Society for Immunotherapy of Cancer (SITC)

Immunotherapy for Treatment of Hematologic Malignancies

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MUSC
HOLLINGS CANCER CENTER
A National Cancer Institute Designated Cancer Center

Disclosure

National Institute
of Allergy and
Infectious Diseases

Bone Marrow Transplantation (BMT)
Hematopoietic Stem Cell Transplantation (HSCT)

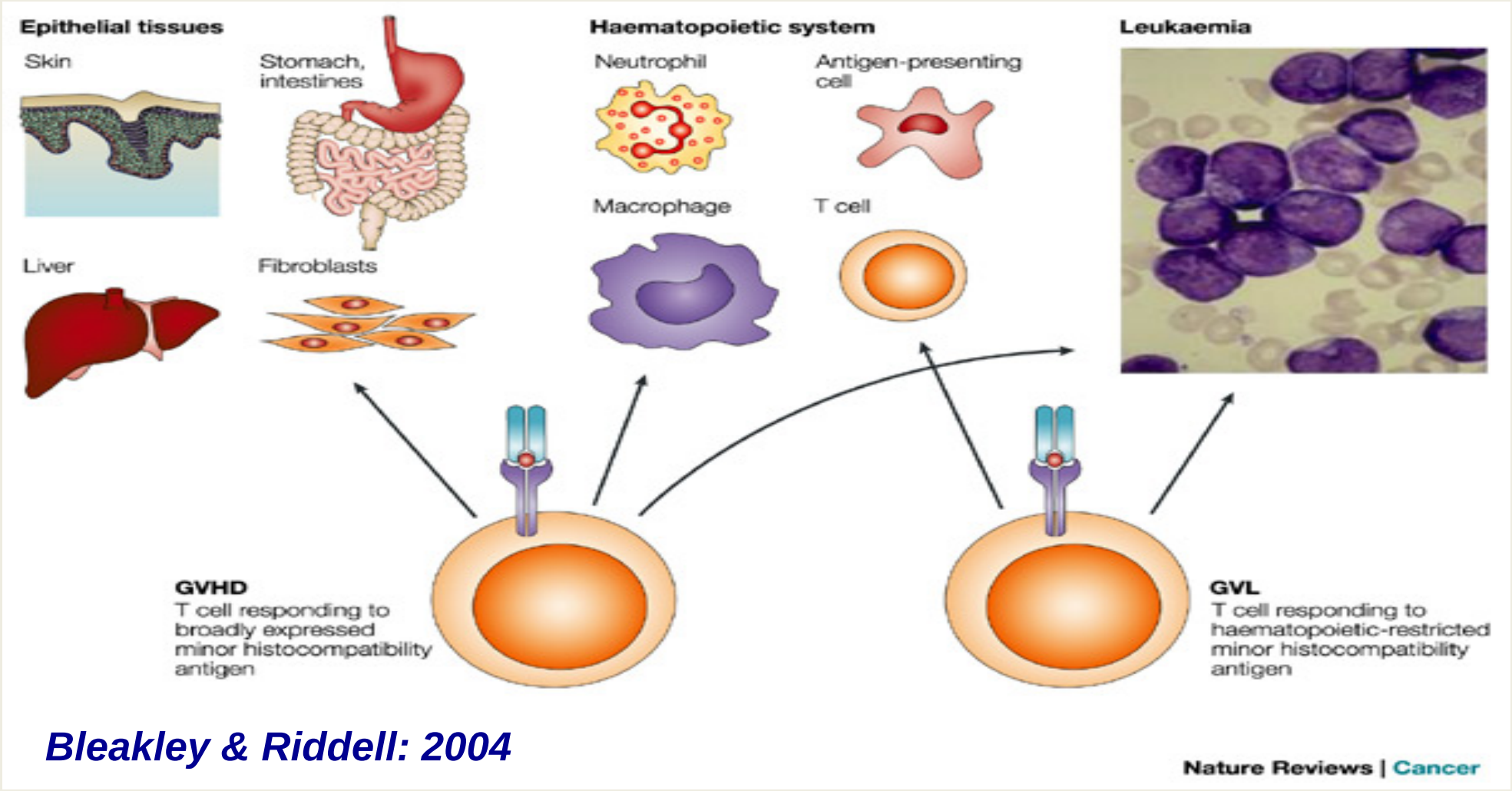
Applications

Hematological disorders
Hematological malignances
Solid tumors

Complications

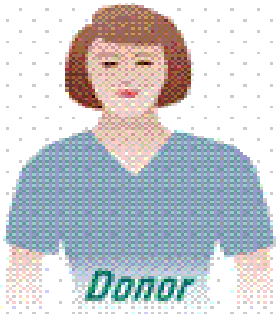
Graft-versus-host diseases
Tumor relapse
Infection
Graft rejection

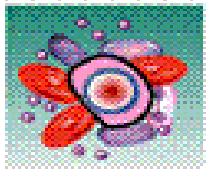
Separating GVHD and GVL effects



Bleakley & Riddell: 2004

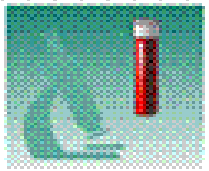
The Allogeneic Transplant Process





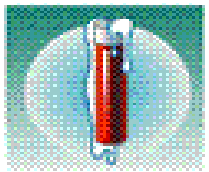
1 Collection

Stem cells are collected from the patients bone marrow or blood.



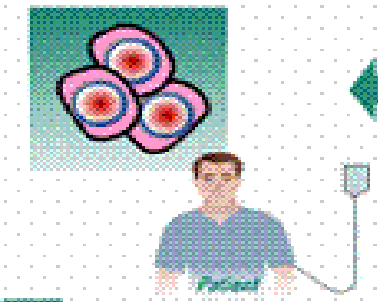
2 Processing

Bone marrow or periferal blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process



3 Cryopreservation

Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.



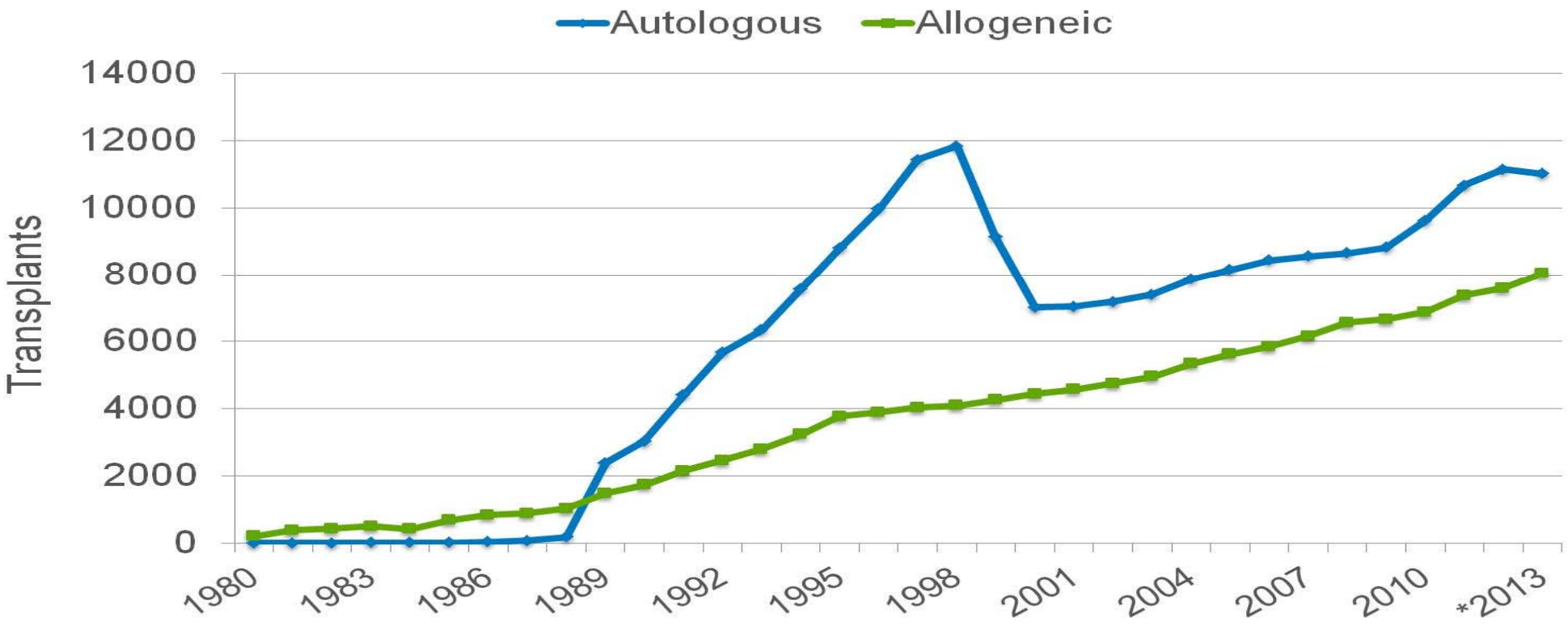
4 Chemotherapy

High dose chemotherapy and/or radiation therapy is given to the patient.

5 Infusion

Thawed stem cells are infused into the patient.

Annual Number of Transplant Recipients in the US by Transplant Type



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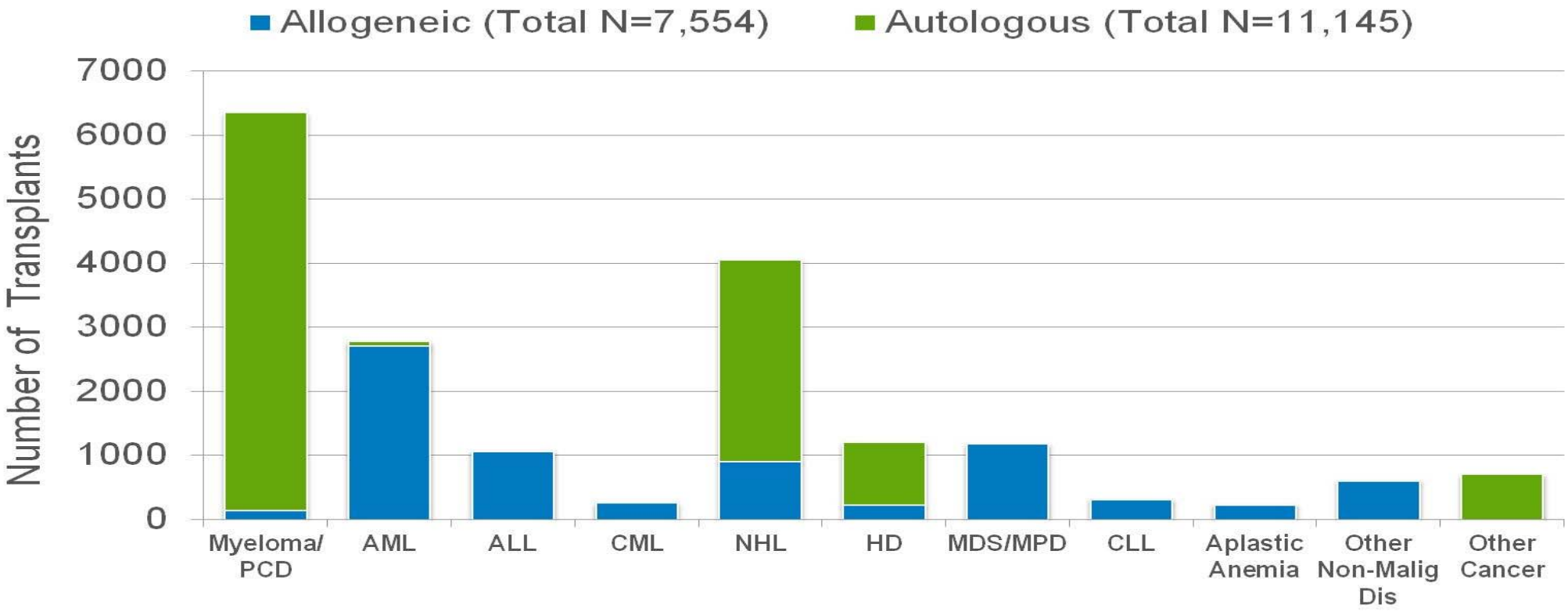
* 2013 Data incomplete

Indications for Hematopoietic Stem Cell Transplants in the US, 2012



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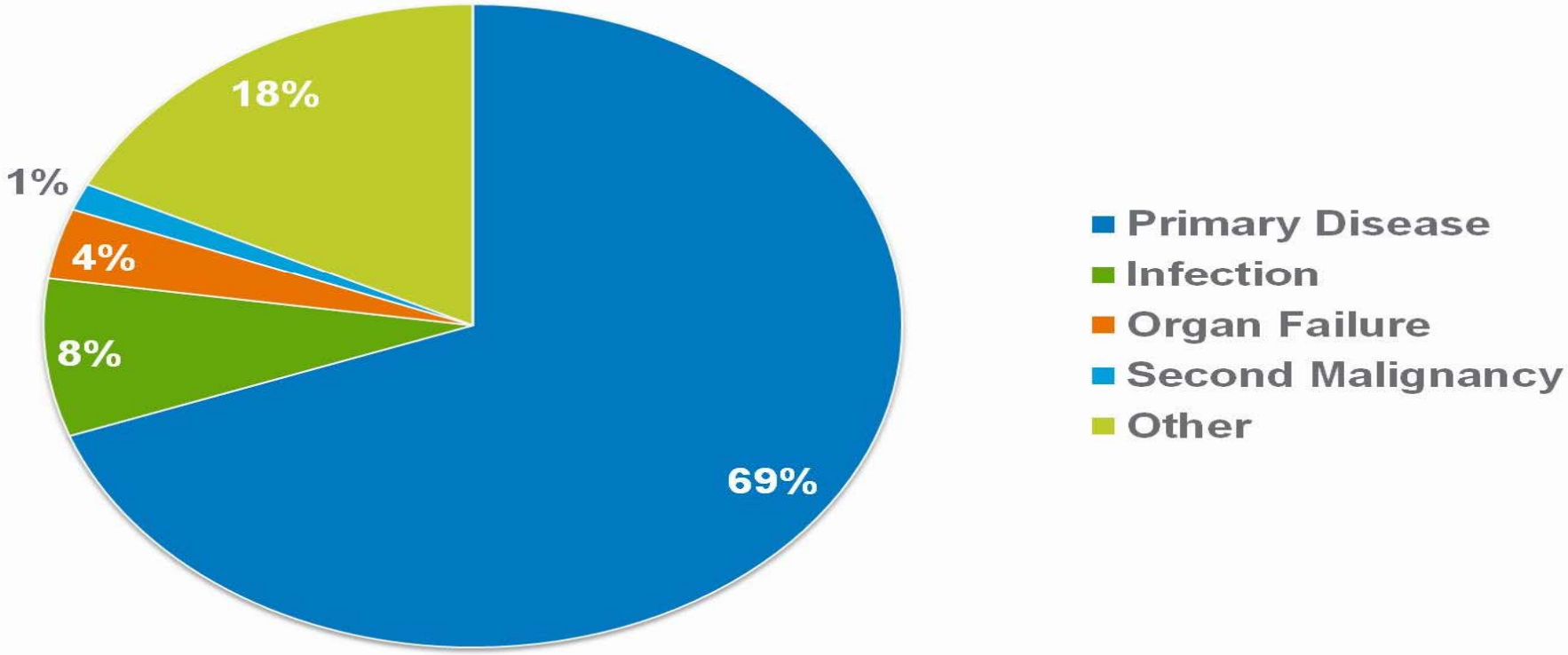
Causes of Death after Autologous Transplants done in 2010-2011



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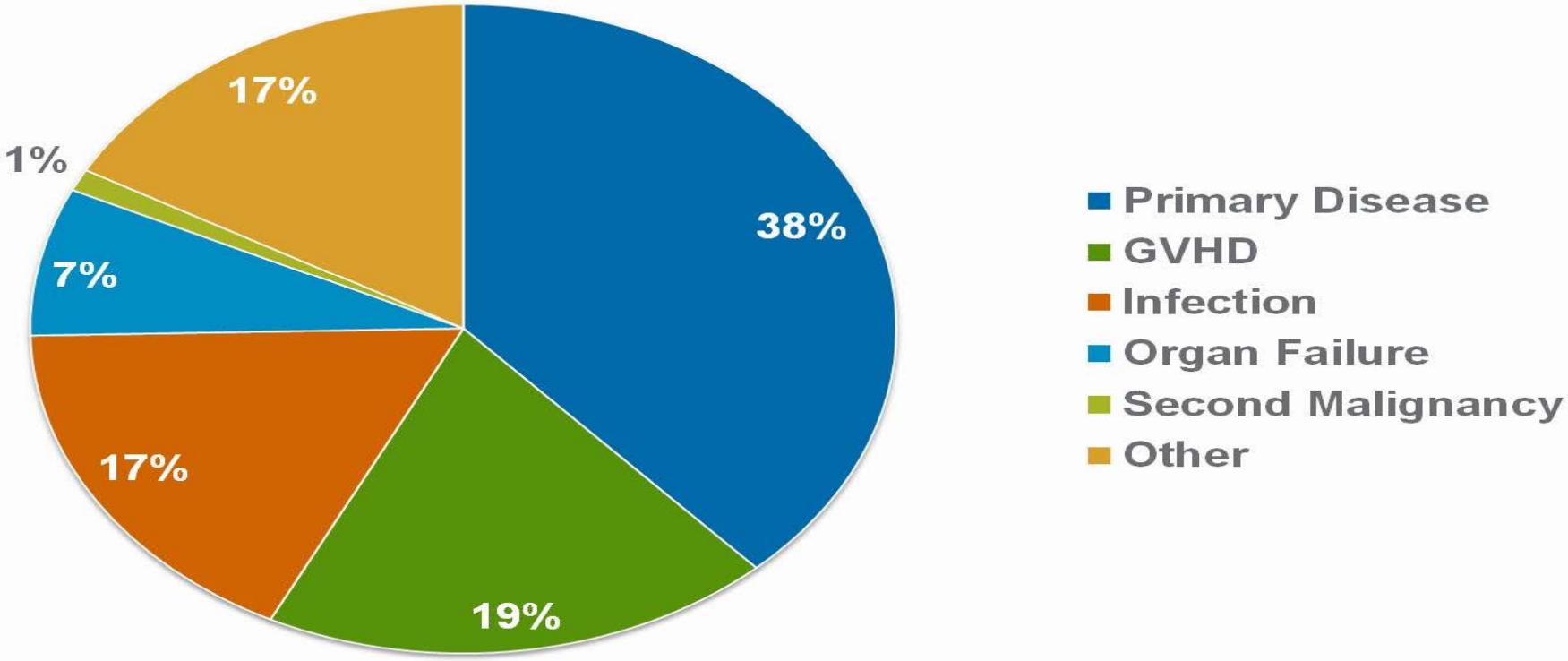
Causes of Death after Unrelated Donor Transplants done in 2010-2011



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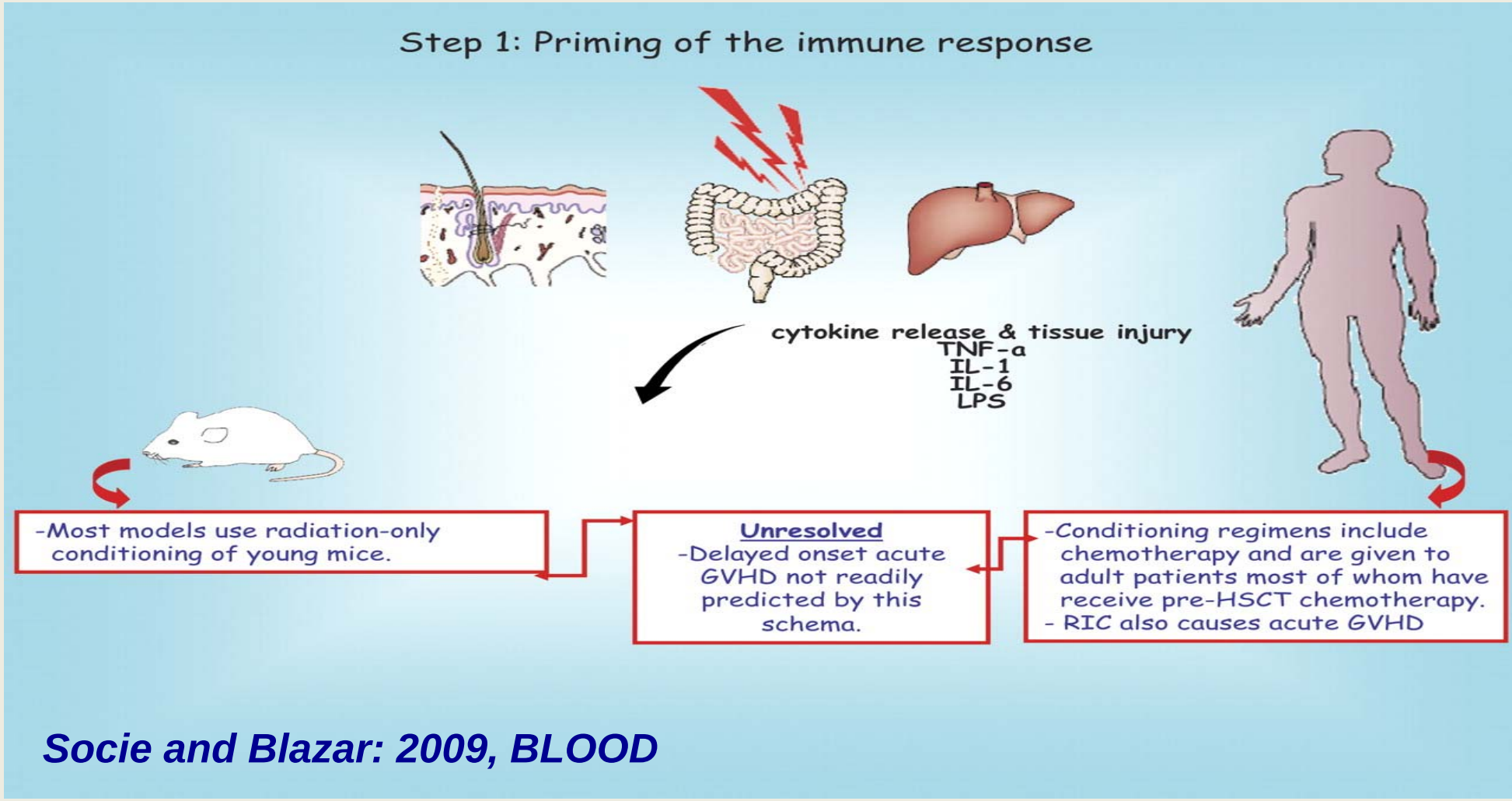
Billingham's GVHD Criteria

- Genetic disparity between donor and host
- Immune deficiency
- Immune cells present in donor graft

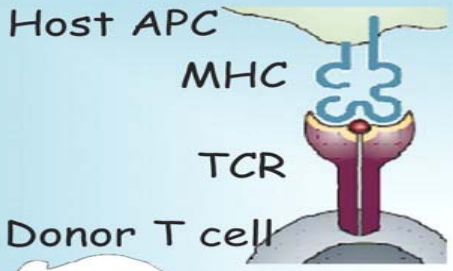
Priming of the immune response

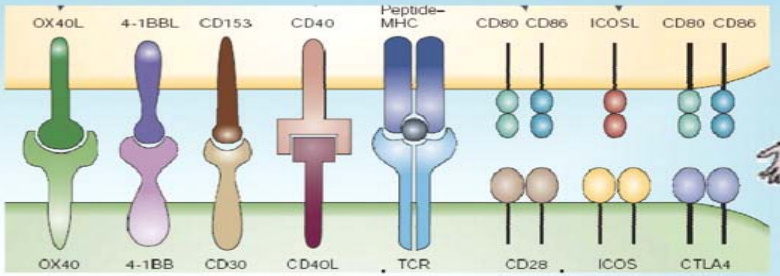


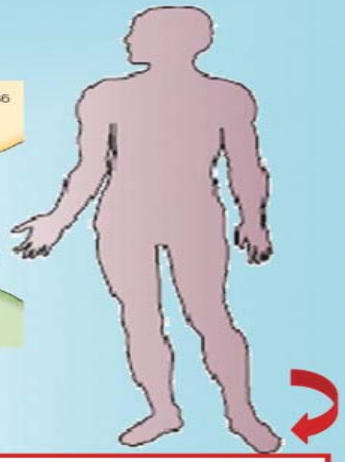
Socie and Blazar: 2009, BLOOD

T-cell activation and costimulation

Step 2: T-cell activation and co-stimulation





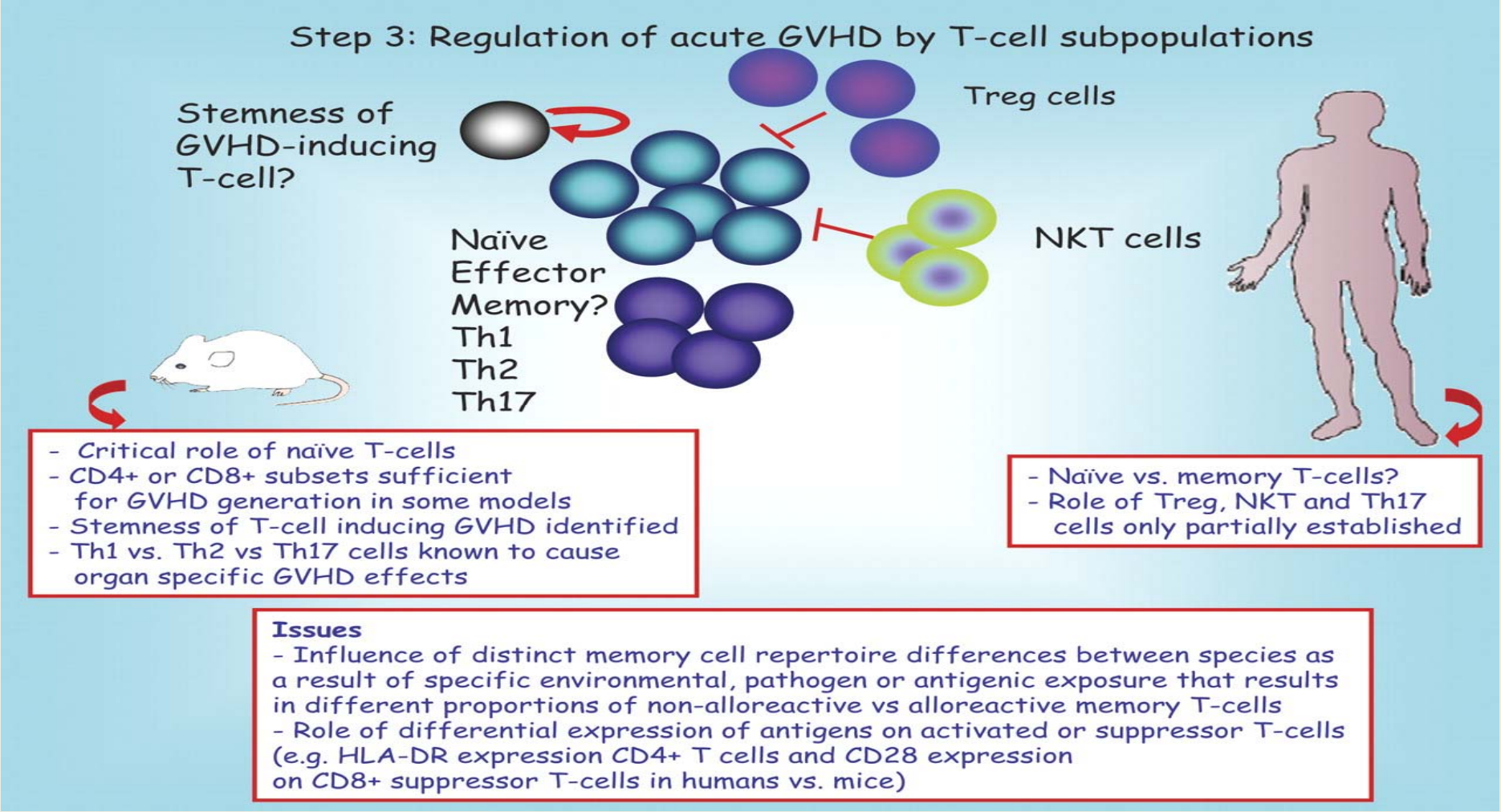


-MiH antigenic disparities that cause acute GVHD have been identified
- Host APCs proven to initiate GVHD
- Critical role of positive and inhibitory co-stimulatory molecules proven

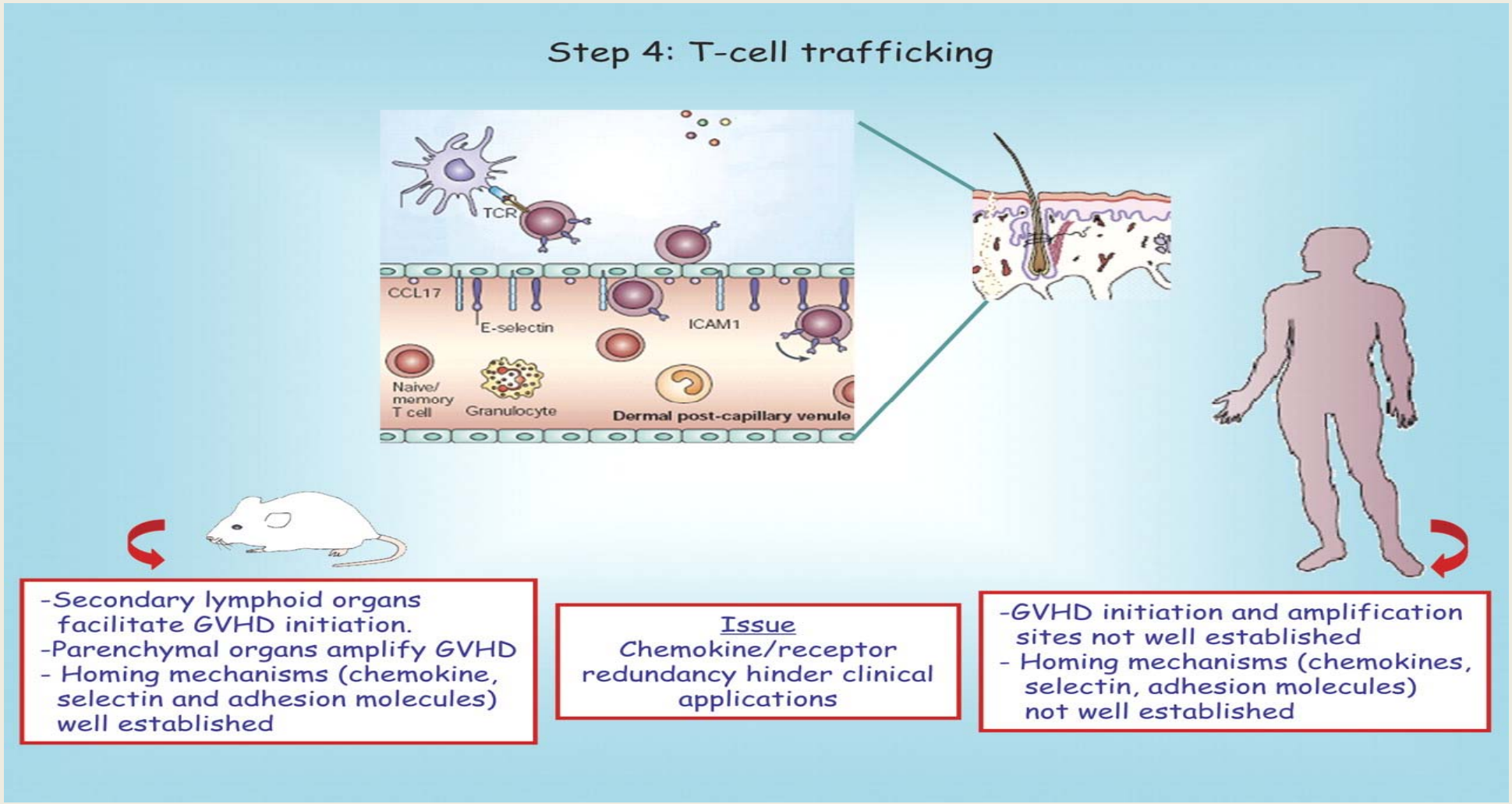
- HLA antigen disparities that cause acute GVHD have been identified. Only a few MiHa antigens that cause GVHD have been identified.
- Host APCs in GVHD not well studied to date
- Role of positive and inhibitory co-stimulatory molecules expression in vivo not well studied

Issues
Reagents tested in mice or large animals may have different functional effects due to distinct species-specific expression patterns or targeted epitopes (e.g. cytokine syndrome see with anti-CD28 Ab in humans but not large or small animals)

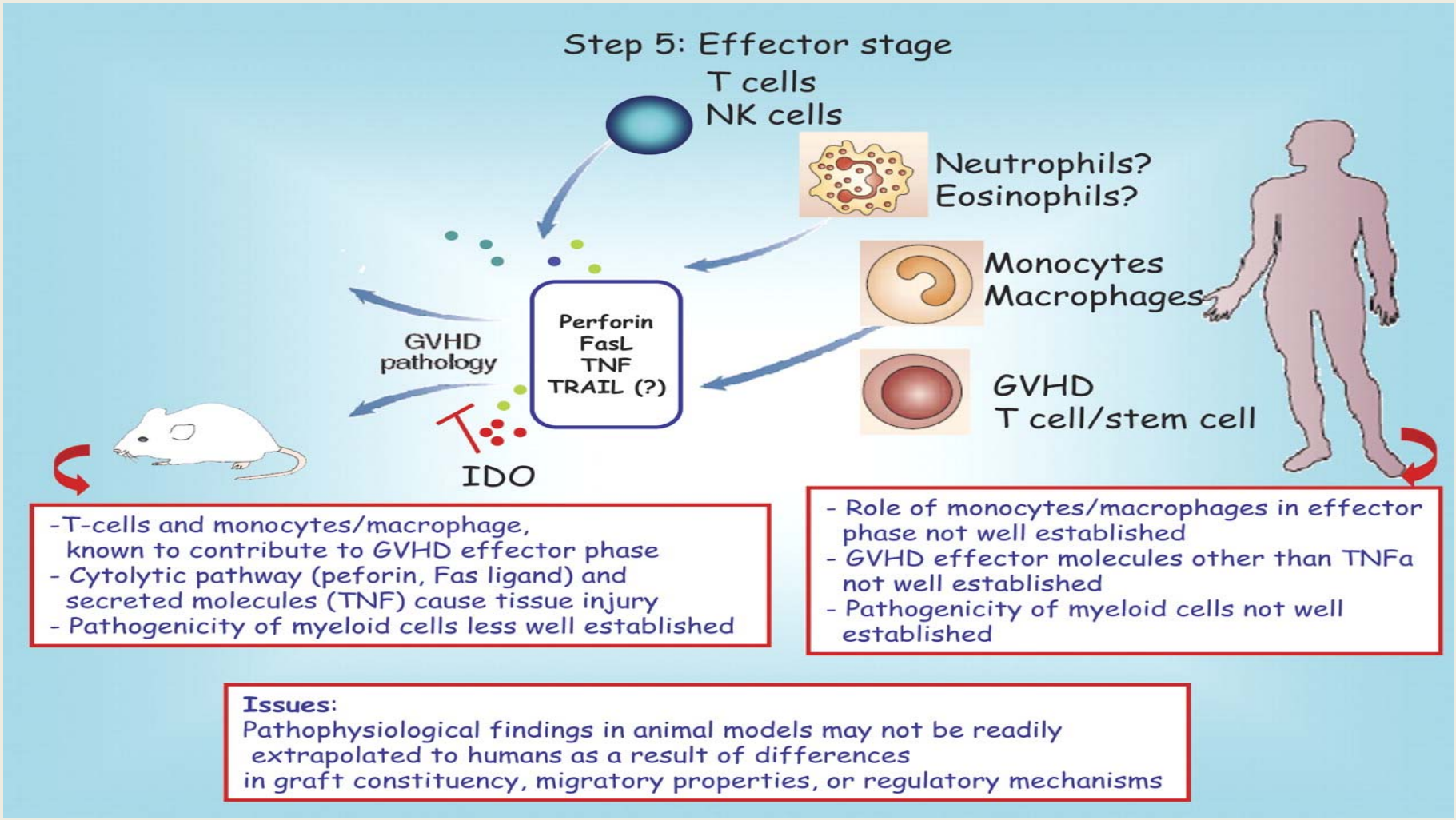
Regulation of acute GVHD by T-cell subsets



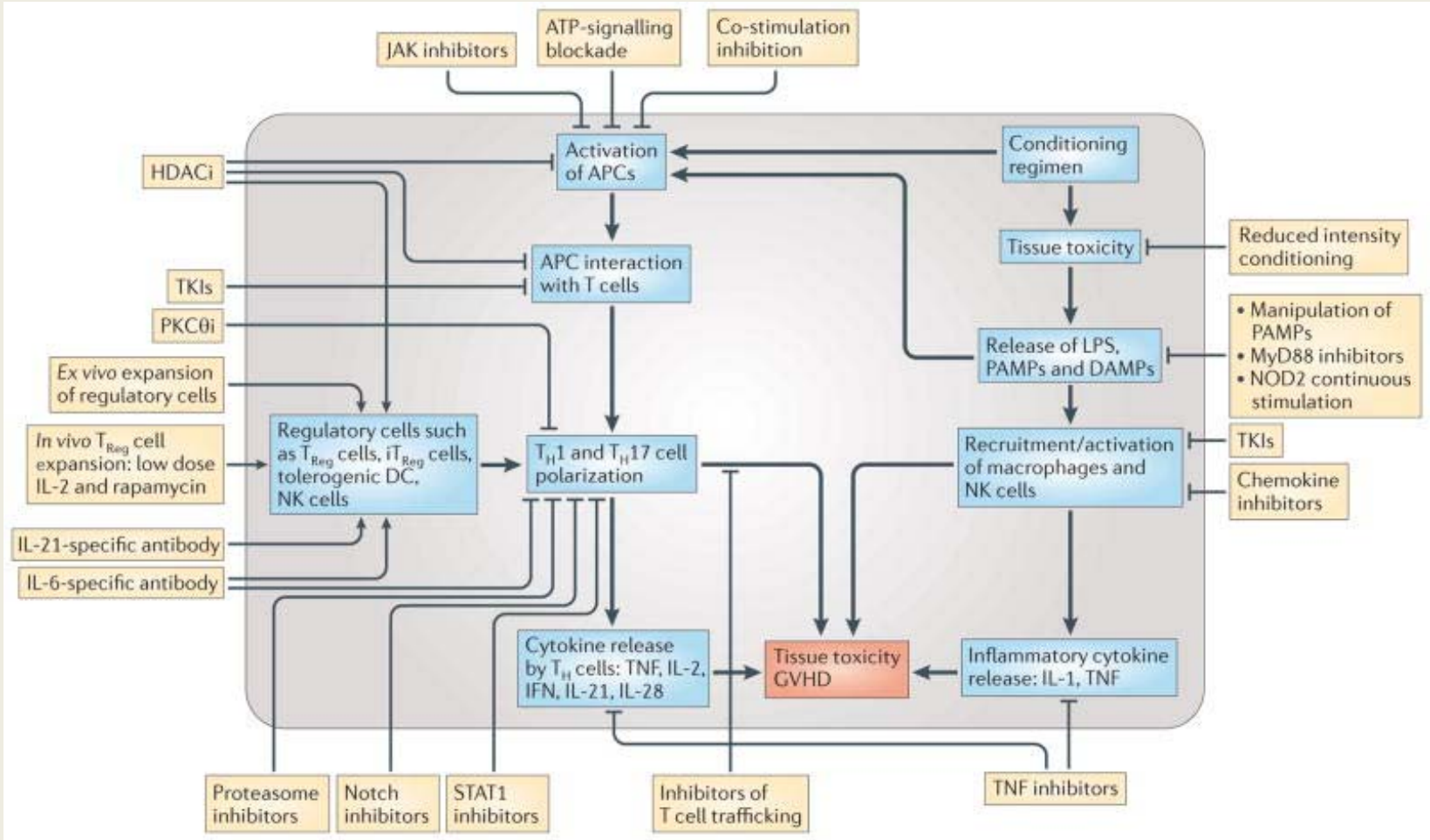
T-cell trafficking



Effector Phase



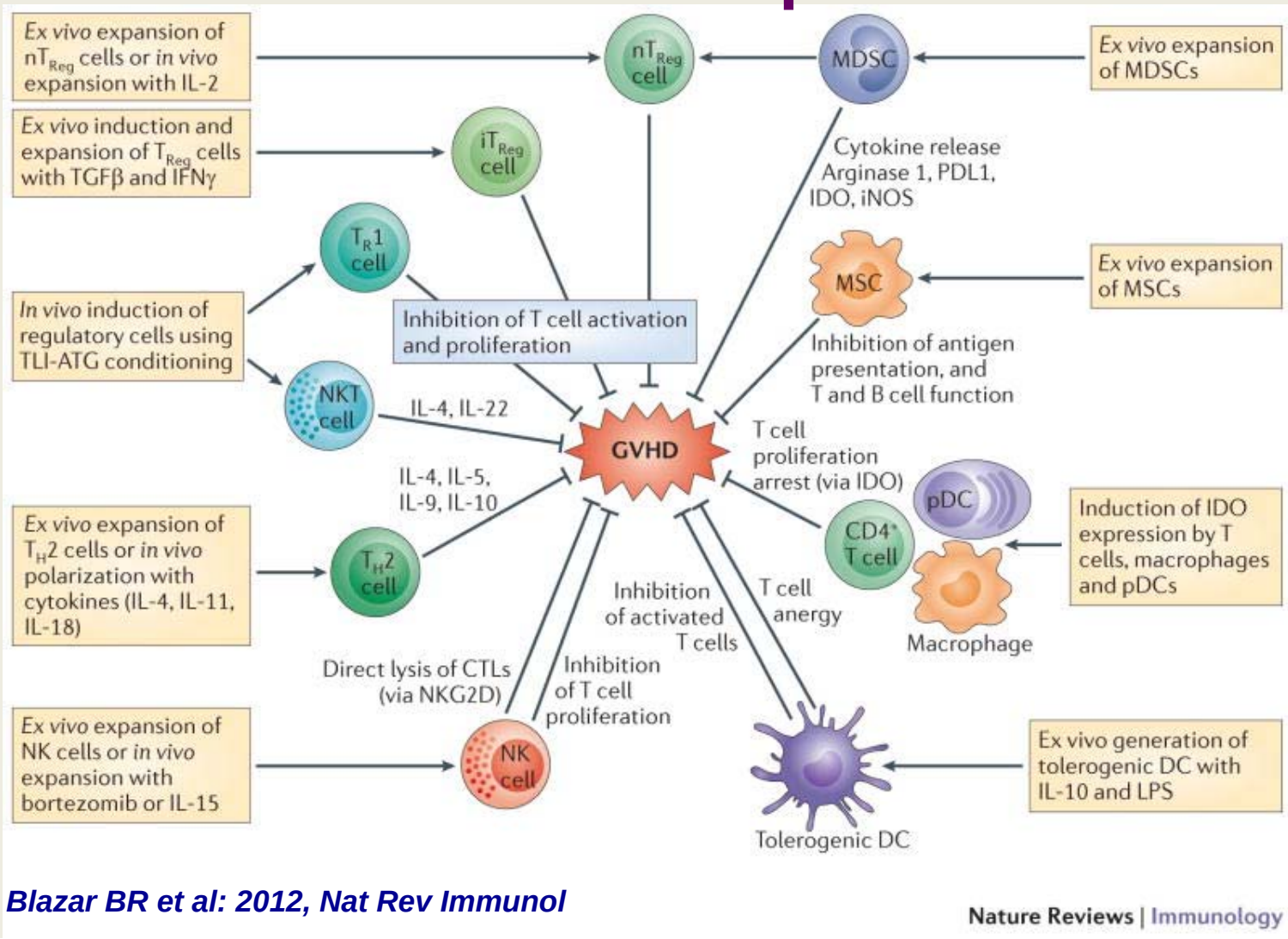
Therapeutic Approaches for GVHD



Blazar BR et al: 2012, Nat Rev Immunol

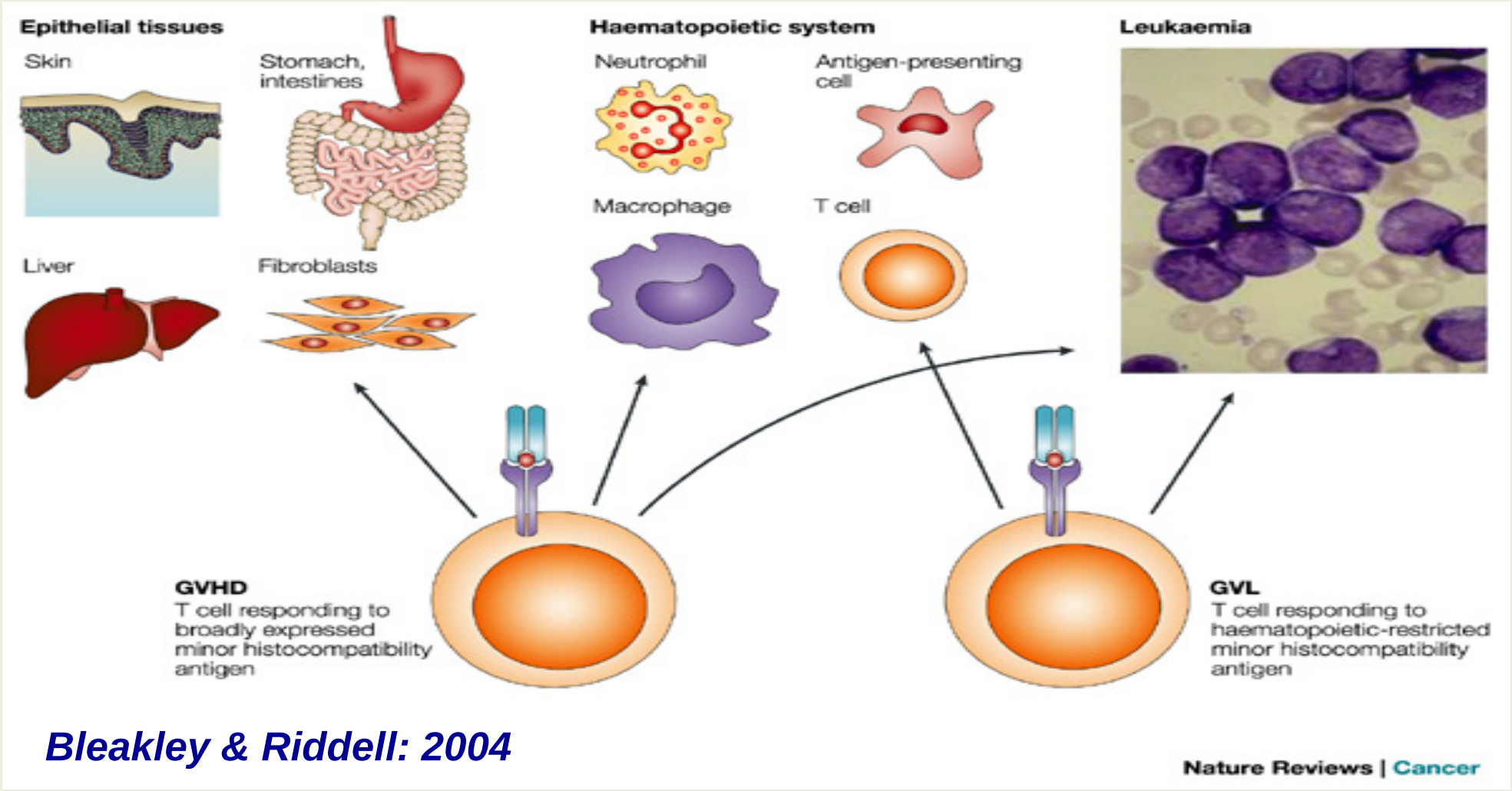
Nature Reviews | Immunology

Cellular Immunotherapies in GVHD



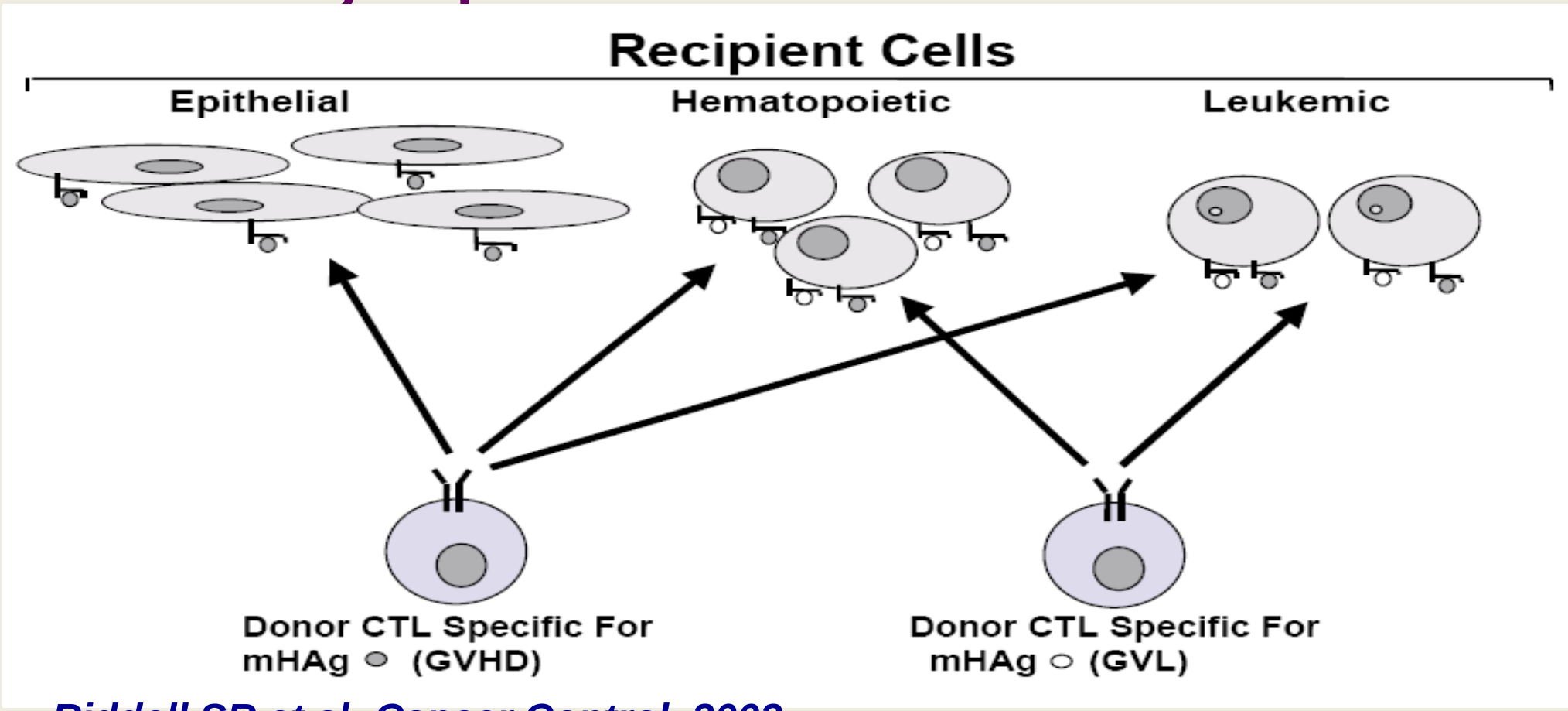
Blazar BR et al: 2012, Nat Rev Immunol

Separating GVHD and GVL effects



Bleakley & Riddell: 2004

Tissue-specific mHAgs may separate GVL and GVHD



Riddell SR et al: Cancer Control, 2002

Human mHAgs

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.

Bleakley & Riddell: 2004

HY-directed responses

Table 8. Effect of donor/recipient sex on death

Donor/recipient sex	Adjusted hazard ratio*	95% CI	*P*
Female/male	1	NA	NA
Male/female	0.82	0.72-0.94	.004
Female/female	0.81	0.72-0.92	.002
Male/male	0.87	0.78-0.97	.01

NA indicates not applicable.

*Adjusted for patient and donor age, GVHD prophylaxis, disease status, conditioning regimen, and patient/donor CMV serostatus.

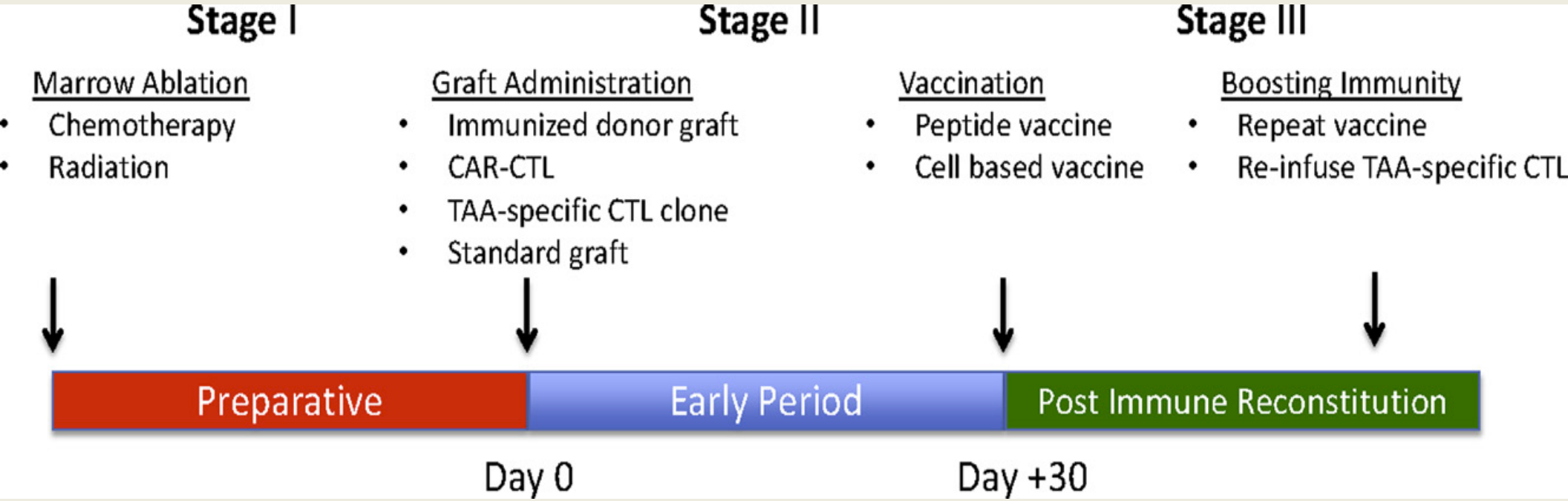
Randolph SB et al: Blood, 2004

Leukemia Associated Antigens

Leukemia antigens				
Class	**Example(s)**	**Pros**	**Cons**	
Tumor-associated antigens (TAAs)	WT-1 [25], hTERT [26], PRAME [27], HMMR/Rhamm [28]	- multiple candidates identified- often shared by > 1 malignancy	- present on normal tissue	**- self antigens that generate low-avidity T-cells- must be successfully processed and presented by the MHC of the malignant cell**
Tumor differentiation antigens	PR1 [29], CG1 [30], CD33 [31]	- more restricted distribution than TAAs	- present on subset of normal cells, which can include hematopoietic stem cells	
Cancer testis (CT) antigens	Cyclin-A1 [32], NY-ESO-1 [33] , MAGE [34]	- frequently restricted to non-essential tissues and tumor	- few identified in leukemia	
Minor histocompatibility antigens (mHAs)	HA-1 [35], ACC1 [36], T4A [37], LB-LY75-IK [38]	- result in high avidity allo T-cells since epitopes are foreign to donor- some are largely restricted to hematopoietic compartment	- Necessitate rescue with mHA-negative stem cells to restore normal hematopoiesis- need for allogeneic TCRs	**- must be successfully processed and presented by the MHC**
Tumor-specific antigens (neoantigens)	BCR-ABL [39], FLT3-ITD [40], B-cell receptor idiotype [41]	- result in high avidity autologous T-cells- many derive from proteins critical in leukomogenesis	- individual-specific- few identified in leukemia since mutation rate is low	
Oncoviral antigens	HTLV-I Tax protein [42]	- generate very high-avidity T-cells	- only relevant to virus-initiated malignancies	
Extracellular antigens	CD19 (see CD19 section), Lewis Y [43], CD22 [44], ROR1 [45]	**-MHC-independent**- interaction with CAR is high-affinity	- many are present on normal tissues	- **require CAR for targeting**, which can mediate on-target, off-tumor adverse effects

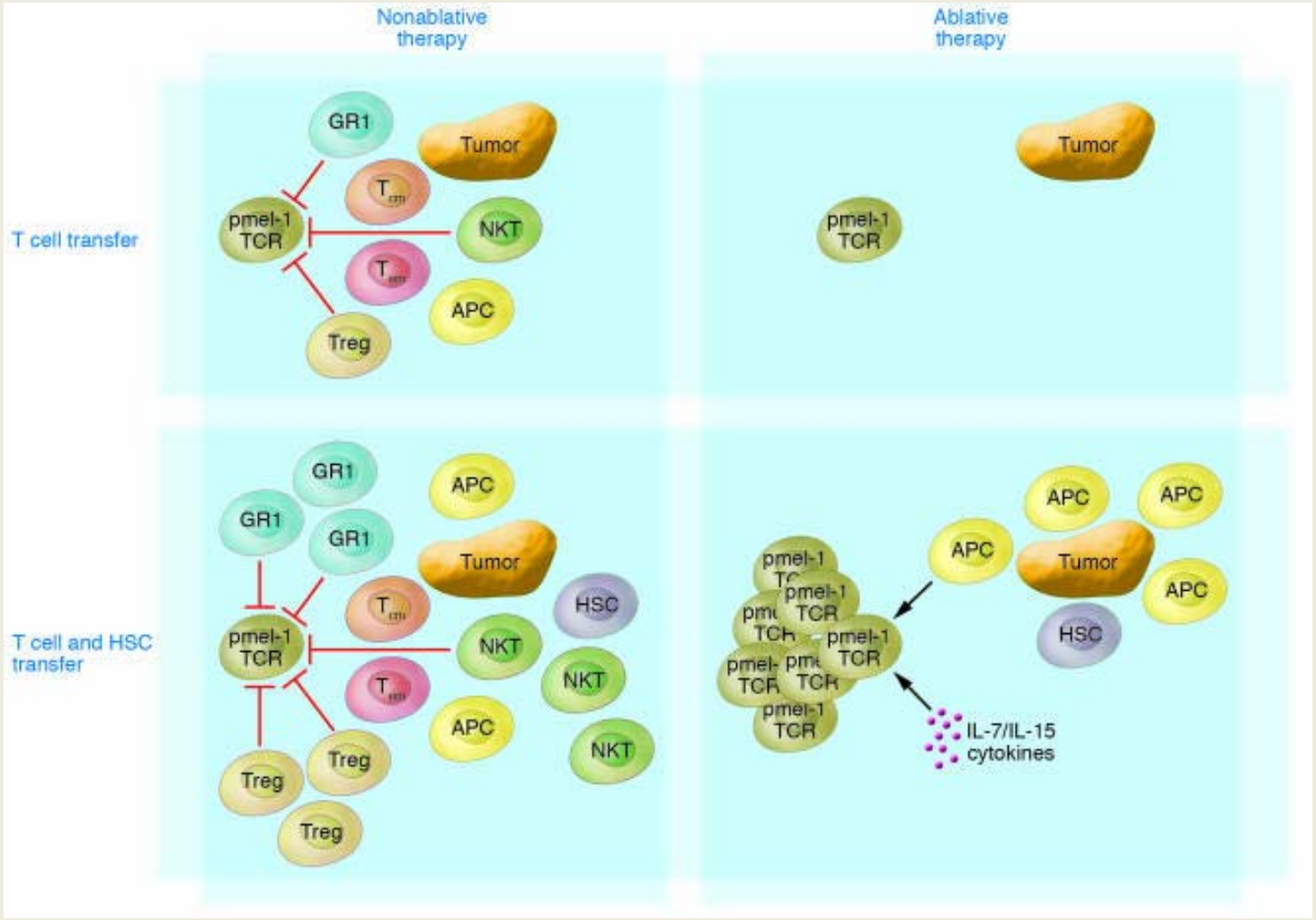
Garber HR et al: Mol & Cell Therapies, 2014:2:25

Tumor-associated Antigen-targeting Therapies



Garber HR et al: Mol & Cell Therapies, 2014:2:25

Myeloablation and HSC Enhance Immunotherapy



Anasetti & Mule: J Clin Invest, 2007

Research in Yu's Lab

- **Control T-cell differentiation**
- **Modify T-cell costimulation**
- **Target kinases for T- and B-cell activation**
- **Adoptive T-cell therapy: effector and regulatory**
- **Combinational therapy with HSC and T cells for solid tumor, such as melanoma**

Take Home Messages

- **HSCT is a classic cancer immunotherapy through GVL effect**
- **GVHD is a major complication**
- **Separating GVH and GVL response is a major challenge**
- **Anti-tumor effect can be enhanced by targeting mHAg or TAA**
- **Combinational therapy with HSC and T cells increases the efficacy of immunotherapy**

Questions

1. Hematopoietic stem cell transplantation (HSCT) is a therapeutic procedure. What is the major application of HSCT?

A. Genetic or congenital defects
B. Hematological disorders
C. Hematological malignances
D. Solid tumors

Questions

2. It is a major challenge to suppress GVHD while preserving GVT effect after allogeneic HSCT. Targeting what antigen(s) is promoting GVT effect while limiting GVHD?

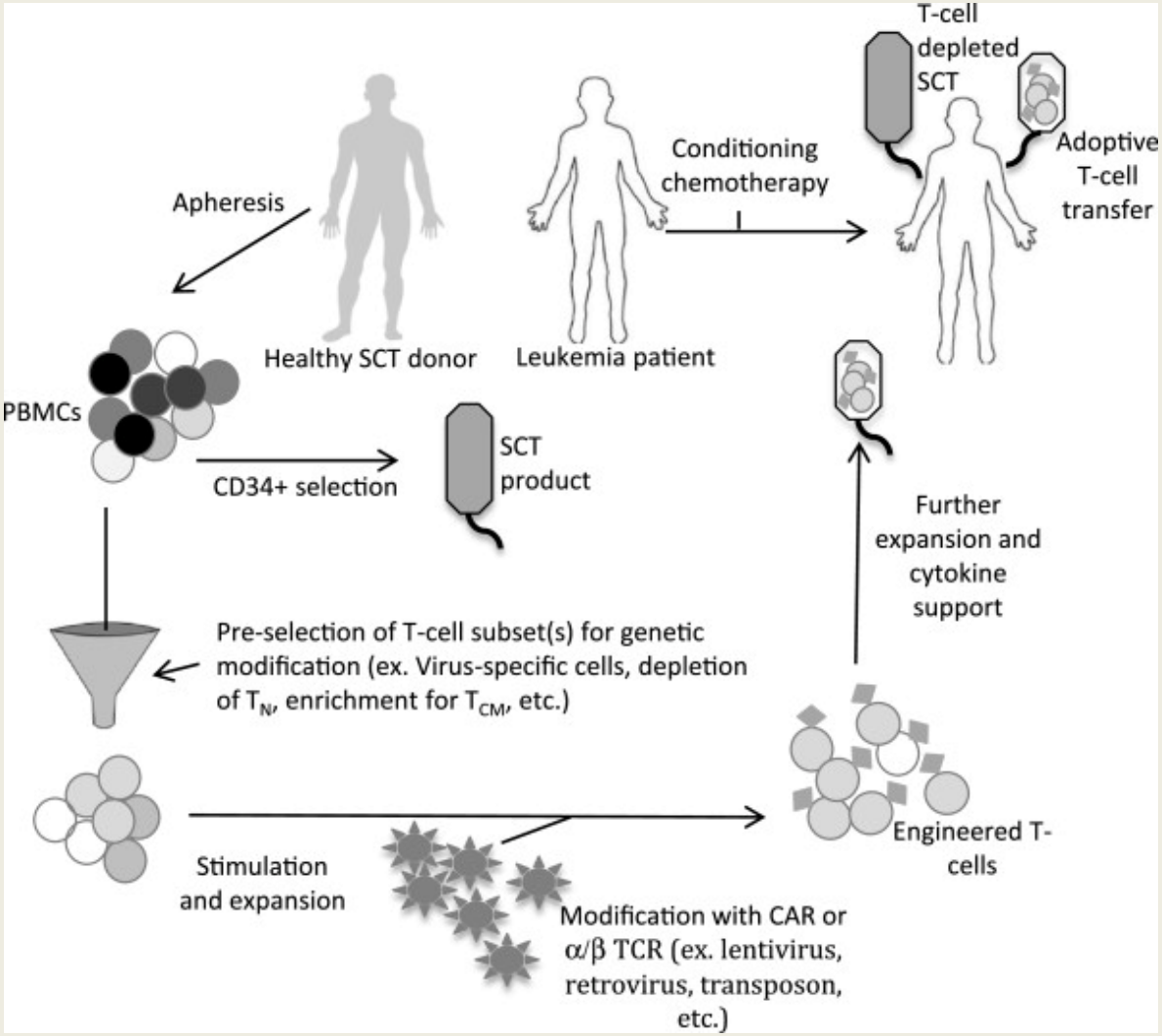
A. MHC antigens
B. Minor histocompatibility antigens (miHA)
C. Tumor associated antigens (TAA)
D. miHA and TAA

Questions

3. How does HSCT enhance adoptive T-cell immunotherapy against cancer?

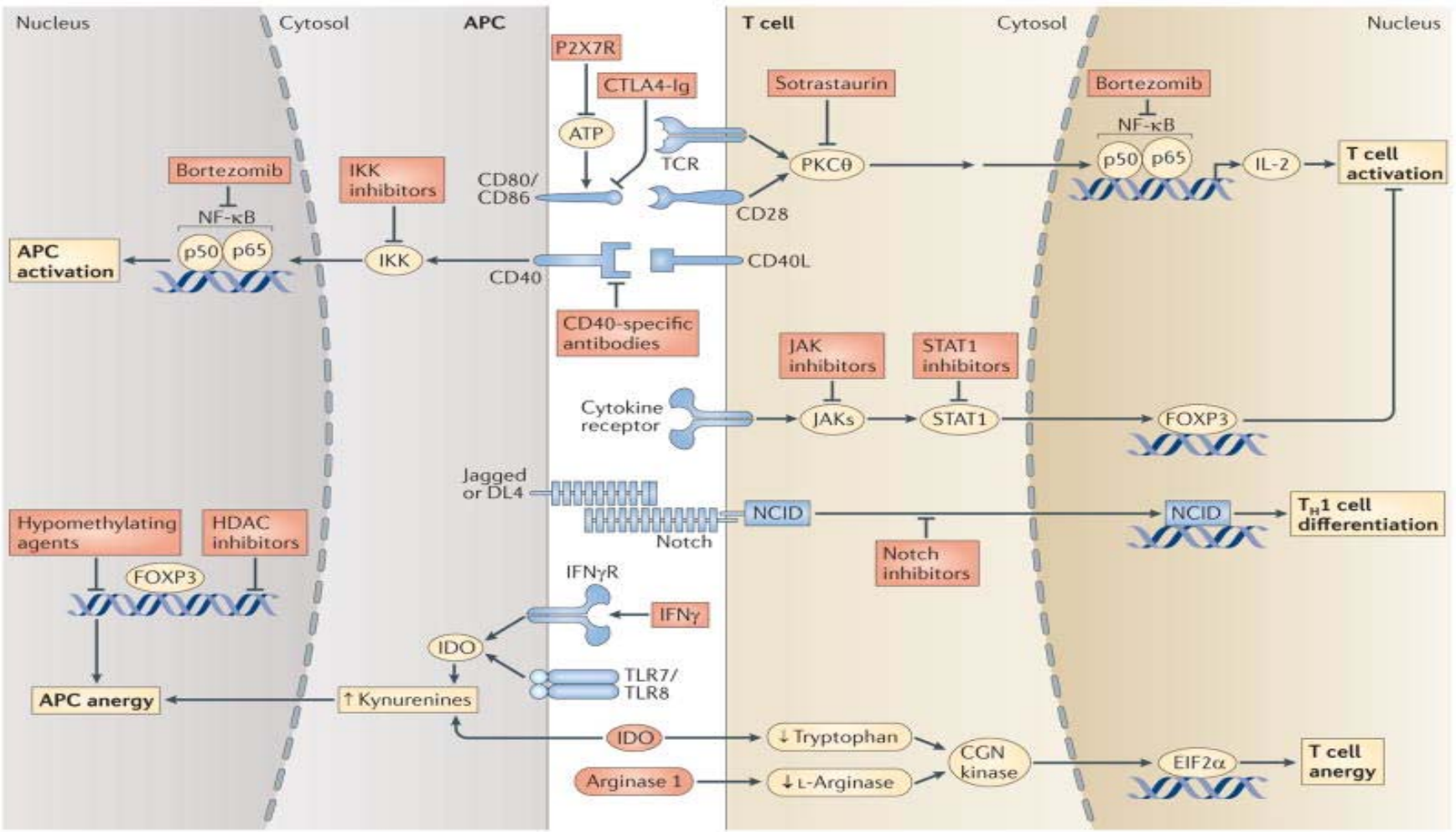
A. Myeloablative conditioning depletes inhibitory cells, such as Tregs, NKT, and suppressive monocytes
B. Enhances cytokine availability due to removing cytokine sink
C. HSC produces APCs and T-cell homeostatic cytokines (e.g. IL-7 and IL-15)
D. All of above

Adoptive Immunotherapy with donor T cells



Garber HR et al:
Mol & Cell Therapies
2014:2:25

T cell/APC Interaction and Intervention



Blazar BR et al: 2012, Nat Rev Immunol

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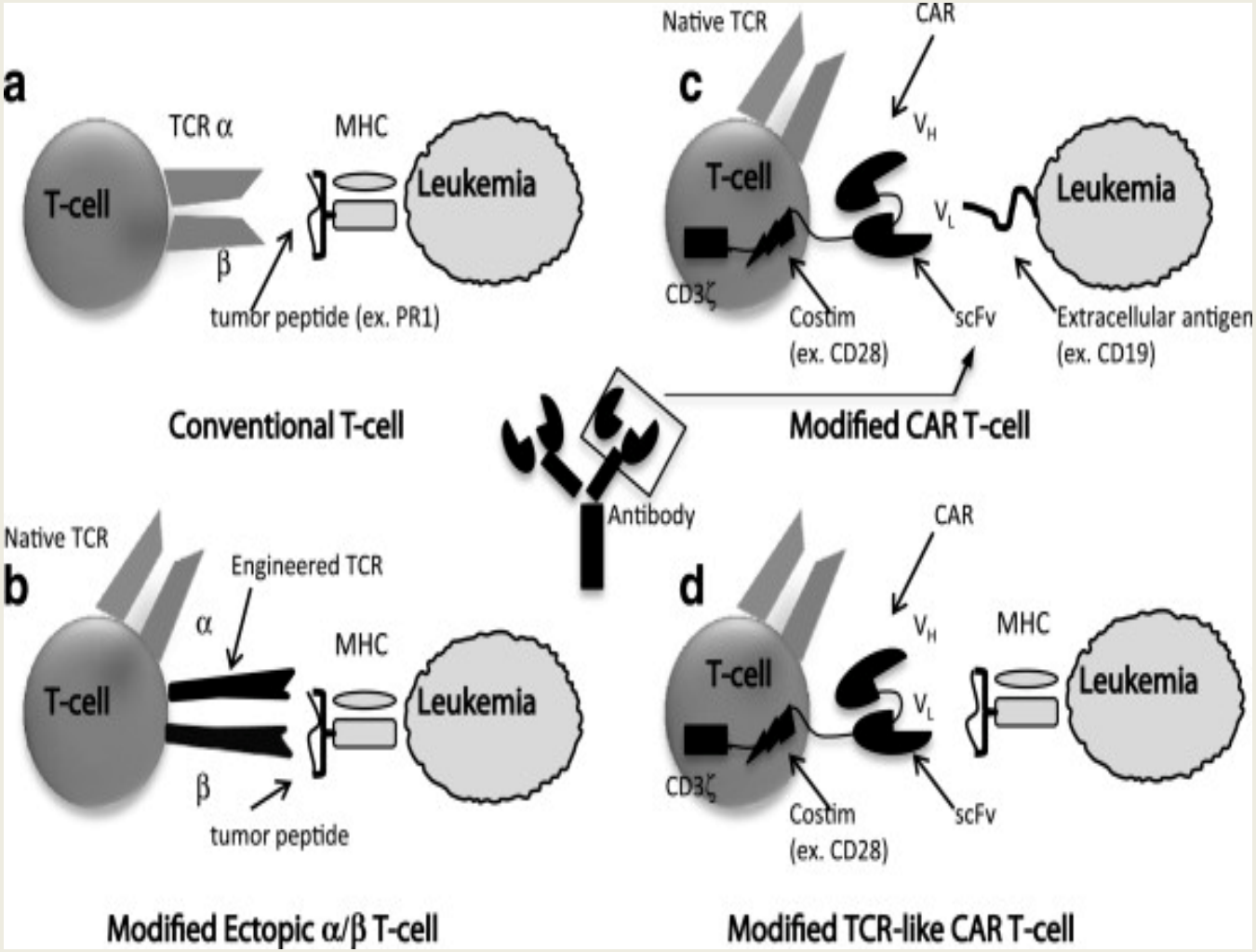
T cell Approaches to Target Leukemia Antigens



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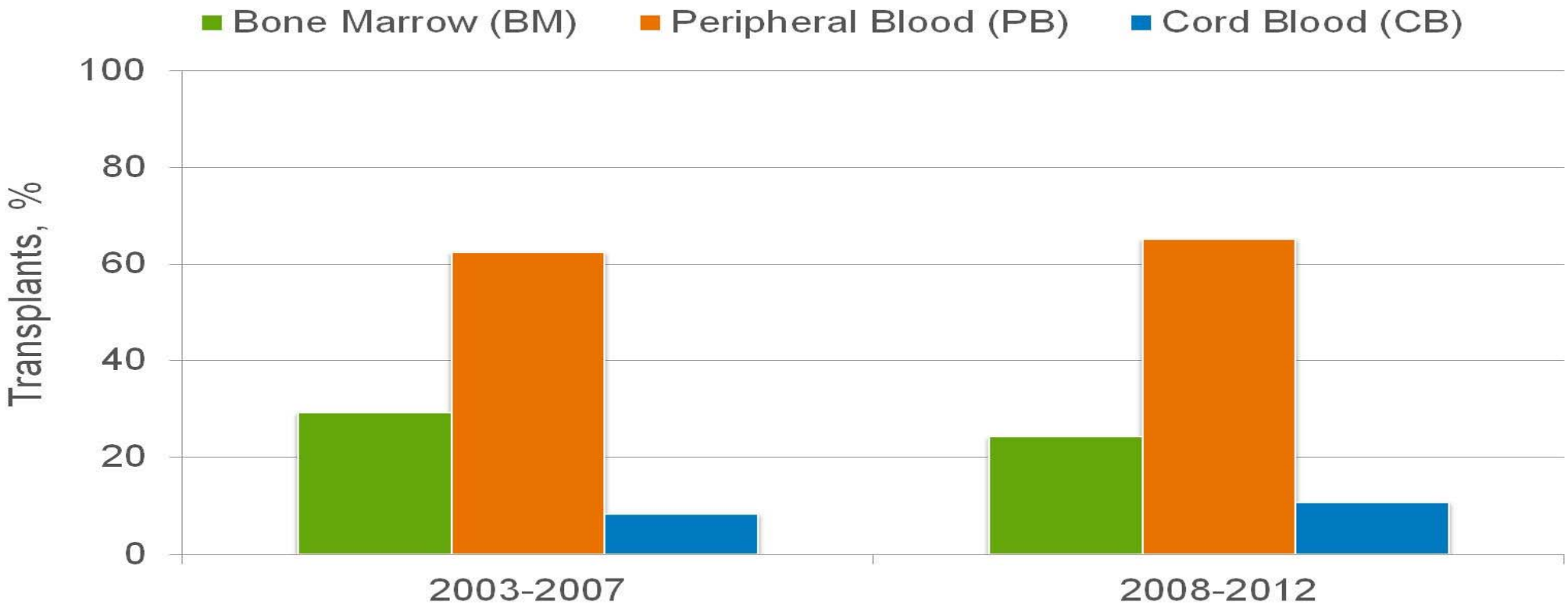
Stem Cell Sources for Allogeneic Transplants by Year



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