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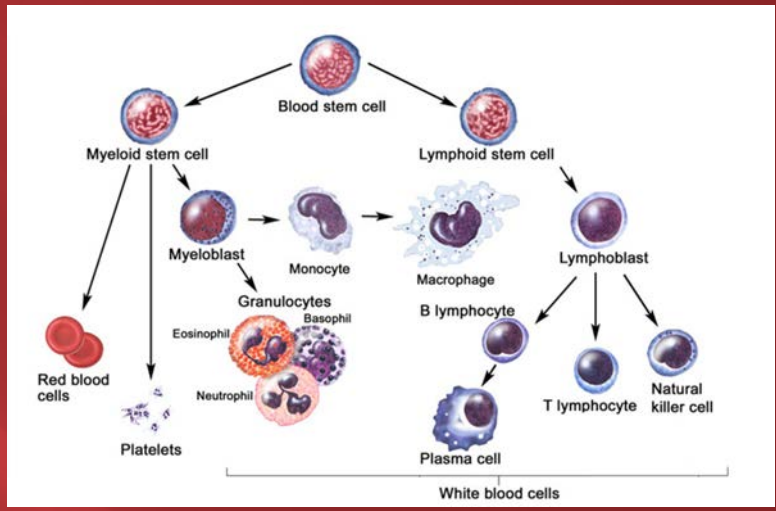
Pediatric Blood / Marrow Transplant Overview

Pediatric Blood / Marrow Transplant Overview



Aims

What are potential Hematopoietic Stem Cell Sources?

What are indications for HSCT in Pediatrics?

What are outcomes for HSCT in Pediatric Patients / diseases?

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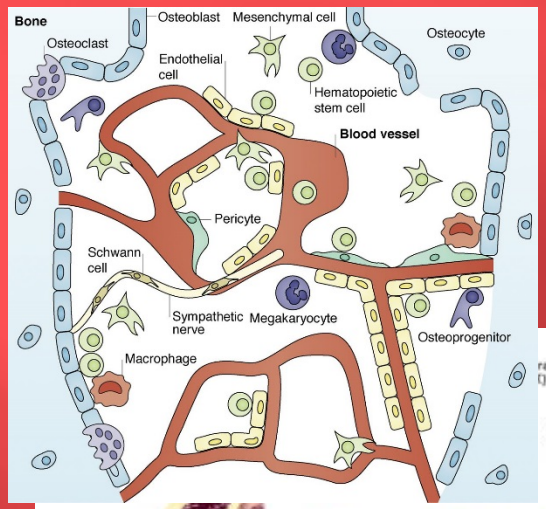

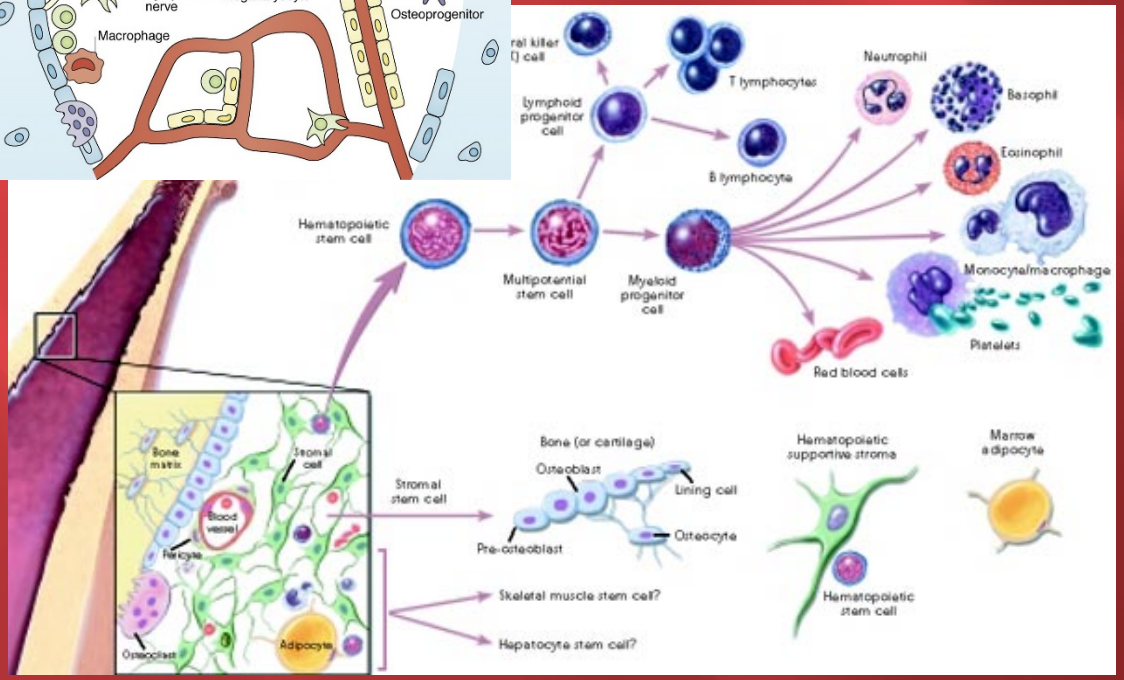

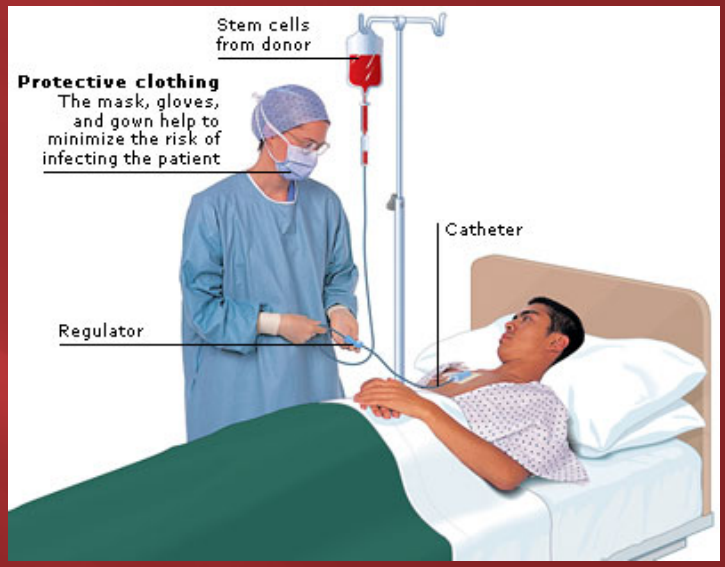

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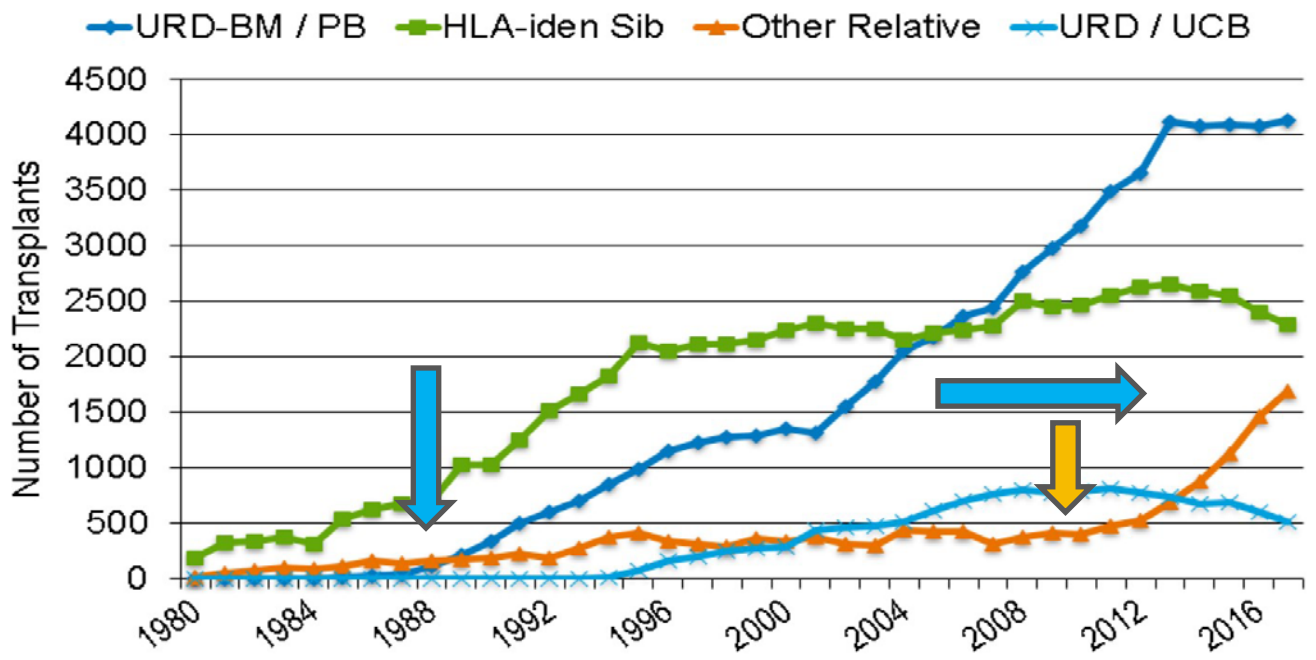
Pediatric Blood / Marrow Transplant Overview

Allogeneic HCT Recipients in the US, by Donor Type



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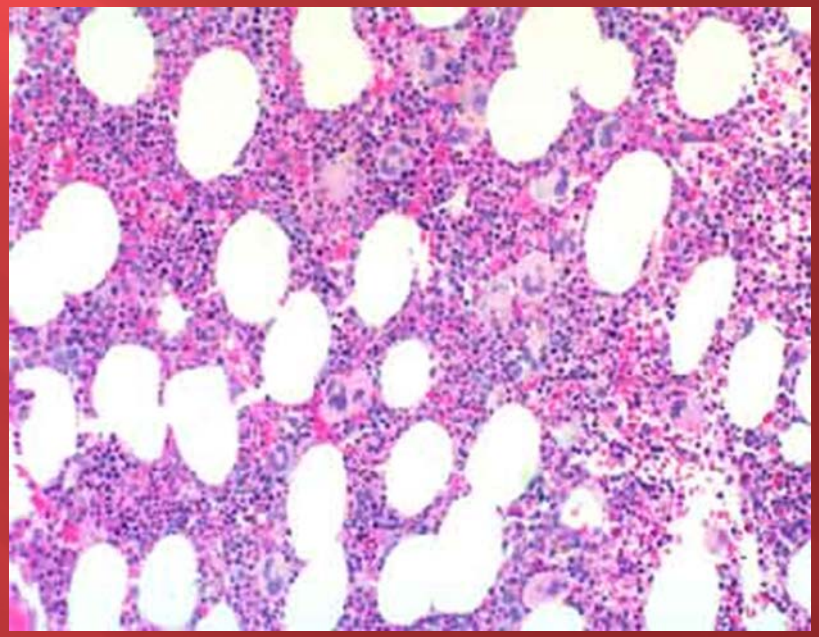

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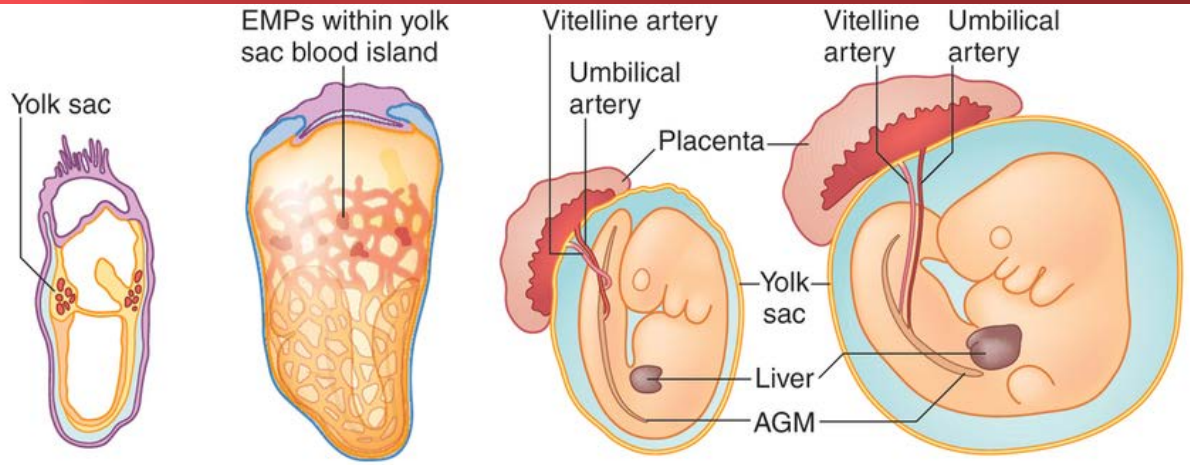

	Embryonic stage			
	E7	**E8.25**	**E9**	**E10.5**
Wave 1	Primitive erythroid progenitors macrophages megakaryocytes	Primitive erythroid progenitors macrophages megakaryocytes	Primitive macrophages	Primitive macrophages
Wave 2		EMPs	EMPs B lymphoid cells T lymphoid cells	EMPs (yolk sac) B lymphoid cells (AGM, yolk sac) T lymphoid cells (AGM, yolk sac)
Wave 3				Hematopoietic stem cells (AGM)

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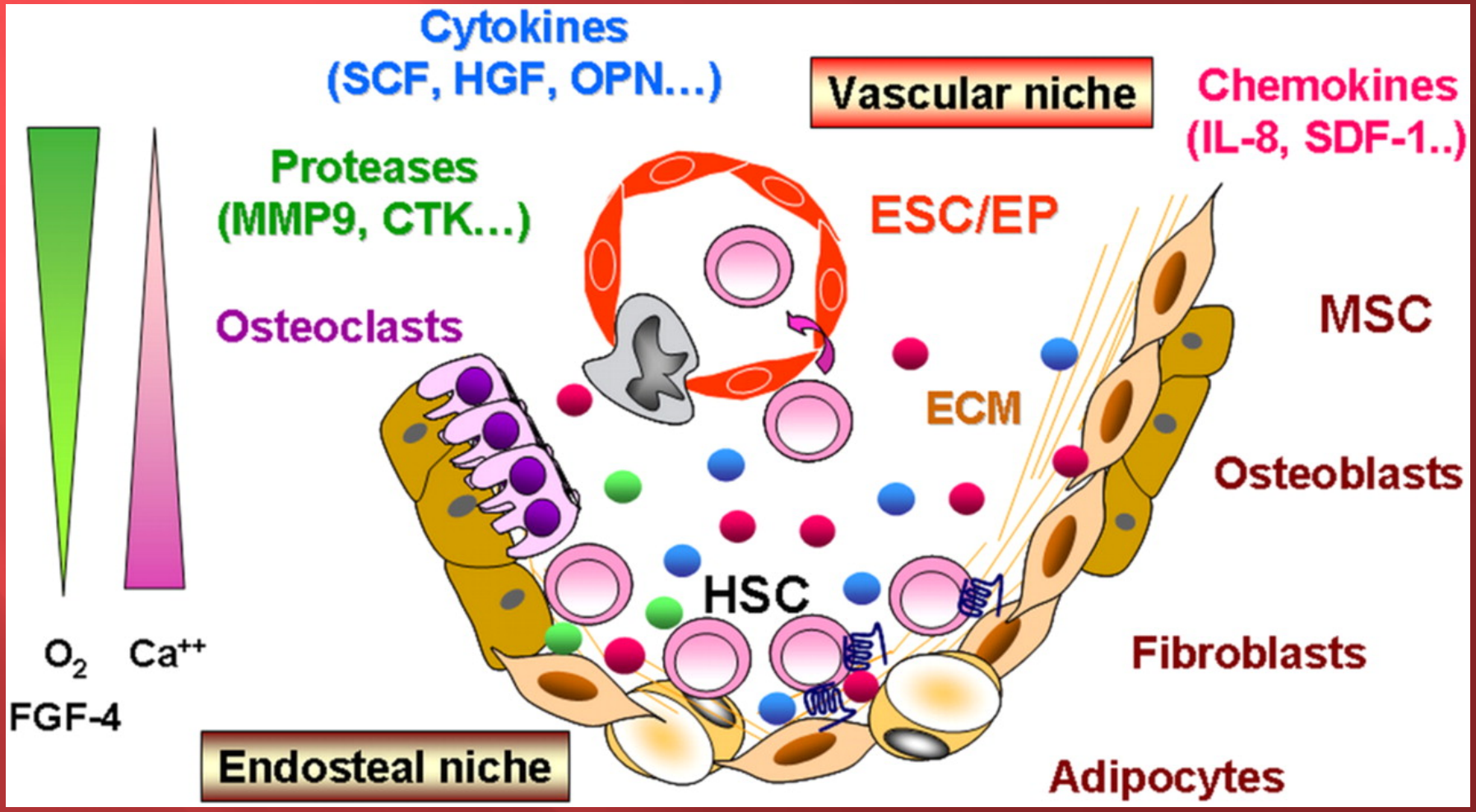

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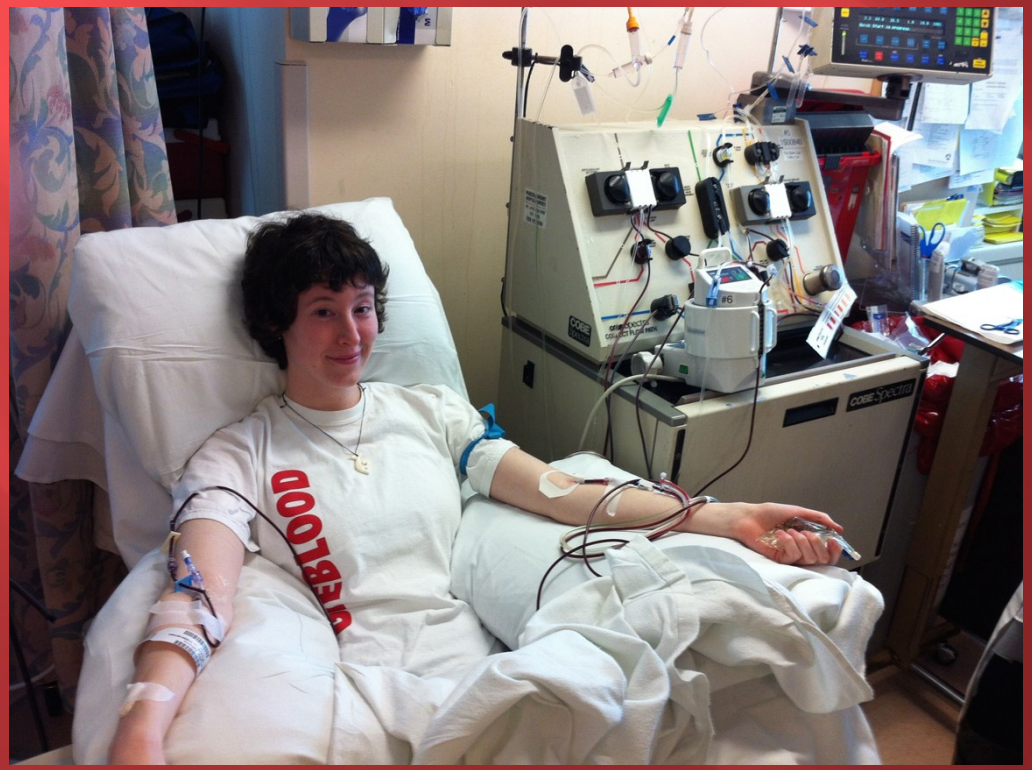
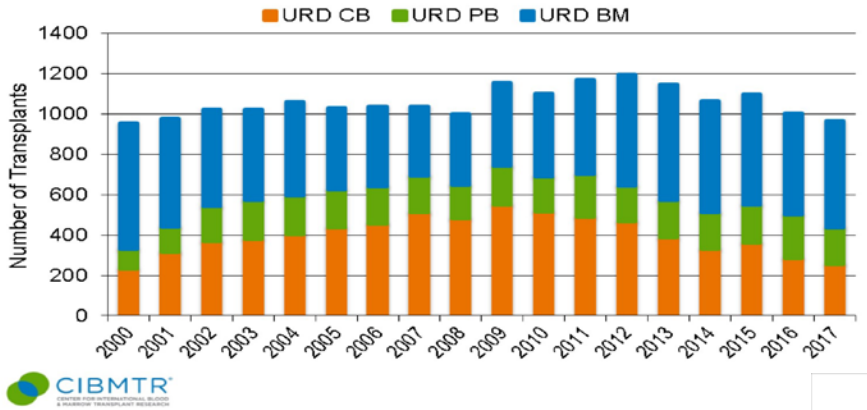


Pediatric Blood / Marrow Transplant Overview

Unrelated Donor Allogeneic HCT in Patients <18 Years



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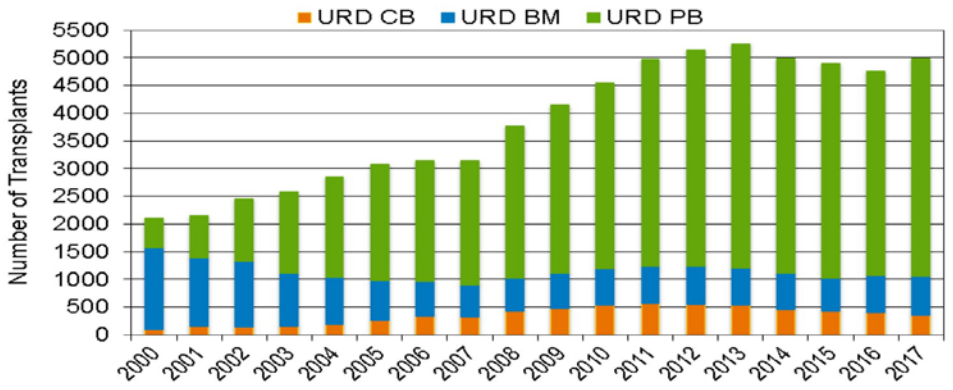
Unrelated Donor Allogeneic HCT in Patients Age ≥18 Years



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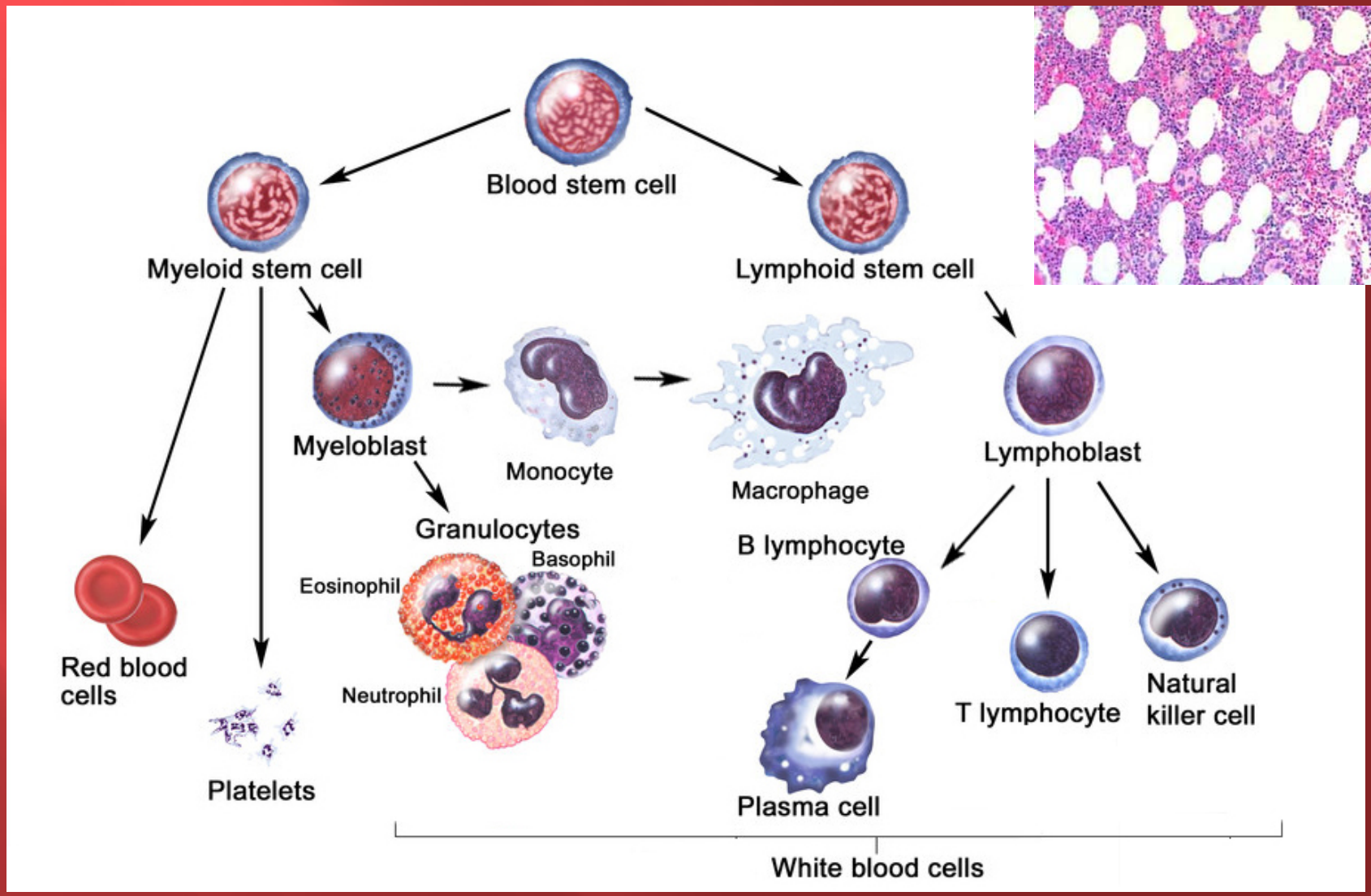
Pediatric Blood / Marrow Transplant Overview



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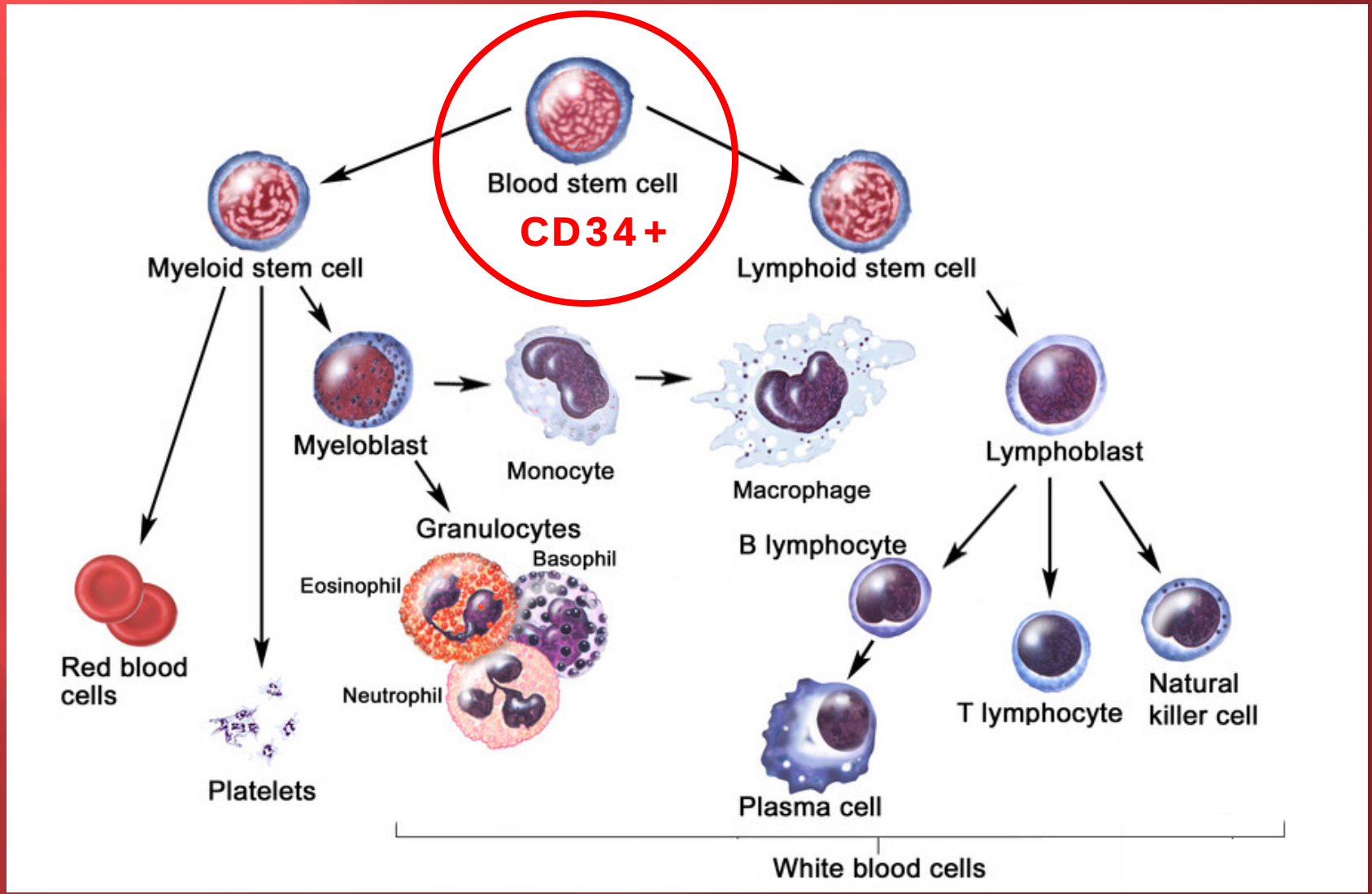

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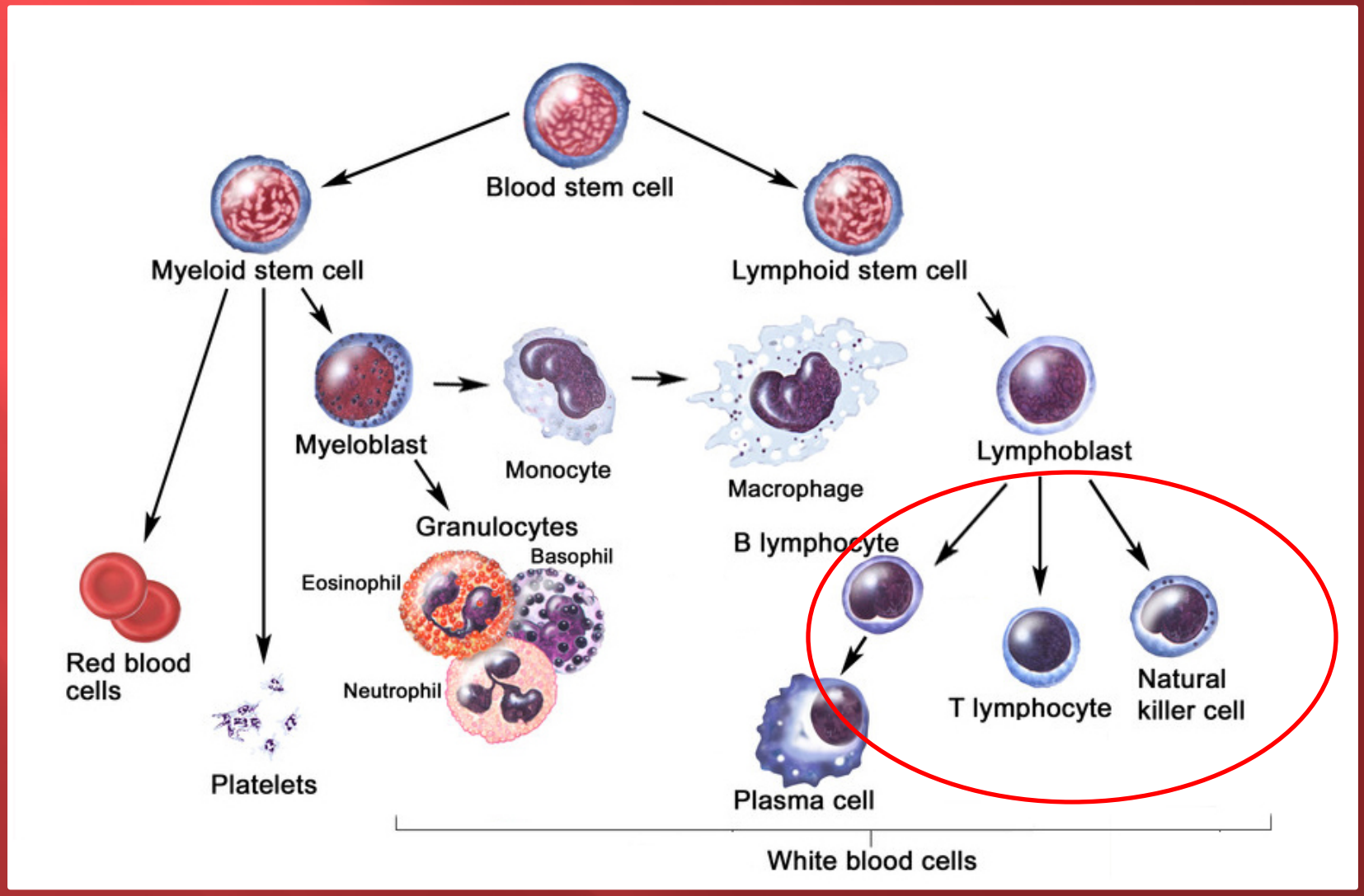

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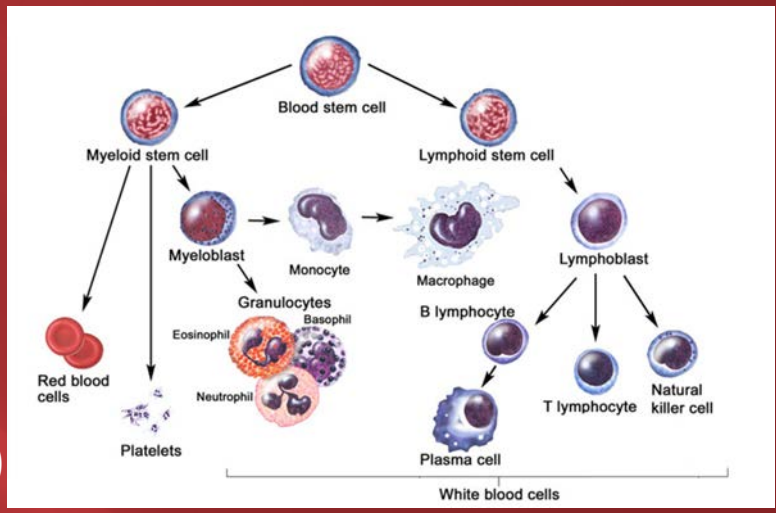
HSC / HPC Sources



Marrow

Peripheral Blood

Mobilization: G-CSF +/- chemoRx, CXCR4<—>SDF-1 inhib (Plerixafor)
(SDF = stromal cell derived factor)

Umbilical Cord Blood

Total Nucleated Cells (TNC): ~10^{7-8}/kg
Mononuclear Cells (MNC): ~10^{7-8}/kg
CD 34+ Cells: ~10^{5-6}/kg

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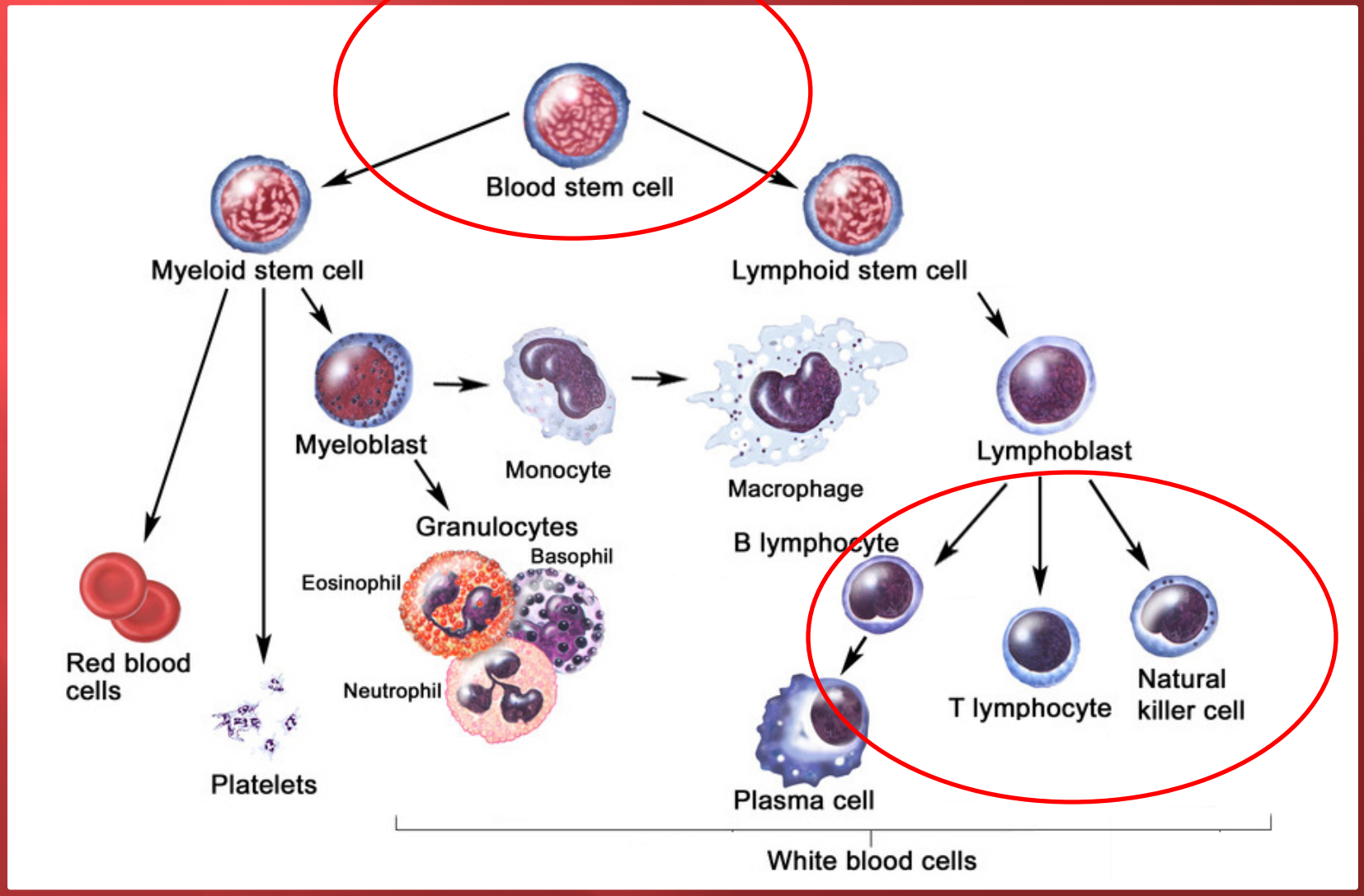

Pediatric Blood / Marrow Transplant Overview

***In Vitro* T-cell depletion**

- ***Sheep RBC Rosettes***
- ***Mab + Complement***
- ***Immunotoxin linked to Anti-T-cell mAb***

CD 34 Selection

- ***Isolex Column***
- **Miltenyi device**

Alpha-Beta T-cell depletion

Post HSCT *In Vivo* T-cell depletion

- **Post HSCT Cyclophosphamide**

Pediatric Blood / Marrow Transplant Overview

***In Vitro* T-cell depletion**

- ***Sheep RBC Rosettes***
- ***Mab + Complement***
- ***Immunotoxin linked to Anti-Tcell mAb***

CD 34 Selection

- ***Isolex Column***
- **Miltenyi device**

Pediatric Blood / Marrow Transplant Overview

Post HSCT
Cyclophosphamide in mice

Reduces lethality of GVHD to 0

TABLE 2. The effect of various drugs on GvH mortality

Drug and dose[a] (mg/kg)	Mortality (%)
Cortisol	
40	85
20	85
10	95
5	95
Saline	90
HN2	
3.0	100
1.5	100
0.75	95
0.375	97
0.187	100
Saline	100
CY	
150	95
75	0[b]
37.5	0[b]
18.75	60[b]
Saline	100

[a] Given on days 5, 8, 11, and 14.
[b] Significantly different from saline control.

Owens et Santos Transplantation 1971, 11, 4 p378

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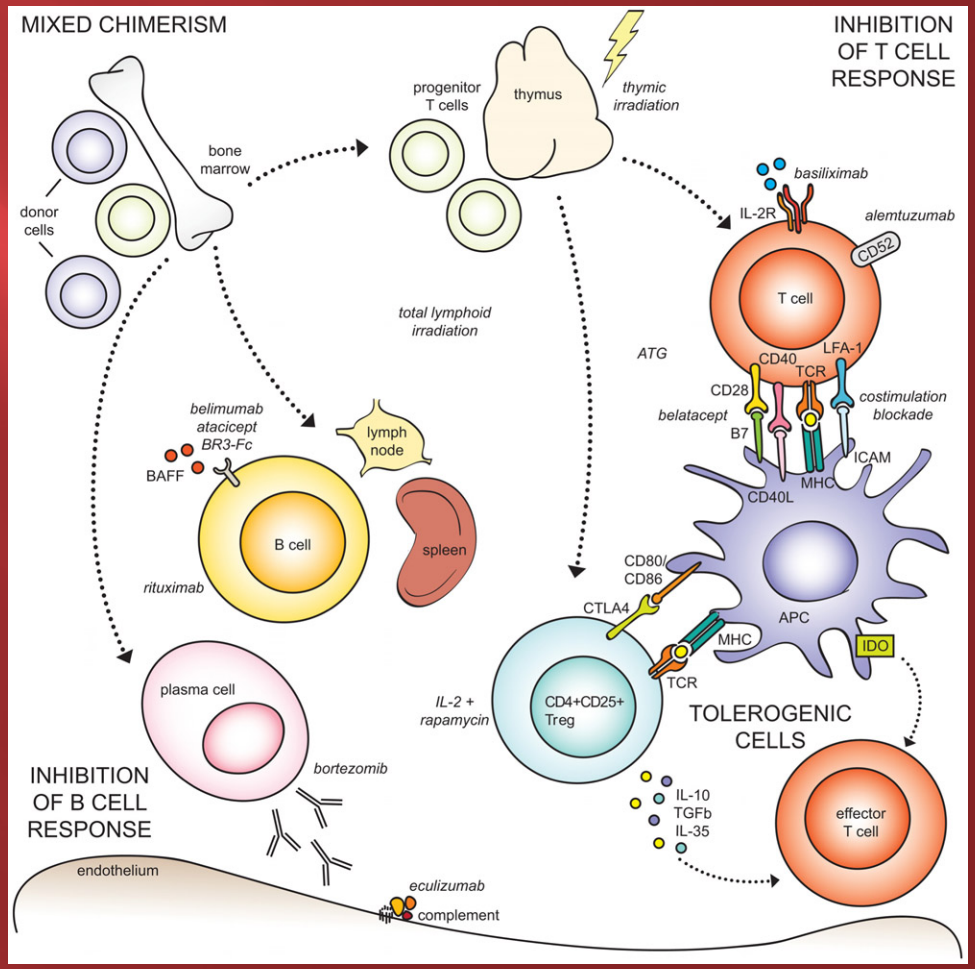
Pediatric Blood / Marrow Transplant Overview

T-cell Tolerance--
a goal of
Allogeneic Transplantation



Pediatric Blood / Marrow Transplant Overview

Parent M

Parent F

Related Donor

Sibling A

Sibling C

Sibling B

Sibling D

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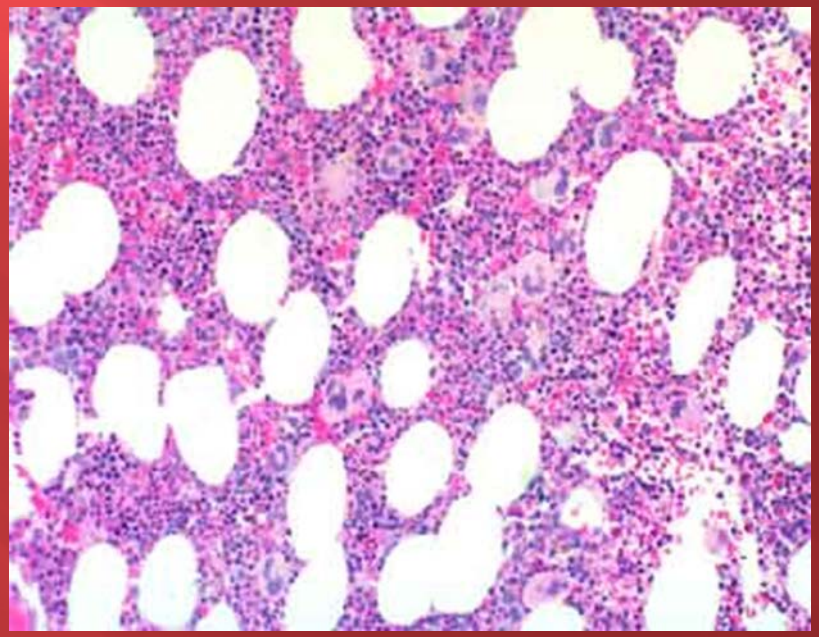

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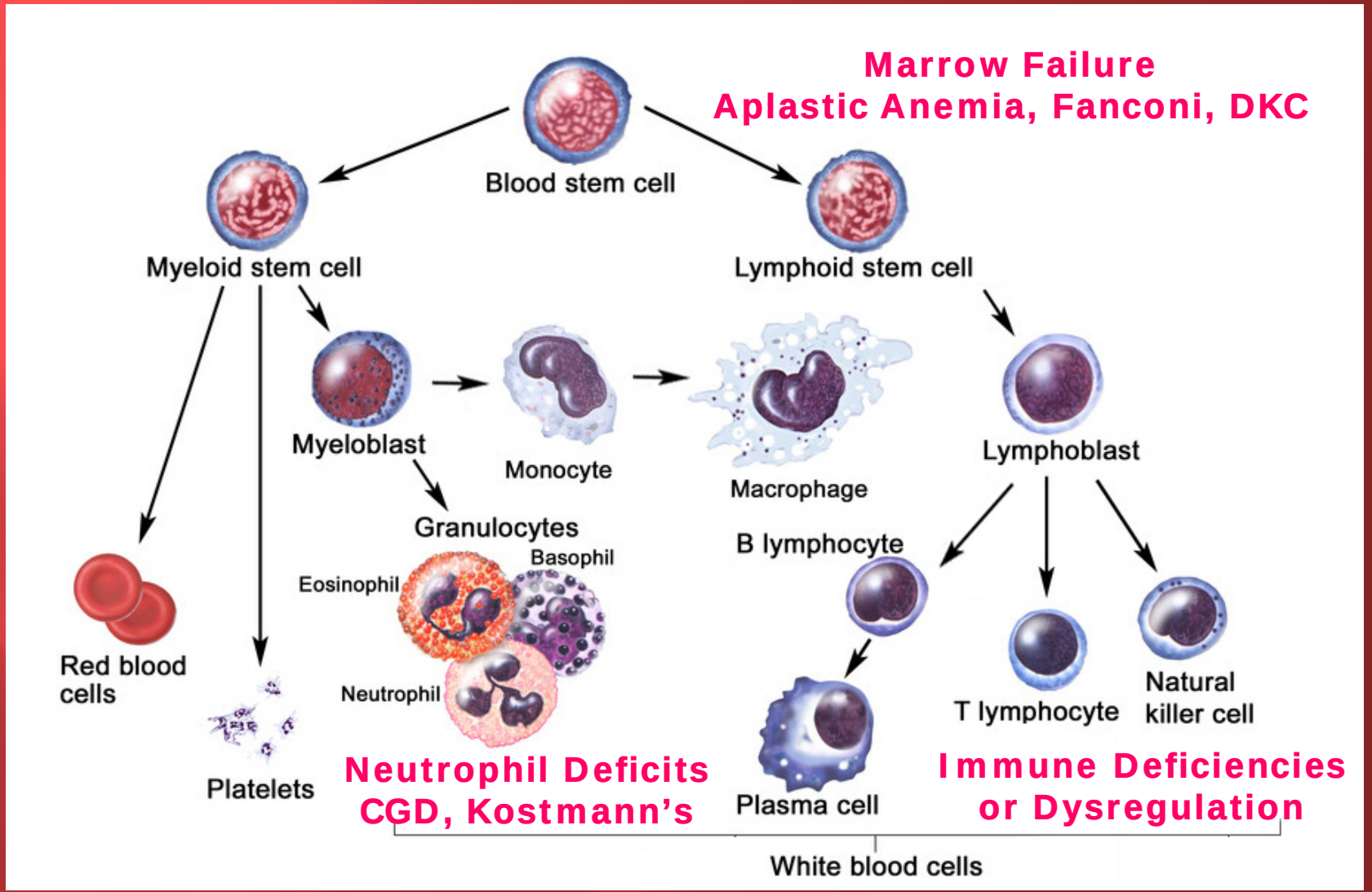

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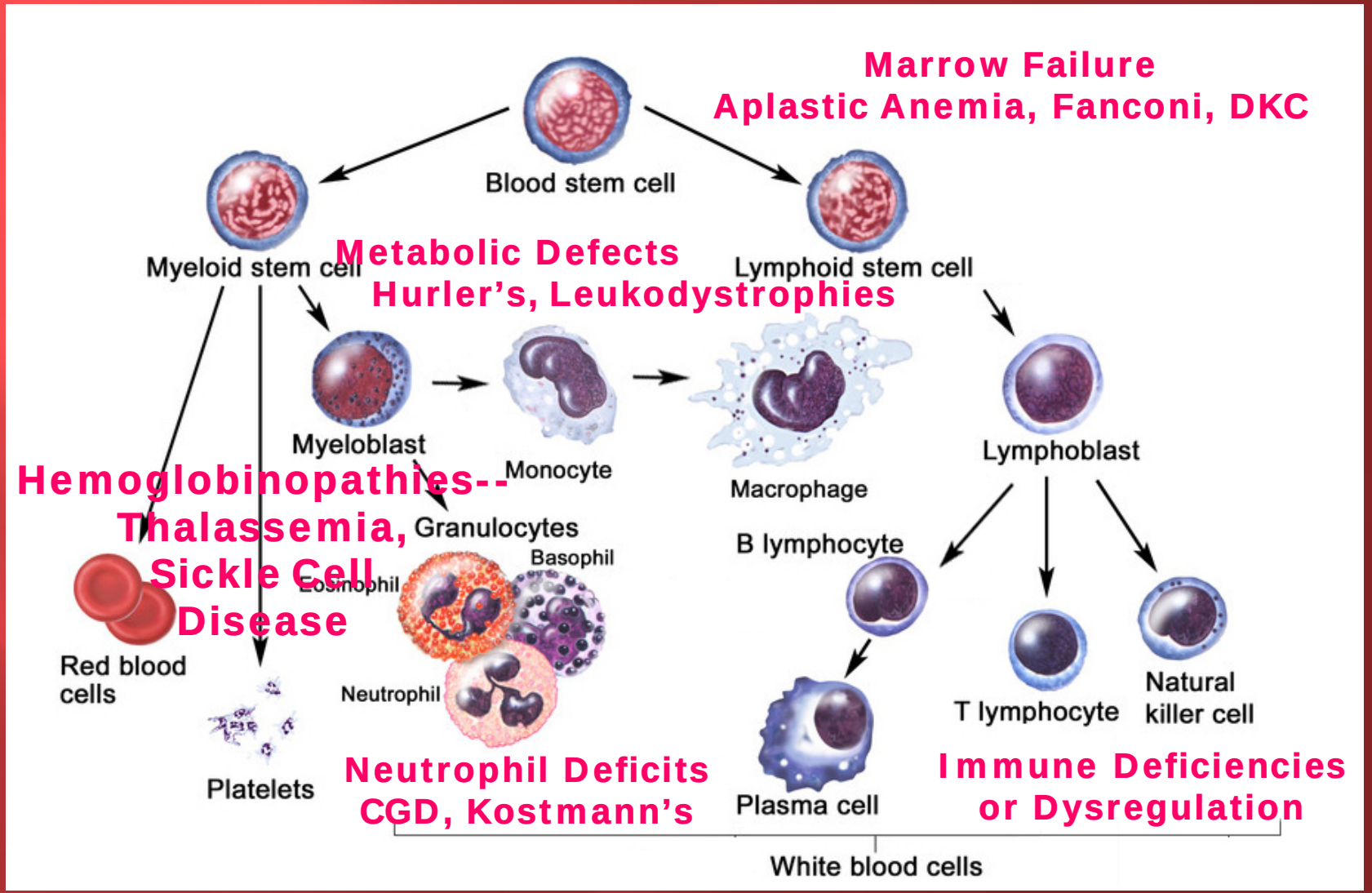

Pediatric Blood / Marrow Transplant Overview

Non-malignant Diagnoses:

Marrow Failure
- Severe Aplastic Anemia, Fanconi, DKC, DBA
- Schwachman-Diamond, Congenital Osteopetrosis

Immune Deficiencies / Dysregulation
- SCID, HLH, WAS, CHS, IPEX, NEMO

Neutrophil Deficits
- CGD, Kostmann's

Metabolic Defects
- Hurler's (Mucopolysacharidoses), Leukodystrophies

Hemoglobinopathies
- Thalassemia, Sickle Cell Disease

Pediatric Blood / Marrow Transplant Overview

Malignant Diagnoses:

Hi-Risk / Resistant Malignancies

Allogeneic:

- **ALL-recurrence, cytogenetics / molecular characteristics**
- **AML-cytogenetics, recurrence, phenotype / molecular**
- **JMML-**
- **NHL-recurrent / refractory disease**
- **HL-recurrent / refractory disease**

Autologous:

- **Neuroblastoma-high risk characteristics**
- **CNS Malignancies-Medulloblastoma, ATRT**
- **NHL-recurrent / refractory disease**
- **HL-recurrent / refractory disease**
- **Germ Cell Tumors**

Pediatric Blood / Marrow Transplant Overview

Hi-Risk / Resistant Malignancies

Allogeneic:

ALL-MRD > 0.01%

CRLF2 rearranged (Ph like)

AML-cytogenetics: 5-, 5q- or 7-,
t w 11q23, t(10,11), t(6,9)
MRD > 0.1%, phenotype –e.g. RAM
molecular: Flt 3 / ITD+

Autologous:

Neuroblastoma-high risk characteristics
St 4—metastases to bone, bone marrow
> 18 mo, N-myc amplified, unfavorable pathology
12 -18 mo N-myc amp, unfav path, DNA Index = 1

St 3: N-myc amp, unfav path or DNA Index = 1

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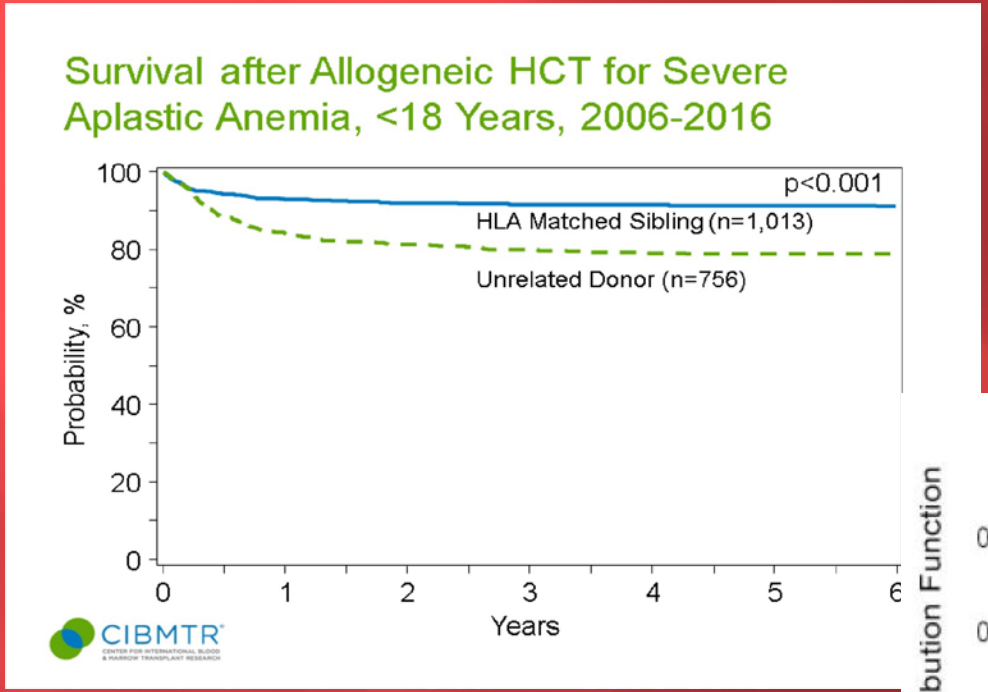

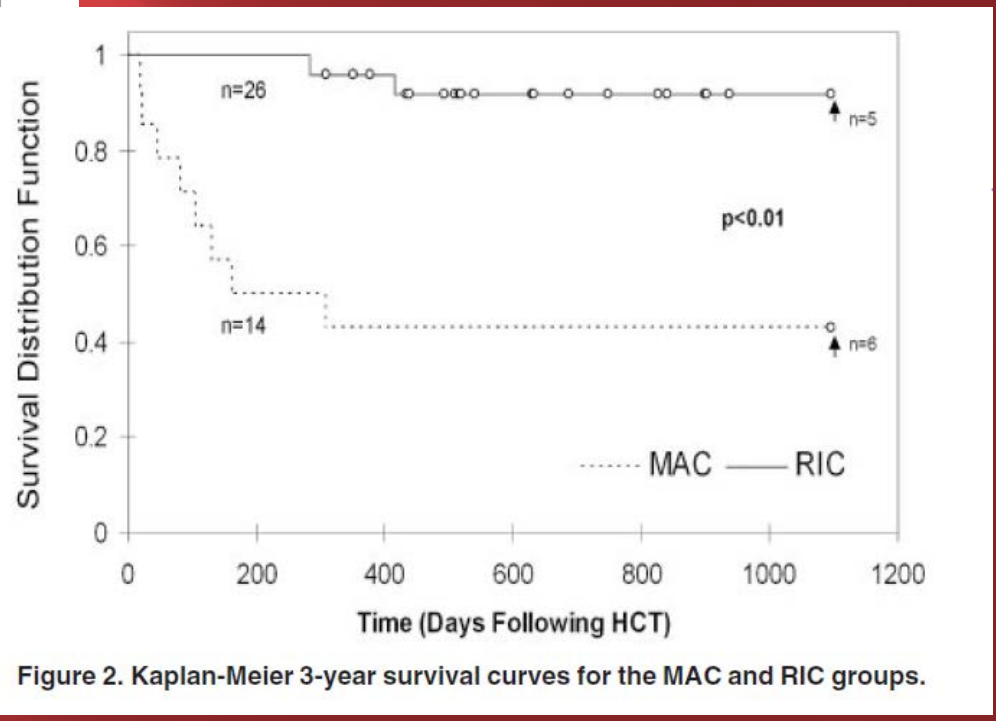

Figure 2. Kaplan-Meier 3-year survival curves for the MAC and RIC groups.

Marsh, et al, Blood, 2010 116 p 5824

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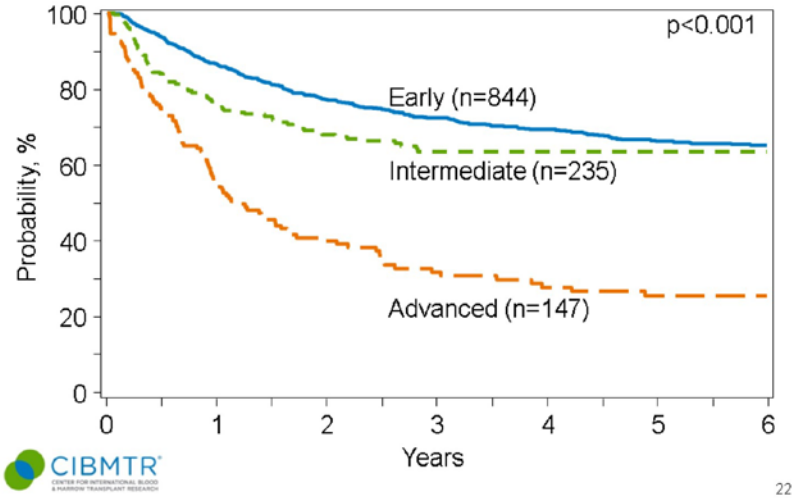
Survival after HLA Matched Sibling Donor HCT for AML, Age <18 Years, 2006-2016



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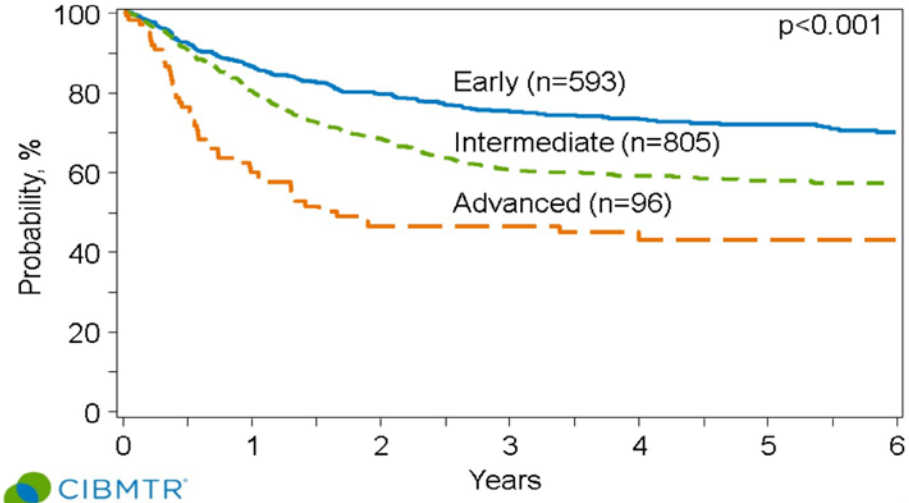
Survival after HLA-Matched Sibling Donor HCT for ALL, Age <18 Years, 2006-2016



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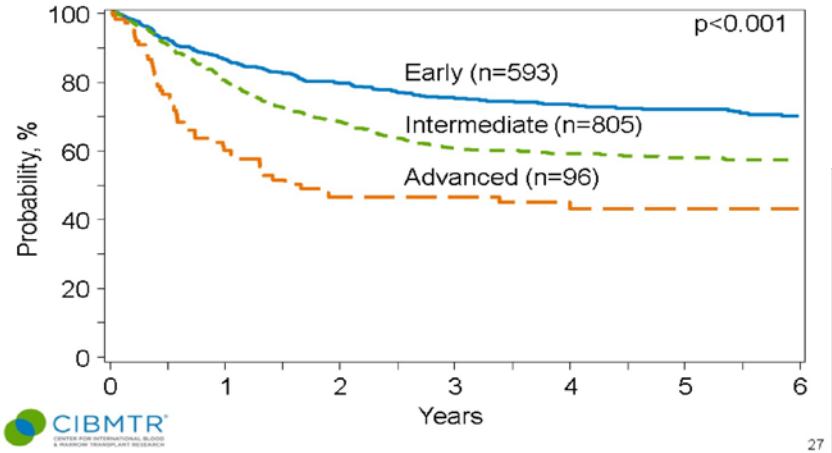
Survival after HLA-Matched Sibling Donor HCT for ALL, Age <18 Years, 2006-2016



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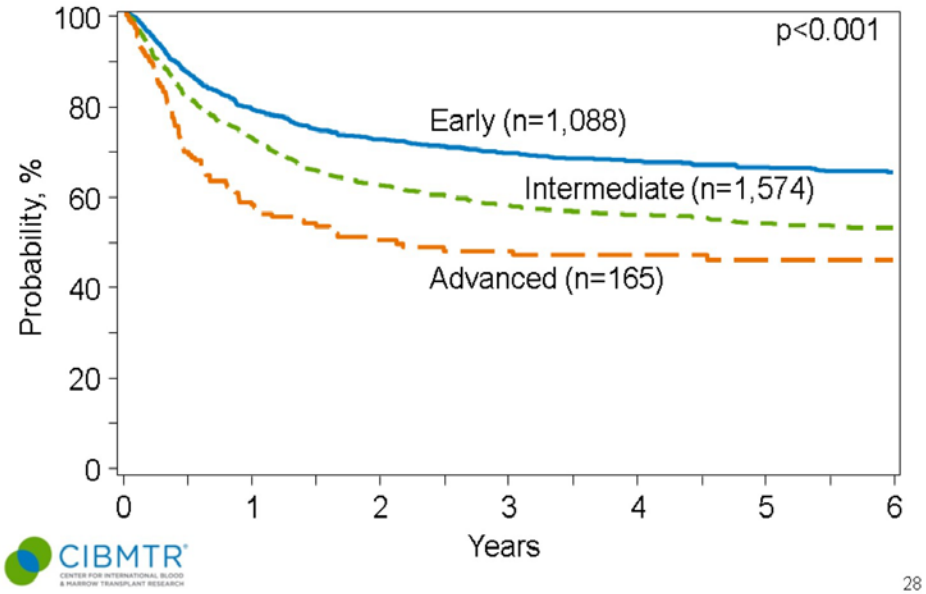
Survival after Unrelated Donor HCT for ALL, Age <18 years, 2006-2016



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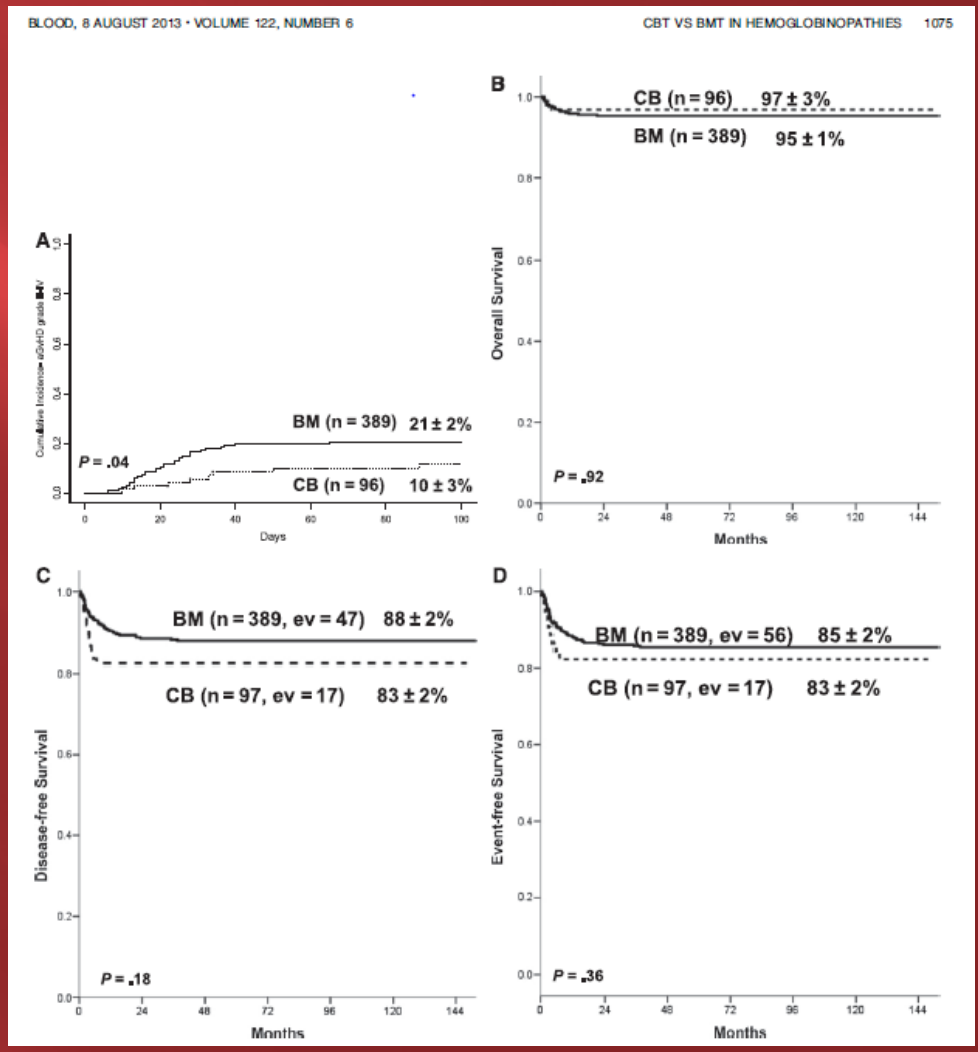
Sibling Donor Transplant for Thalassemia

Marrow vs Umbilical Cord Blood



Locatelli Blood 2013, 122, 6 p1072

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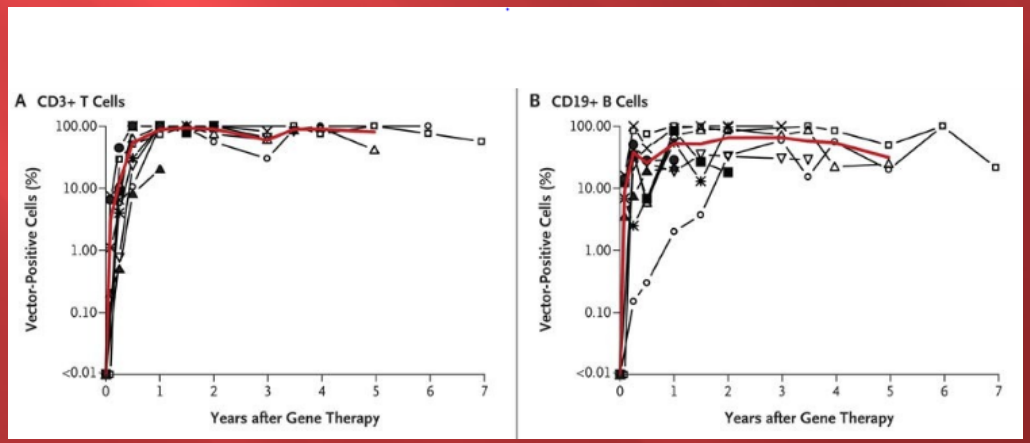
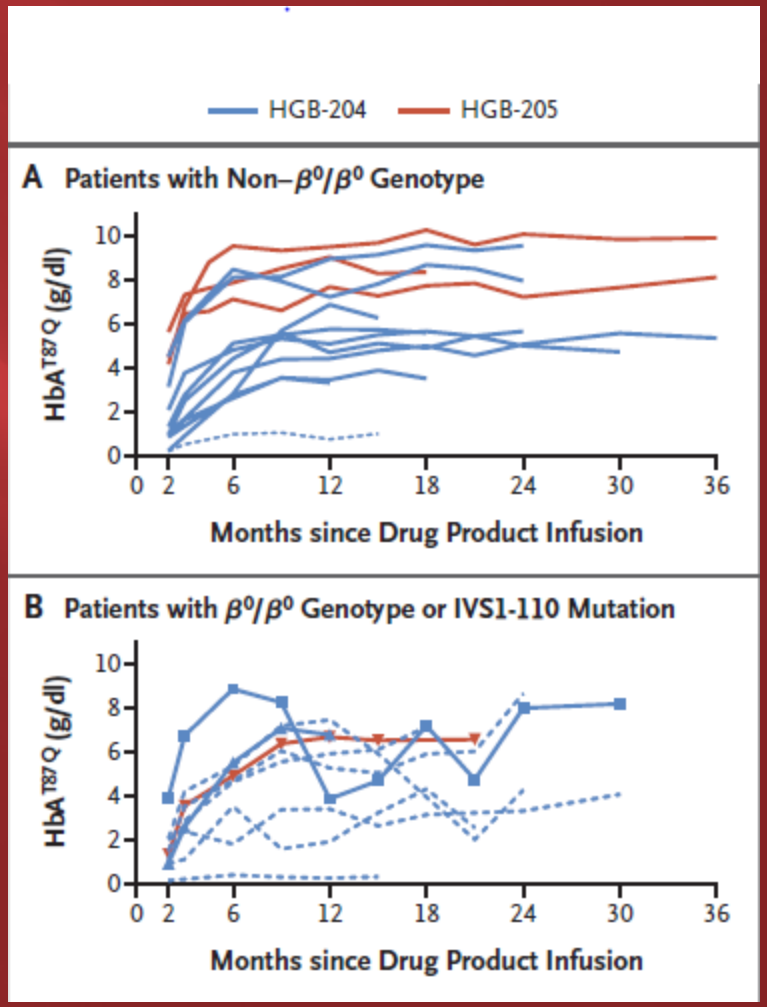
Genetic Modification of Autologous HSC

Persistence of transfected genes-
ADA deficiency
Thalassemia





Thompson et al NEJM 2018, 378, 16 p1479

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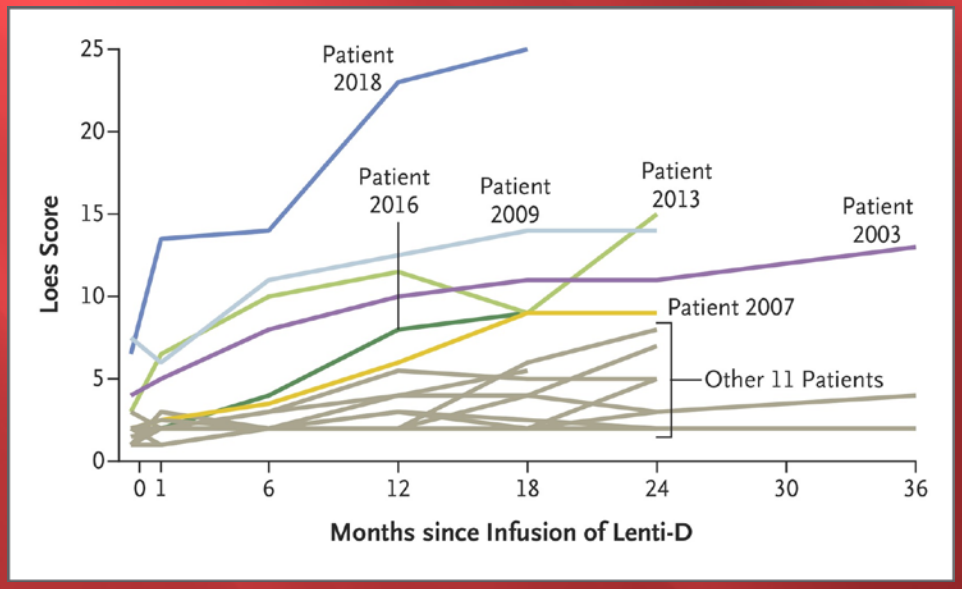
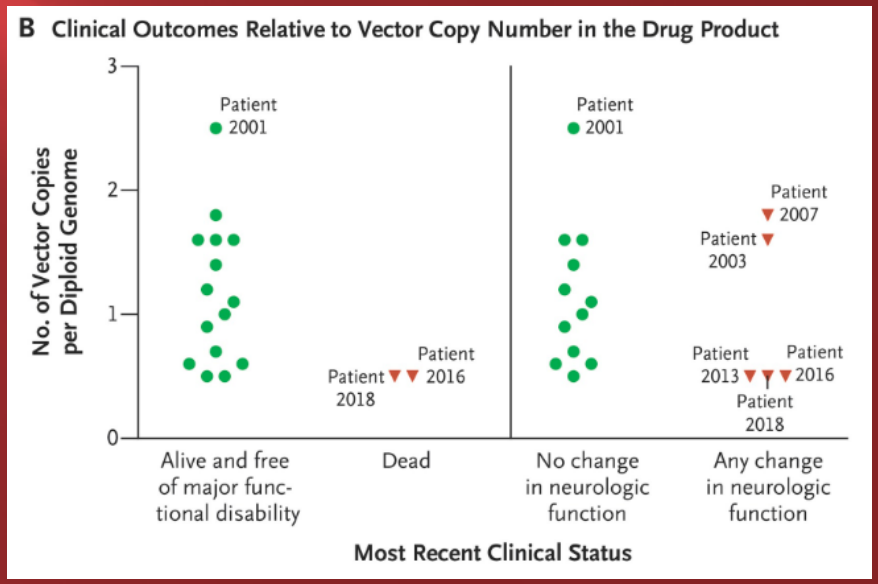
Genetic Modification of Autologous HSC

Dosage of transfected genes- Adrenoleukodystrophy





Pediatric Blood / Marrow Transplant Overview

Summary

HSCT in Pediatrics

- effective for broad range of disease states affecting blood, risk of infection, CNS

- multiple sources for “HSC” including selection for HSC, depletion of T-cells & genetic manipulation of HSC