p = .02$)
Deeg[157], 1997	Hematologic malignancy	CsA (60) vs CsA−MetPred. (62)	73% vs 60% ($p = .01$)
Ratanatharathorn[158], 1998	Hematologic malignancy	MTX+FK506 (165) vs MTX+CsA (164)	31.9% vs 44.4% ($p = .01$)
Chao[159], 1999	Leukemia	CsA+MTX+Pred. (90) vs CsA+MTX (96)	20% vs 18% (p = NS)

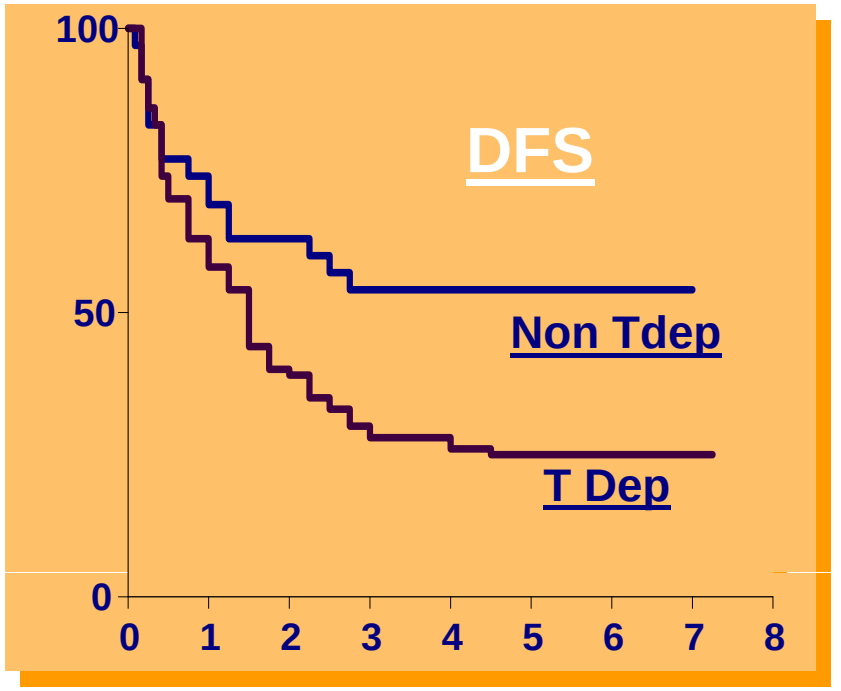
T-cell depletion for the prevention of acute GVHD

Antibody	n	Other GVHD prophylaxis	GVHD incidence	Graft failure	Relapse risk
8 monoclonals	20	CsA, MTX	15%	15%	35%
Anti-CD2	20	CsA	15%	25%	35%
Anti-CD2, 5, 7, or Anti-CD4, 5, 8	58	none	5%	19%	24%
Anti-CD8	36	CsA	28%	11%	8%
Campath-1	282	—	12%	15%	
Anti-CD6	112	none	18%	2.7%	—
SBA/E-rosette	31	none	9.6%	16%	
T10B9/Complement	25	CsA	8%	0	49% (OAS = 80% with DLI)
Campath1M–In vitro	70	None	4%	6%	30%
Campath1G–In vitro	vs	vs	vs	vs	vs
vs	459	CsA+MTX	35%	2%	29%
CsA+MTX (IBMTR)					

T-cell depletion for the prevention of acute GVHD

- **Allogeneic BMT**
  - *GVHD / Relapse*
  - **T Cell depletion**

	T Dep	Non T Dep
N	57	35
Agvhd	5 %	35 %
Cgvhd	13 %	40 %
DC de GVHD	7 %	26 %
Rejet	26 %	0 %
Rechute	47 %	17 %



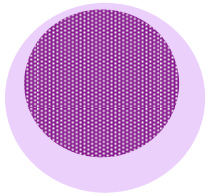
Maraninchi et al., Lancet 1987

The Multifaceted Interactions of Thymoglobuline with the Immune System

T lymphocytes

CD3/TCR,
CD2, CD4, CD5,
CD6, CD7, CD8,
CD25,CD28, CD30,
CD45, CD80, CD86,
CD152, CD49/CD29,
CD11a/CD18, LPAM-1,
CCR5, CCR7, CXCR4,
HLA I, β2-M

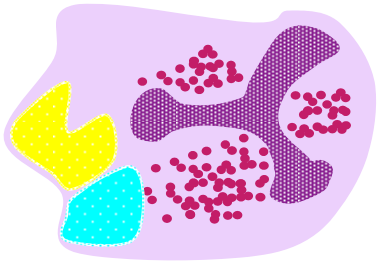
NK Cells



CD2, CD56

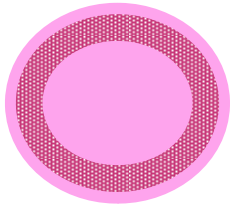
Monocytes

Granulocytes



CD4, CD11a/CD18,
CD32, CD50, CD86,
CD49/CD29, LPAM-1, MHC I

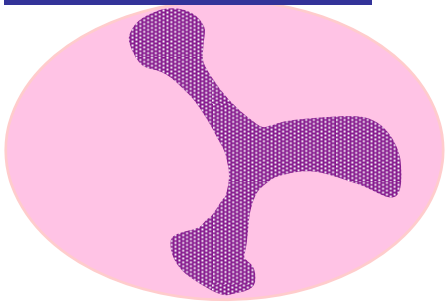
B Lymphocytes



CD19, CD20, CD25,
CD28, CD30, CD32,
CD38, CD40, CD86,
CD95, HLA-ABC, HLA-DR

Plasma Cells

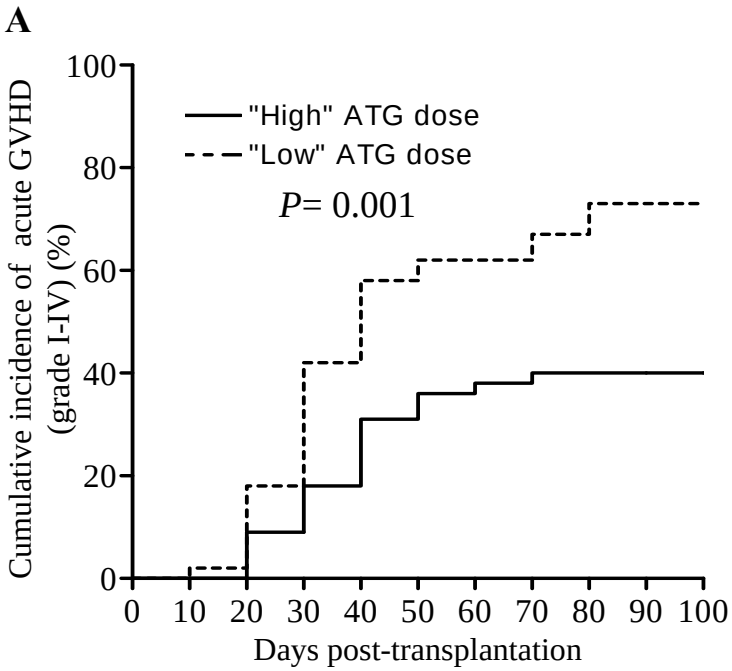
CD138

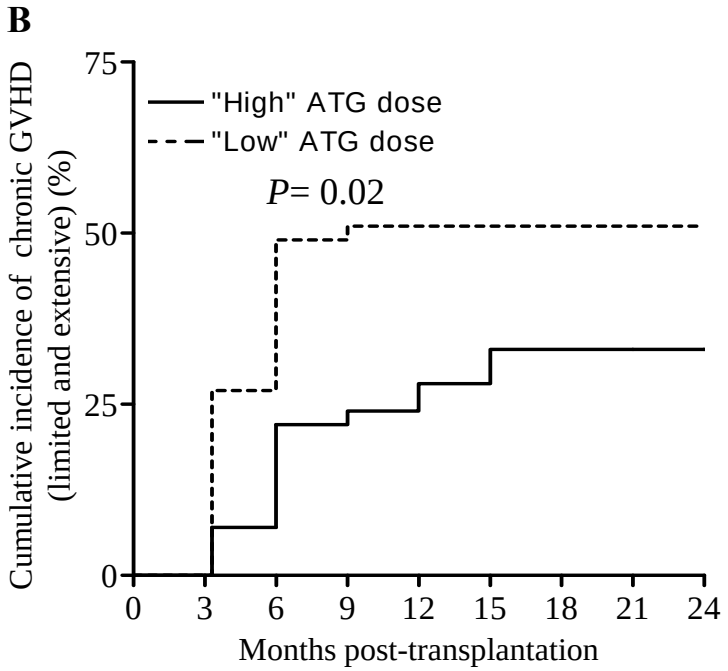


Endothelium

CD50, CD54, CD102

Thymoglobuline Dosage Can Modulate GVHD Incidence and Severity





	N	RR	95% CI	*P*
• *CMV reactivation*	84			
- Graft source (BM)		4.9	2.4 - 10.0	*0.00001*
- Grade 2-4 acute GVHD		2.6	1.3 - 5.1	*0.006*
• *Bacterial infections*	101			
- High dose steroids for refractory aGVHD		4.8	2.2 - 10.7	*0.0001*

Mohty et al., Blood 2003 and Leukemia 2004

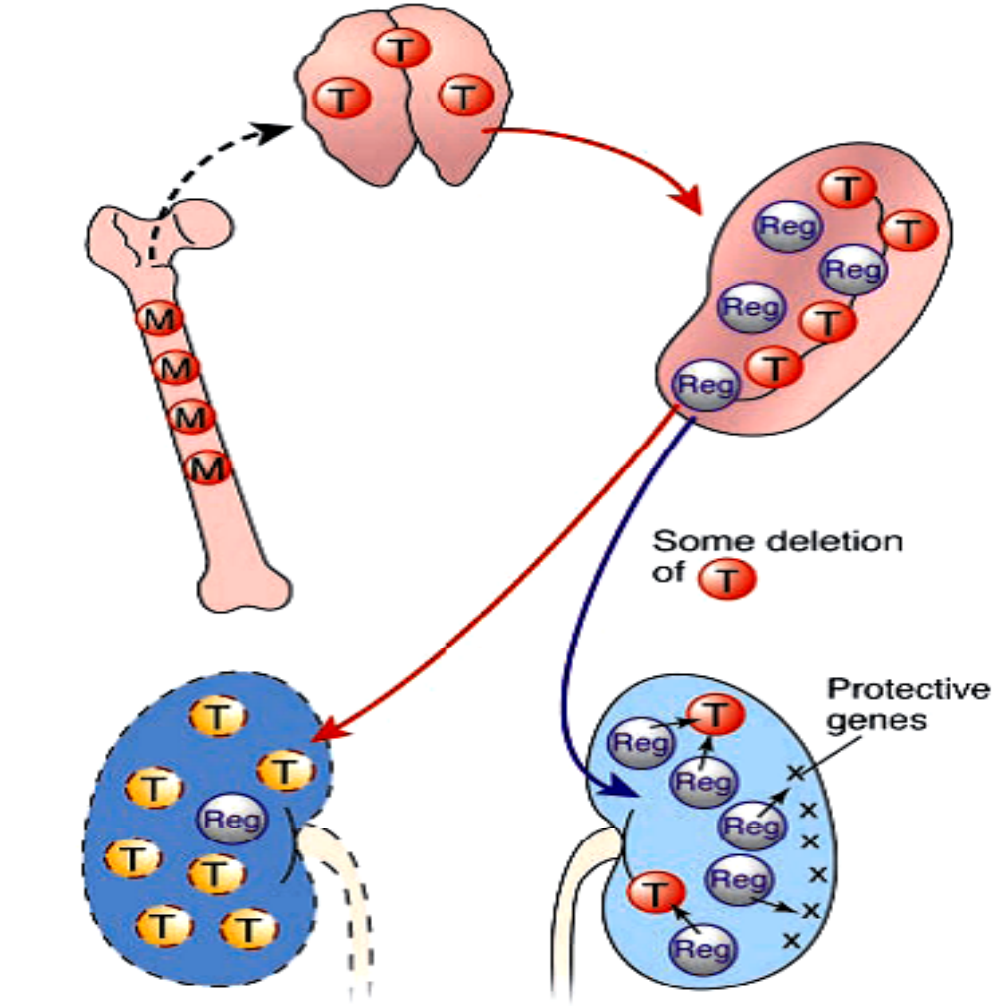
Treatment of acute GVHD

***Cortico-steroids are* the standard for the first-line treatment of acute GVHD**

Monoclonal Ab or receptor antagonist therapy for steroid-resistant acute GVHD

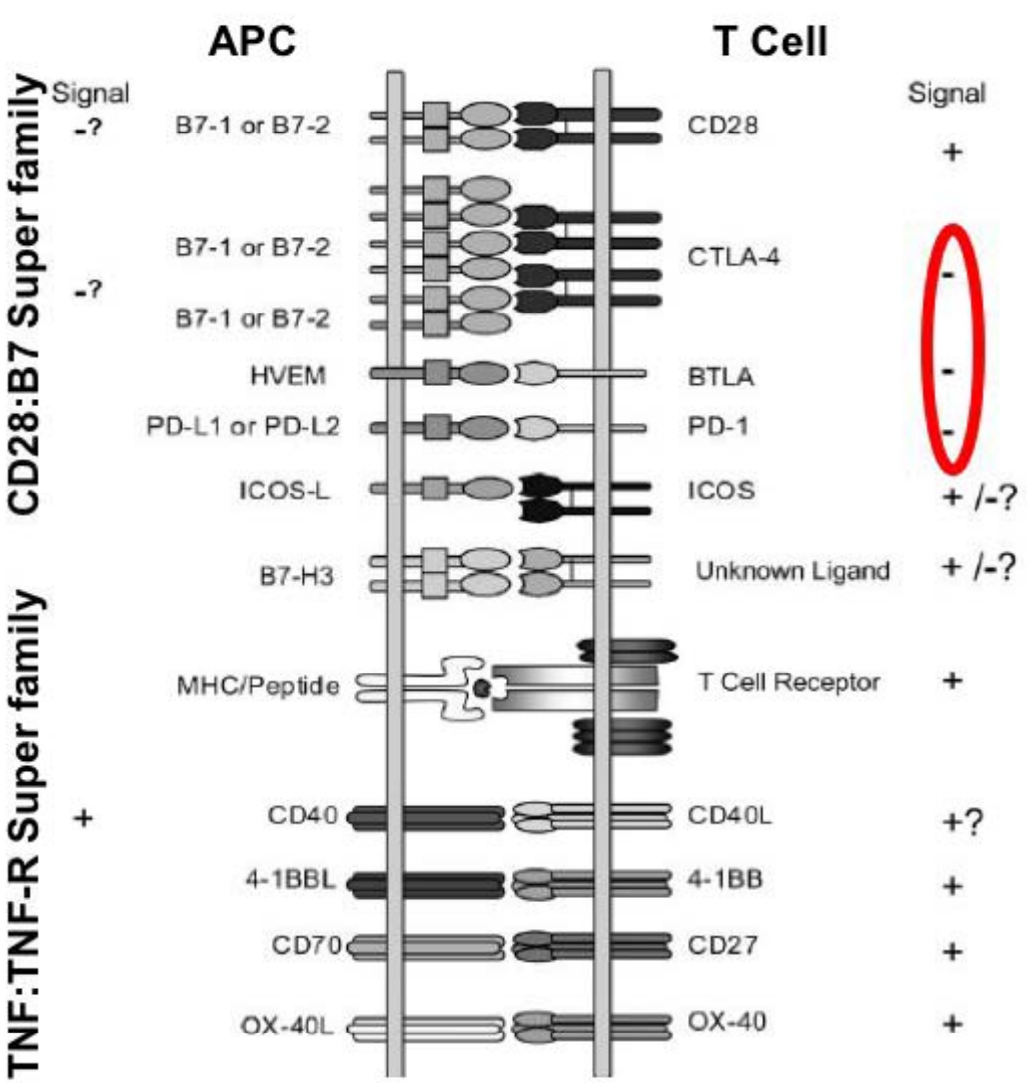
Trial	Other GVHD therapy	Antibody	Description	Dose	Response
Blood 1990; 75:1426	CSA+MP	H65-RTA (Zomazyme)	Anti-CD5 antibody labeled with ricin A chain	0.05 mg/kg/day to 0.33 mg/kg/day IV for up to 14 consecutive days	16–34 durable complete and partial responses
Blood 1990; 75:1426	CSA+MP	B-C7	Anti–TNF-α antibody	0.1–0.4 mg/kg IV daily × 4 days then every other day × 2	74% partial response in 3 days, relapse in most when therapy stopped
Blood 1990; 75:1426	CSA+MP	IL-1ra	IL-1 receptor antagonist	400–3200 mg a day continuous IV infusion for 7 days	10/16 improved
Transplant Int 1991; 4:3	CSA+MP	25.3	Murine anti–LFA-1 (CD11a) antibody	0.1 mg/kg IV over 4 hours daily × 5 days	8/10 (80%) partial response
Blood 1990; 75:1426	Cyc-A+Pred.	Humanized anti-Tac antibody	IL-2α receptor antibody	0.5, 1.0, or 1.5 mg/kg IV over 1 hour single dose, repeated once between 11–48 days after first dose in responding patients	4/20 complete response, 4/20 partial response
BMT 1994; 13:563	TCD, CSA+MP	BT 563 (B-B10)	Murine anti-human IL-2α receptor antibody	0.2 mg/kg IV over 30 min daily (mean 27 days, range 12–70 days) until GVHD < grade II for 48 hours	11/15 complete remission, 2/15 partial remission, 6/13 relapsed
Blood 1990; 75:1426	CSA+MP	BT 563 (B-B10)	Murine anti-human IL-2α receptor antibody	5.0 mg IV bolus daily × 10 days then every other day for 10 days	21/32 complete response, 6/32 partial response, 10/27 relapse
Blood 2000; 95:83	CSA or Tacrolimus +MP	Daclizumab	Humanized monoclonal IgG1 against IL-2 receptor	1.0 mg/kg IV infusion over 30 min on days 1, 4, 8, 15, 22	16/43 complete response (37%) with an overall response rate of 22/43 (51%)

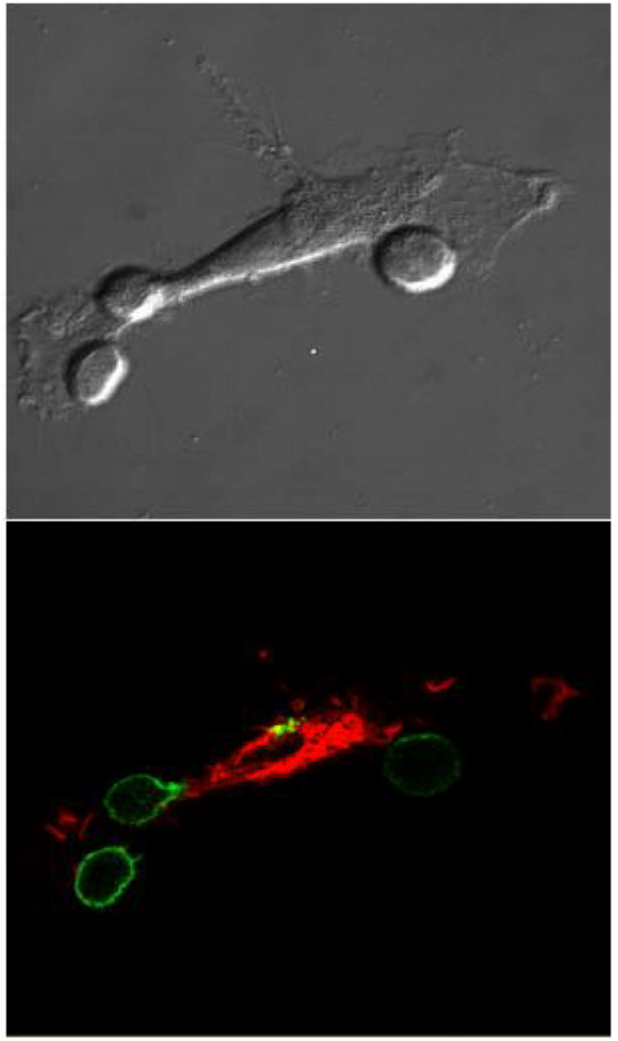
Tolerance Depends on the Local Dominance of Regulatory T Cells



Adapted from Waldmann and Cobbold, Science 2004

Immunosuppression: the Promise of Specificity

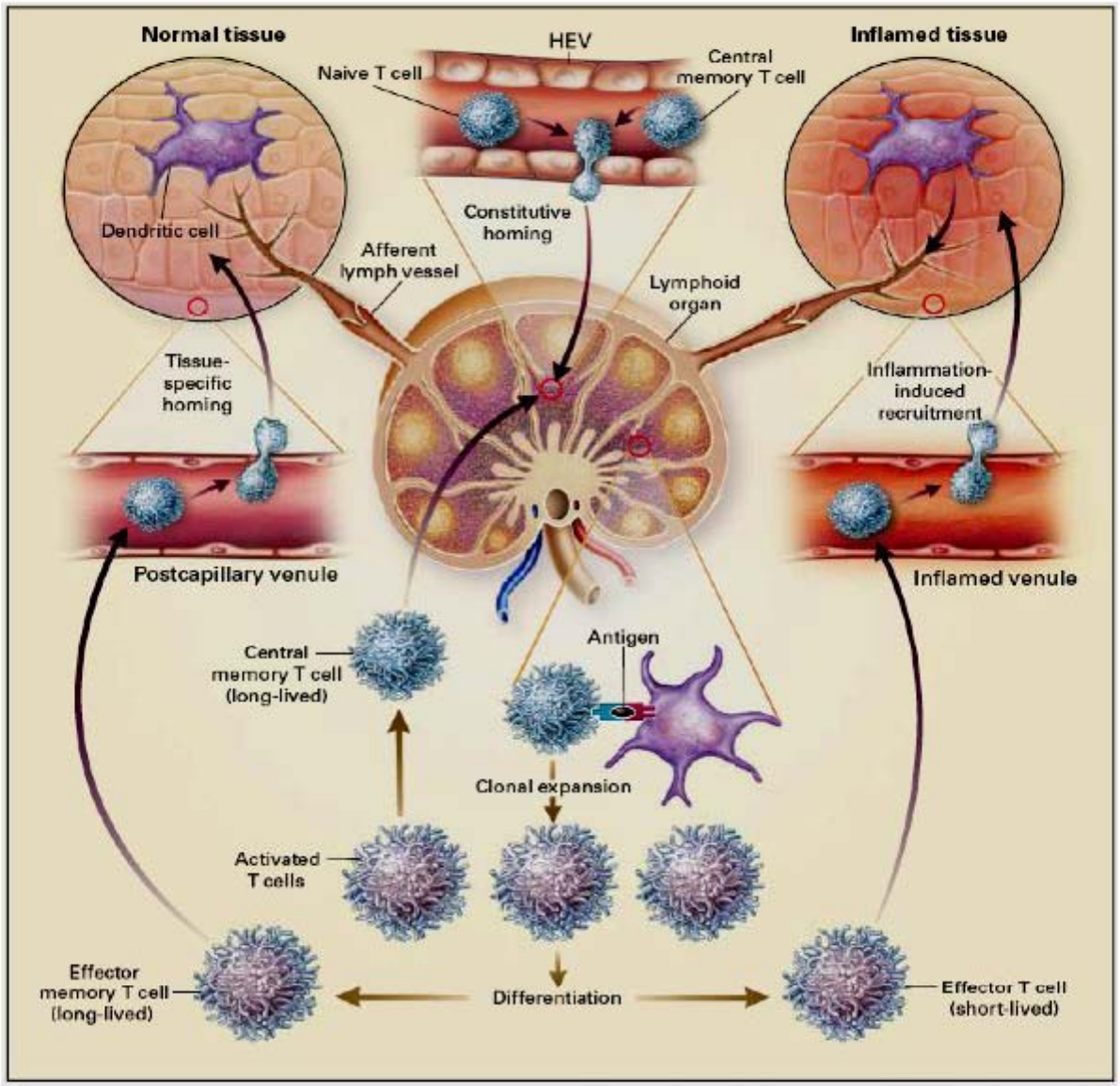




CD83

LAT *(linker for activation of T*

T-Cell Function and Migration: Two Sides of the Same Coin !



Von Andrian and Mackay, N Engl J Med 2000