Introduction to Clinical Hematopoietic Cell Transplantation (HCT)

Oncology for Scientists

George Chen, MD

Thursday May 5, 2016

Goals for Today

- **What is HCT?**
- **How is HCT done and how is it tailored to fit the patient's disease and circumstances?**

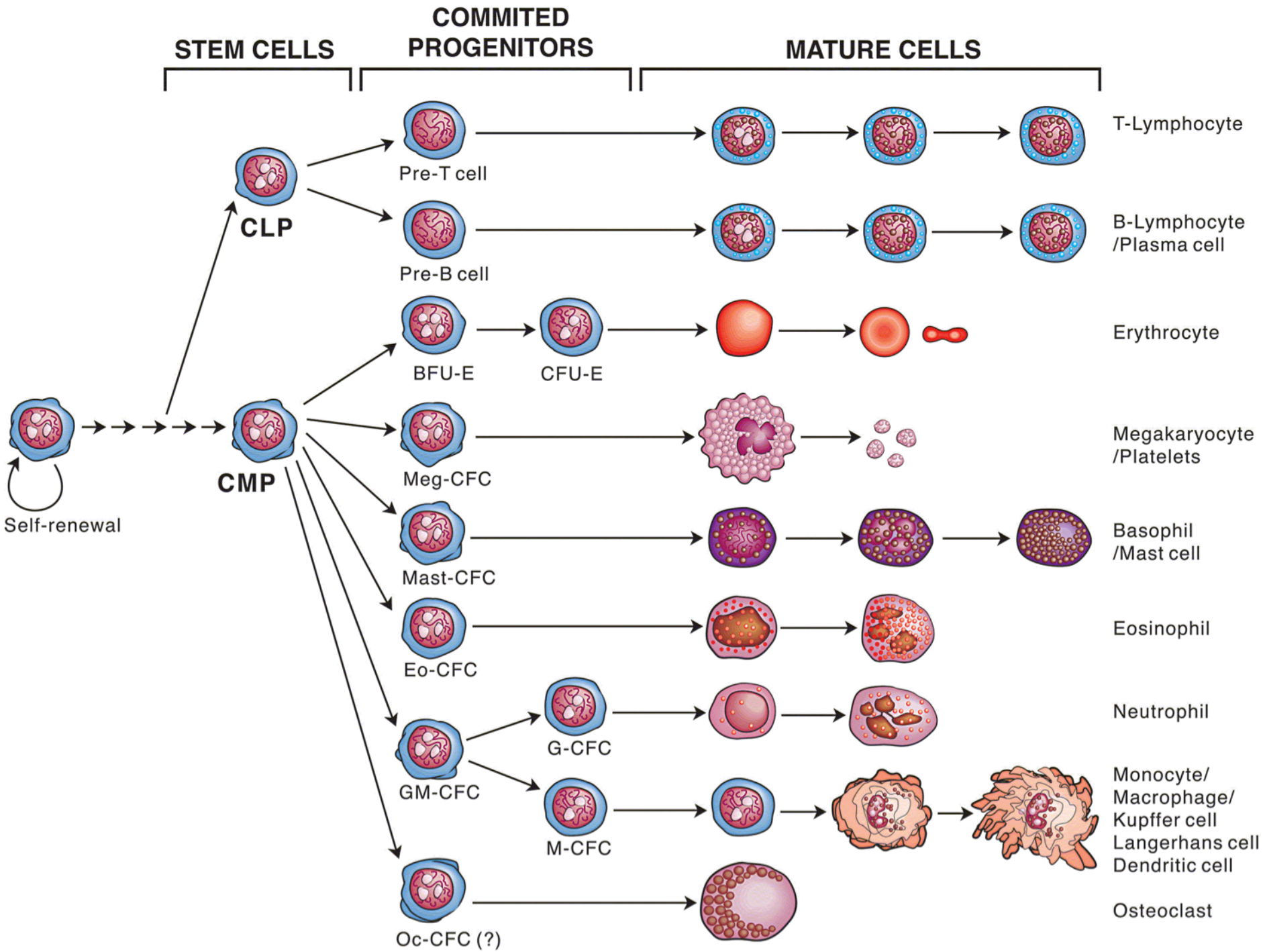
Important Concepts

- **Autologous vs allogeneic HCT**
- **Myeloablative vs reduced intensity conditioning regimens**
- **Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors**
- **Acute vs. chronic graft versus host disease**
- **Donor chimerism**

What is HCT?

The transfer of hematopoietic progenitor and stem cells for therapeutic purposes

- **Bone marrow transplant**
- **Hematopoietic stem cell transplant**
- **Hematopoietic progenitor cell transplant**
- **Peripheral blood stem cell transplant**


STEM CELLS
COMMITED PROGENITORS
MATURE CELLS
Self-renewal
CLP
CMP
Pre-T cell
Pre-B cell
BFU-E
CFU-E
Meg-CFC
Mast-CFC
Eo-CFC
G-CFC
GM-CFC
M-CFC
Oc-CFC (?)
T-Lymphocyte
B-Lymphocyte /Plasma cell
Erythrocyte
Megakaryocyte /Platelets
Basophil /Mast cell
Eosinophil
Neutrophil
Monocyte/ Macrophage/ Kupffer cell Langerhans cell Dendritic cell
Osteoclast

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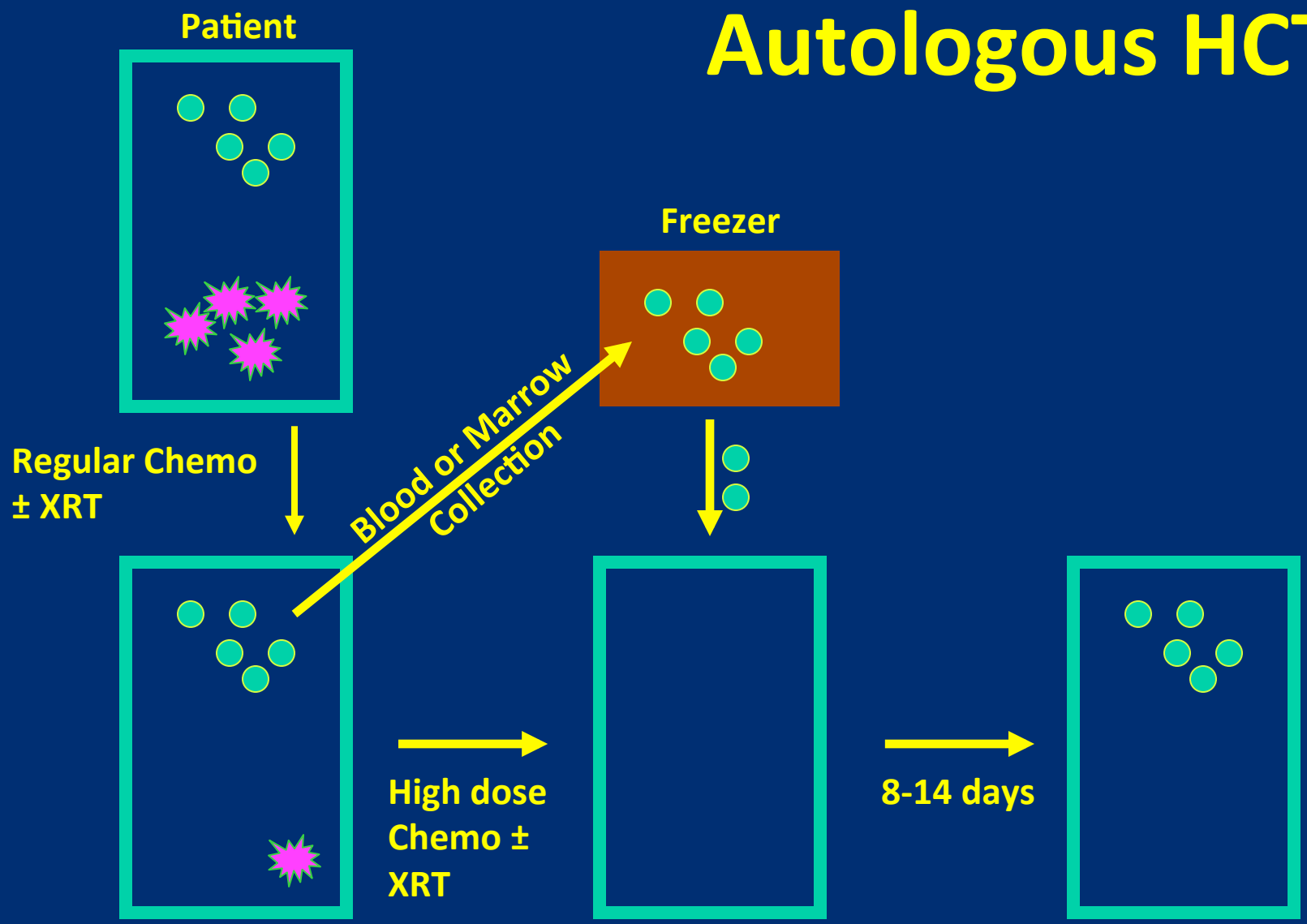
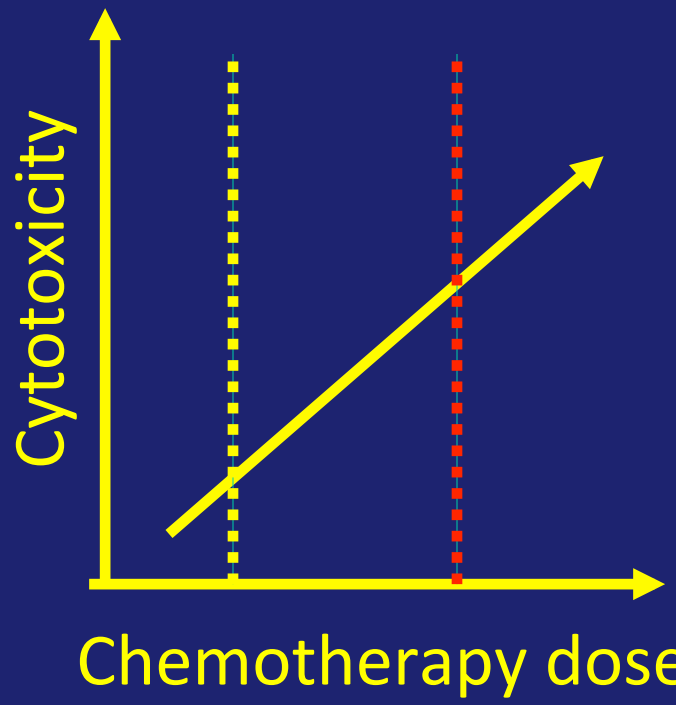
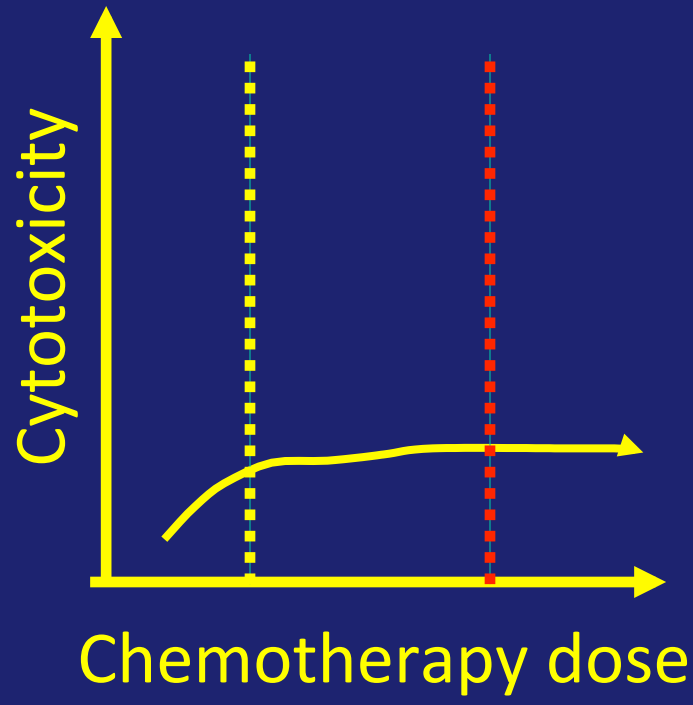
Basic Definitions

- **Autologous HCT – A transplant using a patient's own cells for the graft.**
- **Allogeneic HCT – A transplant using another person's cells for the graft.**

Autologous HCT

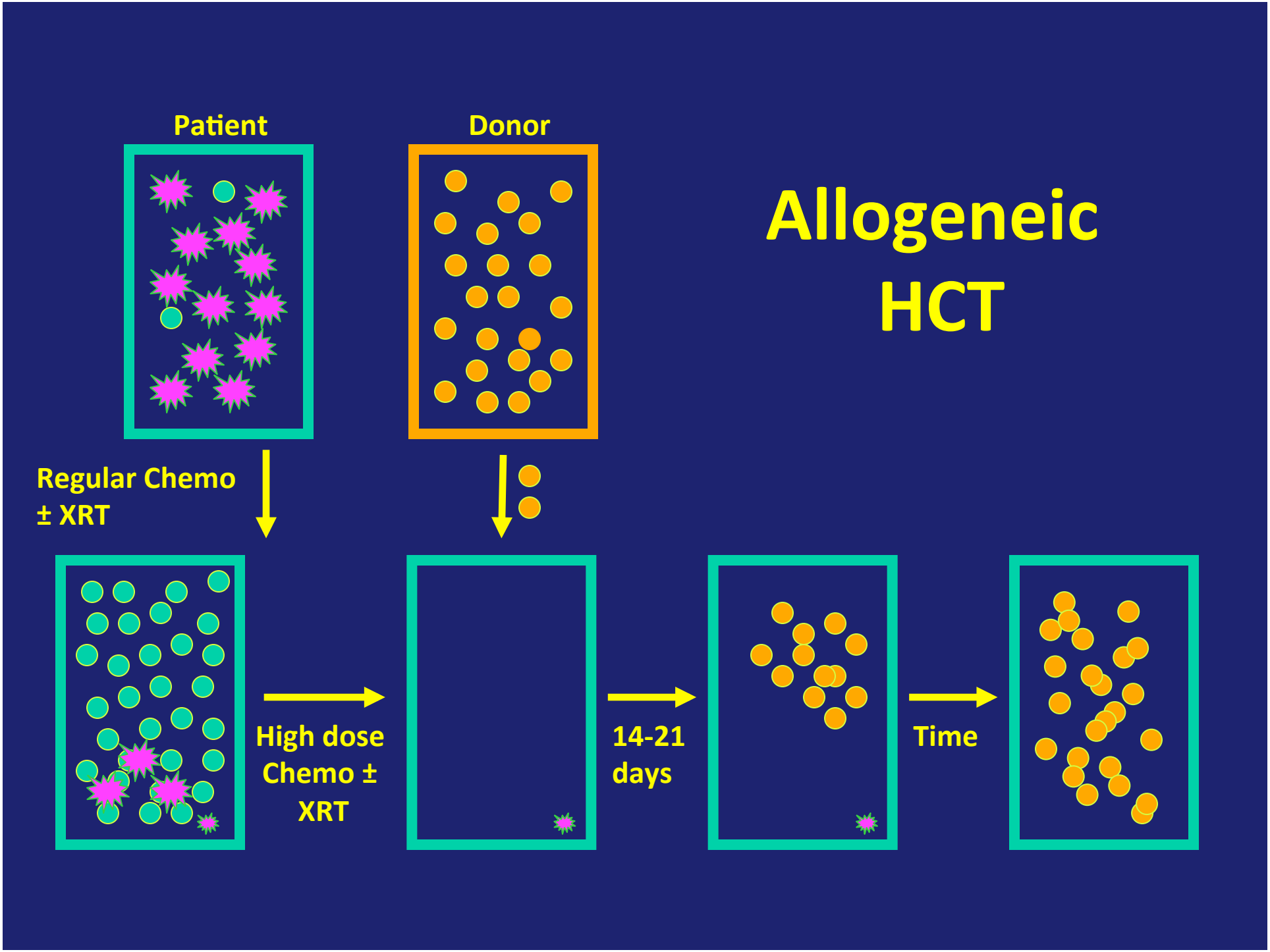



Cytotoxicity
Chemotherapy dose


Cytotoxicity
Chemotherapy dose

Indications for autoHCT

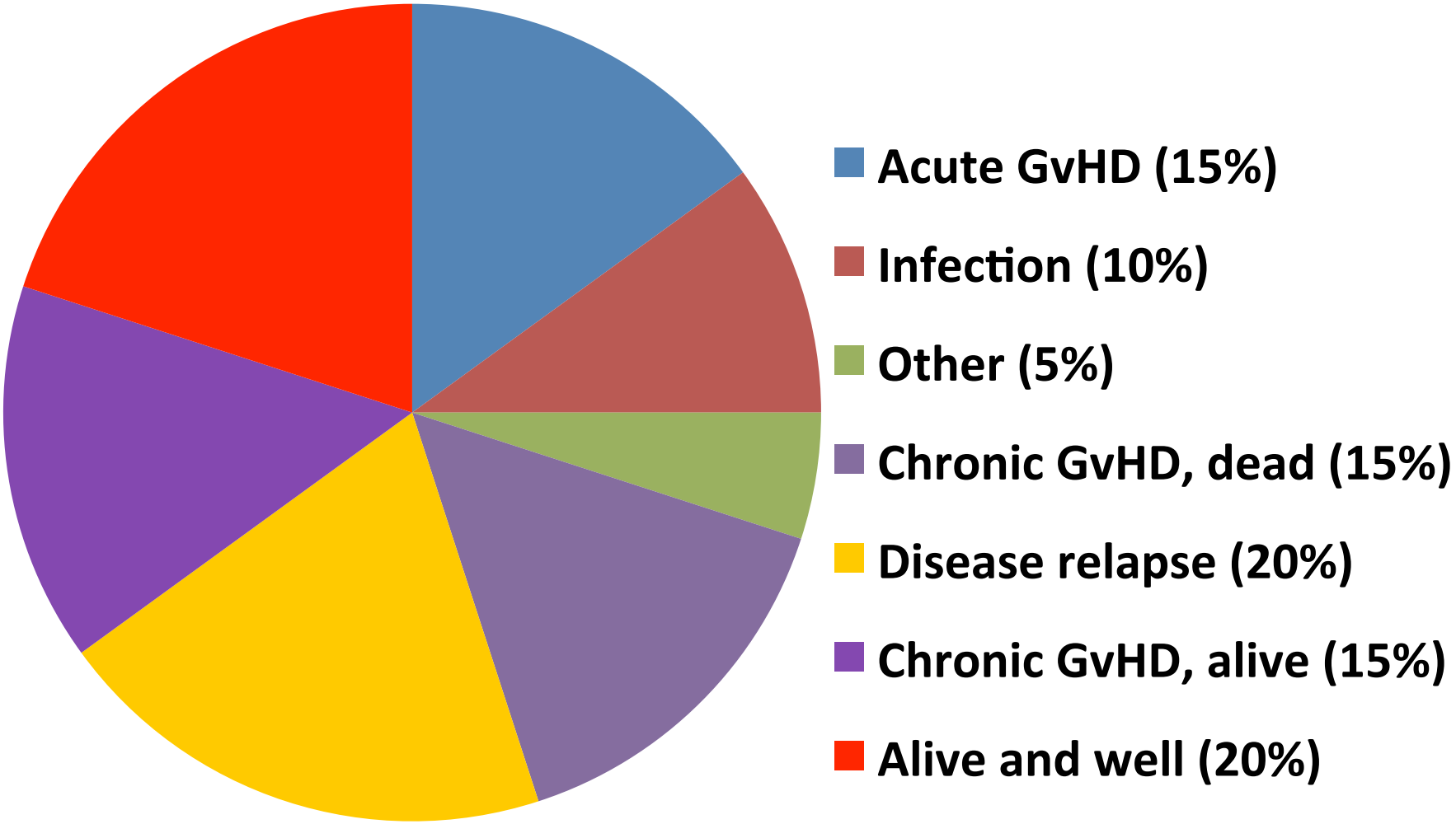
- Diseases in which cytoreduction (by chemotherapy) is effective and dose dependent
  - Germ cell tumors (testicular)
  - Large cell lymphoma
  - Myeloma
- Replacement of hematopoiesis (rescue therapy)


Patient
Donor
Allogeneic HCT
Regular Chemo ± XRT
High dose Chemo ± XRT
14-21 days
Time

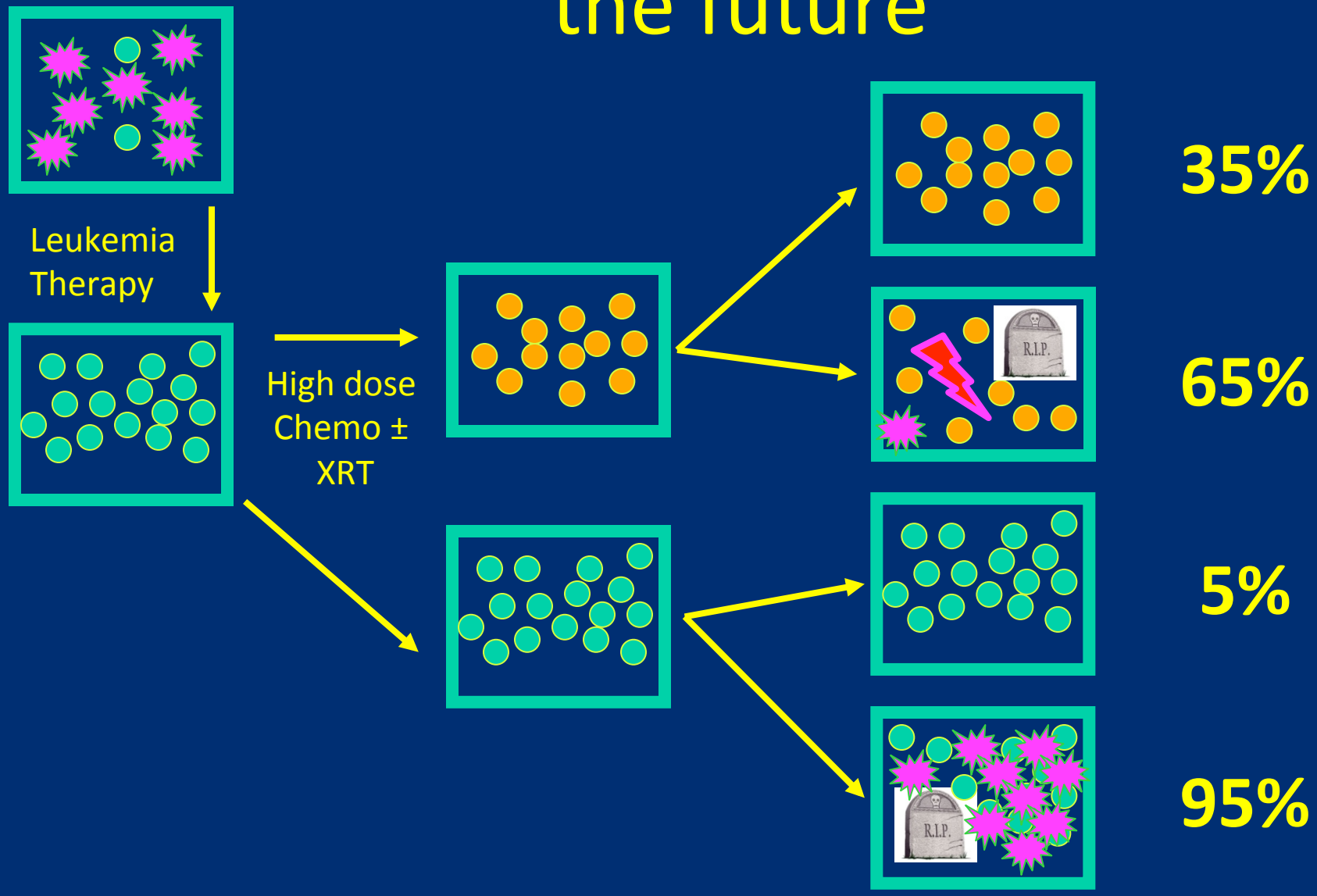
Indications for alloHCT

- Replacement of hematopoiesis
- Immune mediated effect against the underlying malignancy (graft versus tumor effect)
- Prevention of relapse

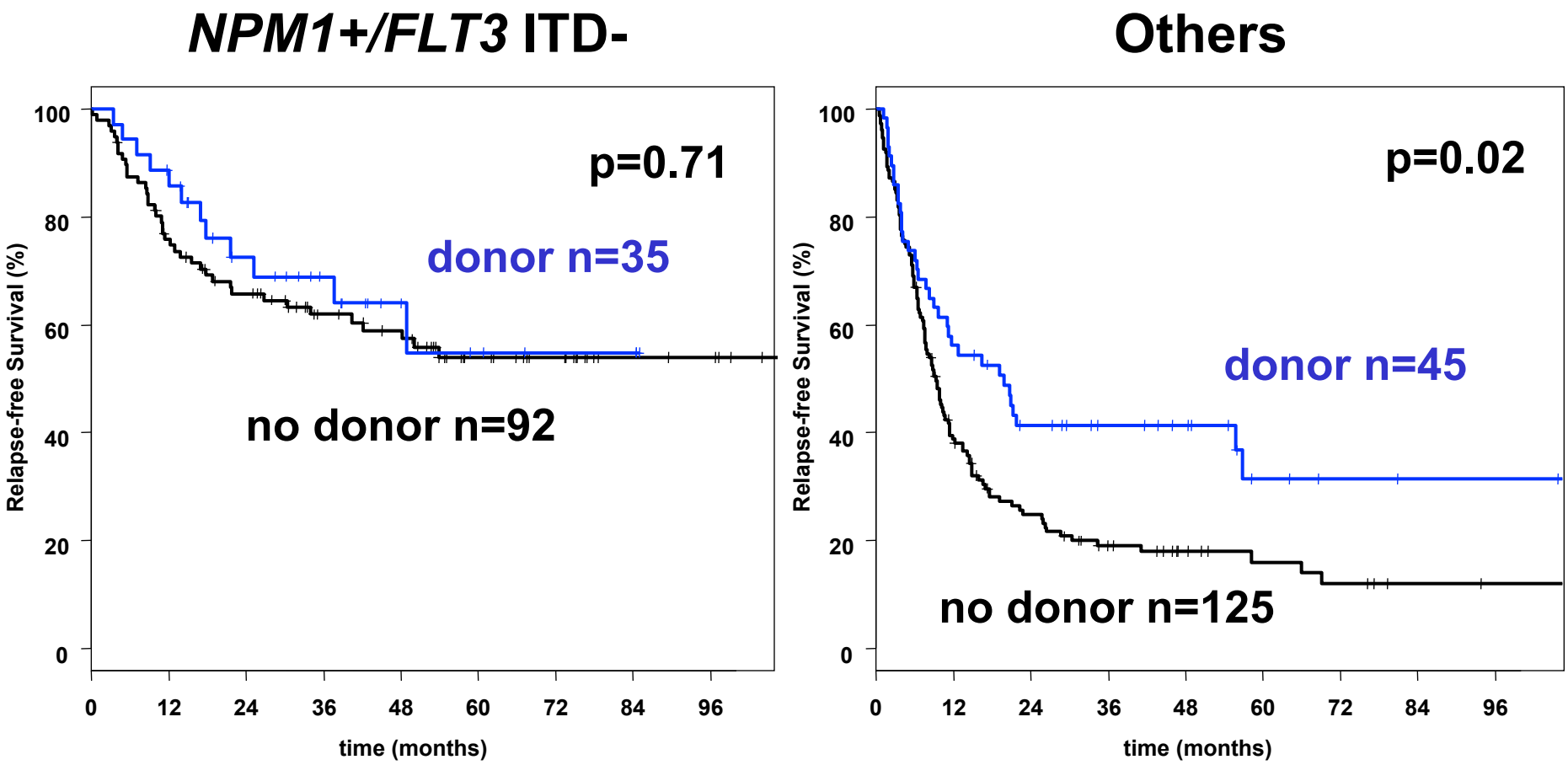
Allogeneic BMT Survival Outcomes (AML)



A transplant is a bet against the future

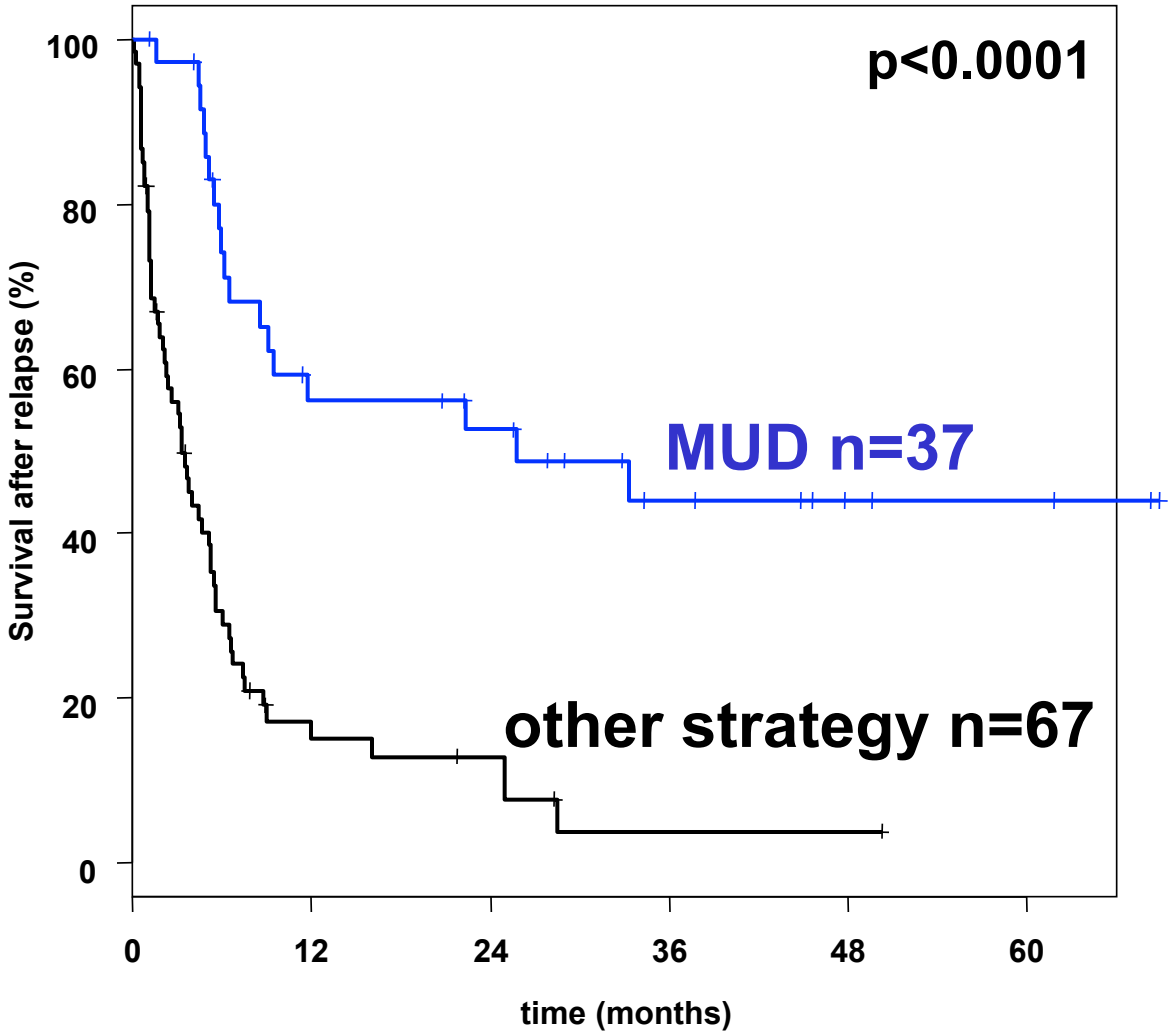


Genetic Subgroup Analysis: RFS



Courtesy of Schlenk R et al, NEJM 2008

MUD Transplantation in Relapsed Patients with Unfavorable Genotype



Important Concepts

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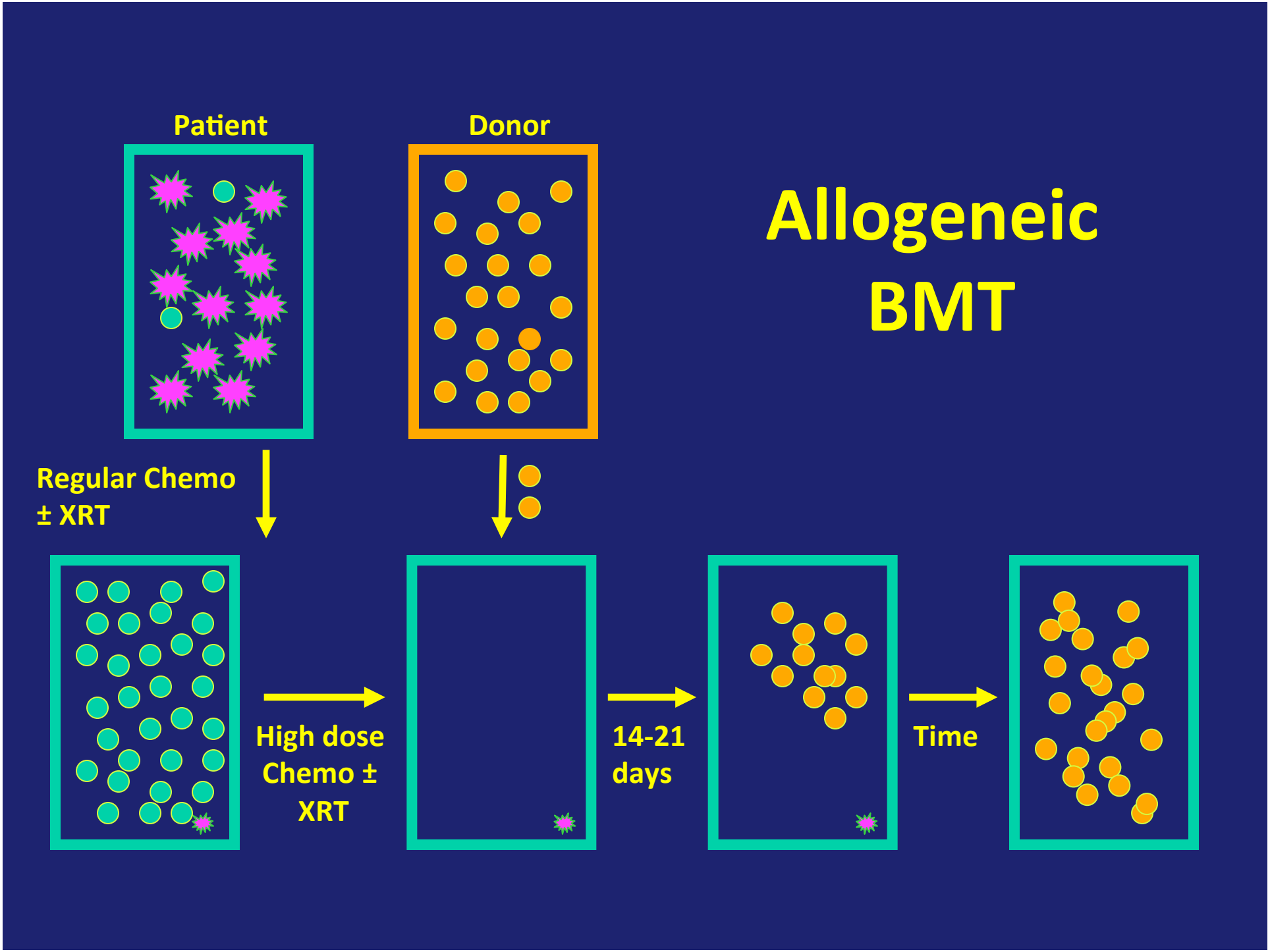
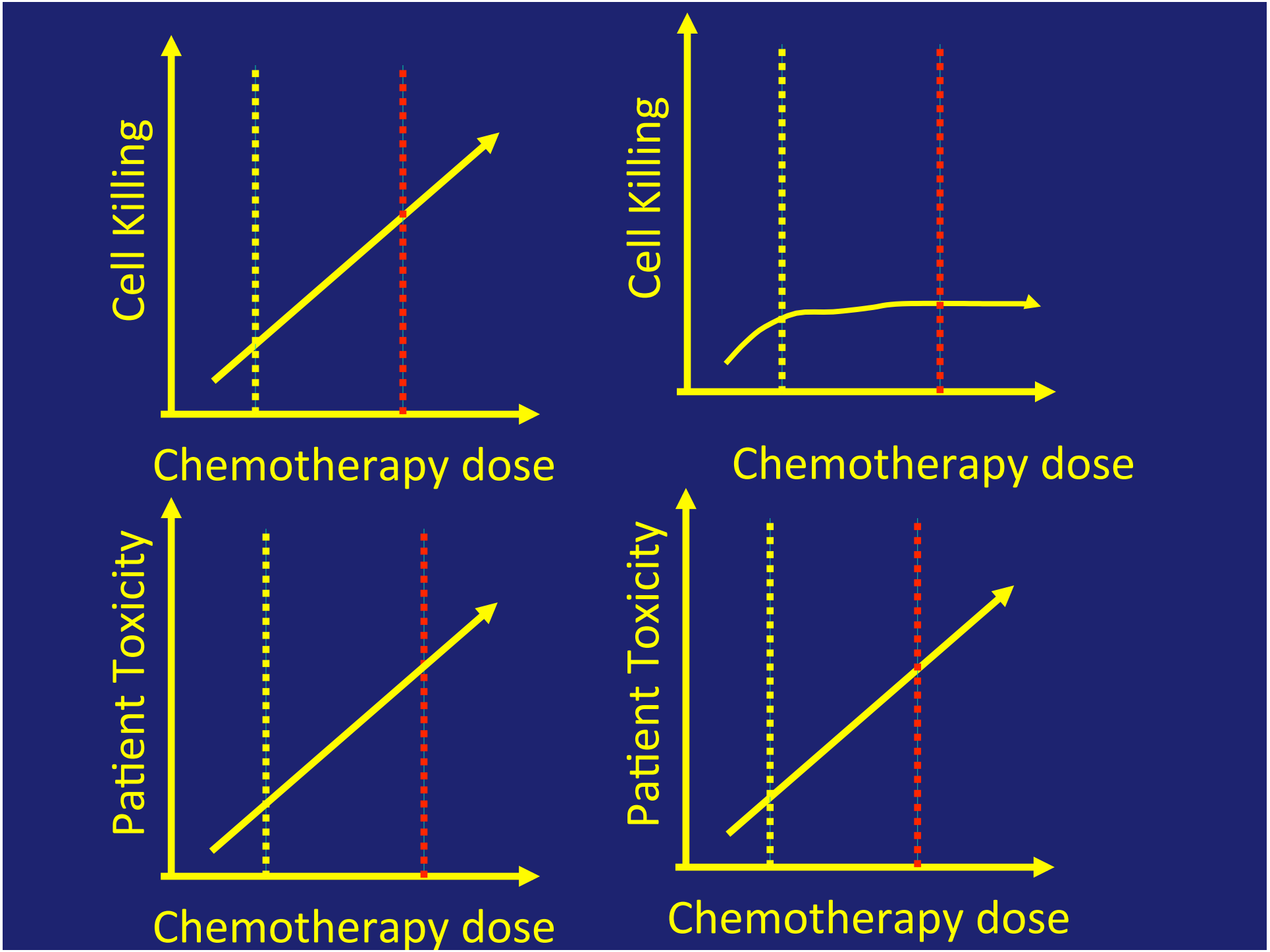
- Acute vs. chronic graft versus host disease
- Donor chimerism

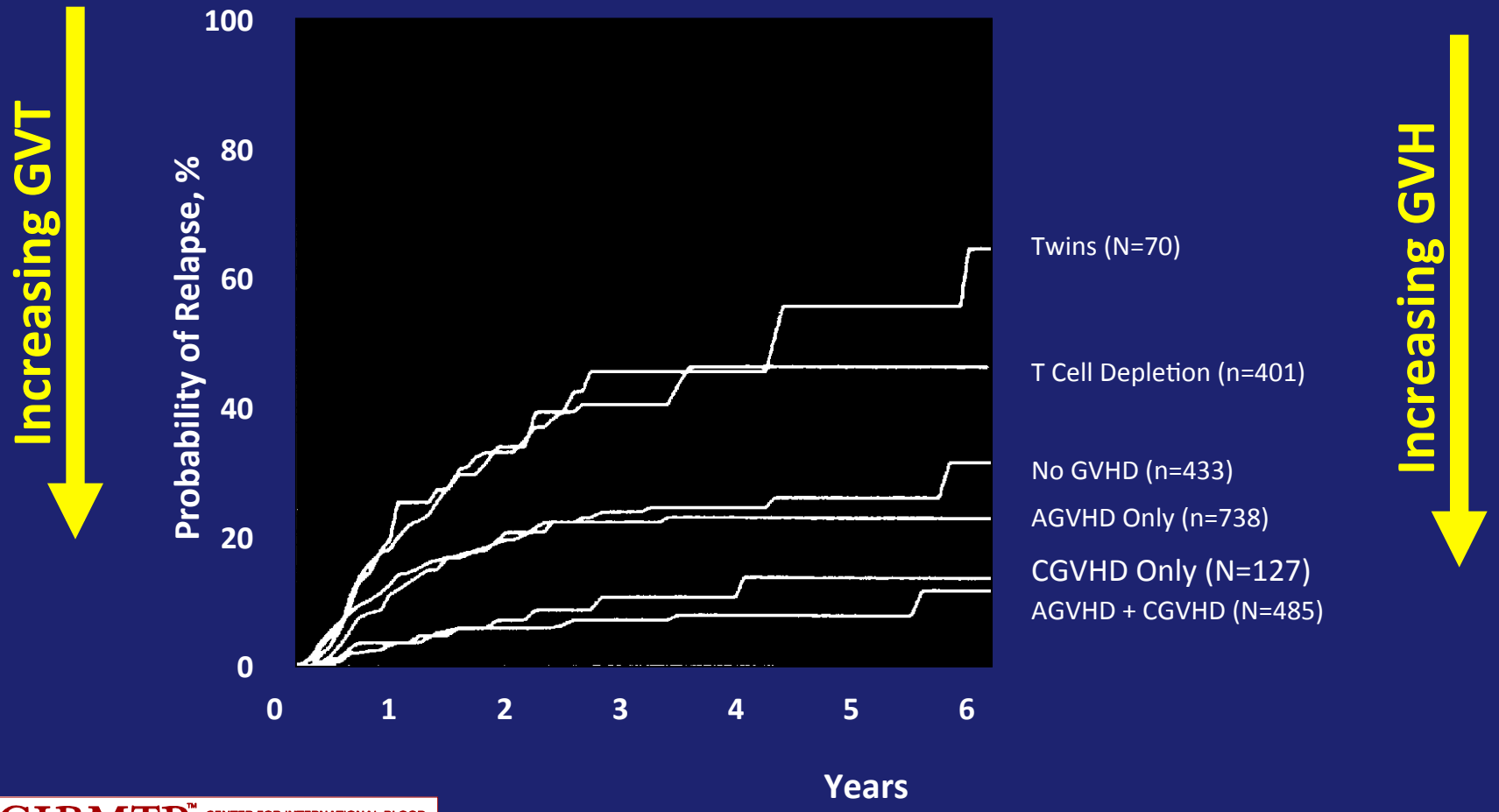

Patient
Donor
Allogeneic BMT
Regular Chemo ± XRT
High dose Chemo ± XRT
14-21 days
Time


Cell Killing
Chemotherapy dose
Cell Killing
Chemotherapy dose
Patient Toxicity
Chemotherapy dose
Patient Toxicity
Chemotherapy dose

Immunologic Effects of Allogeneic Grafts

- **Graft-versus-Tumor Effects – Reaction of the donor immune system against the recipient's malignancy**
- **Graft-versus-Host Effects – Reaction of the donor immune system against the recipient's body tissues.**
- **Different sides of the same coin.**

Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia



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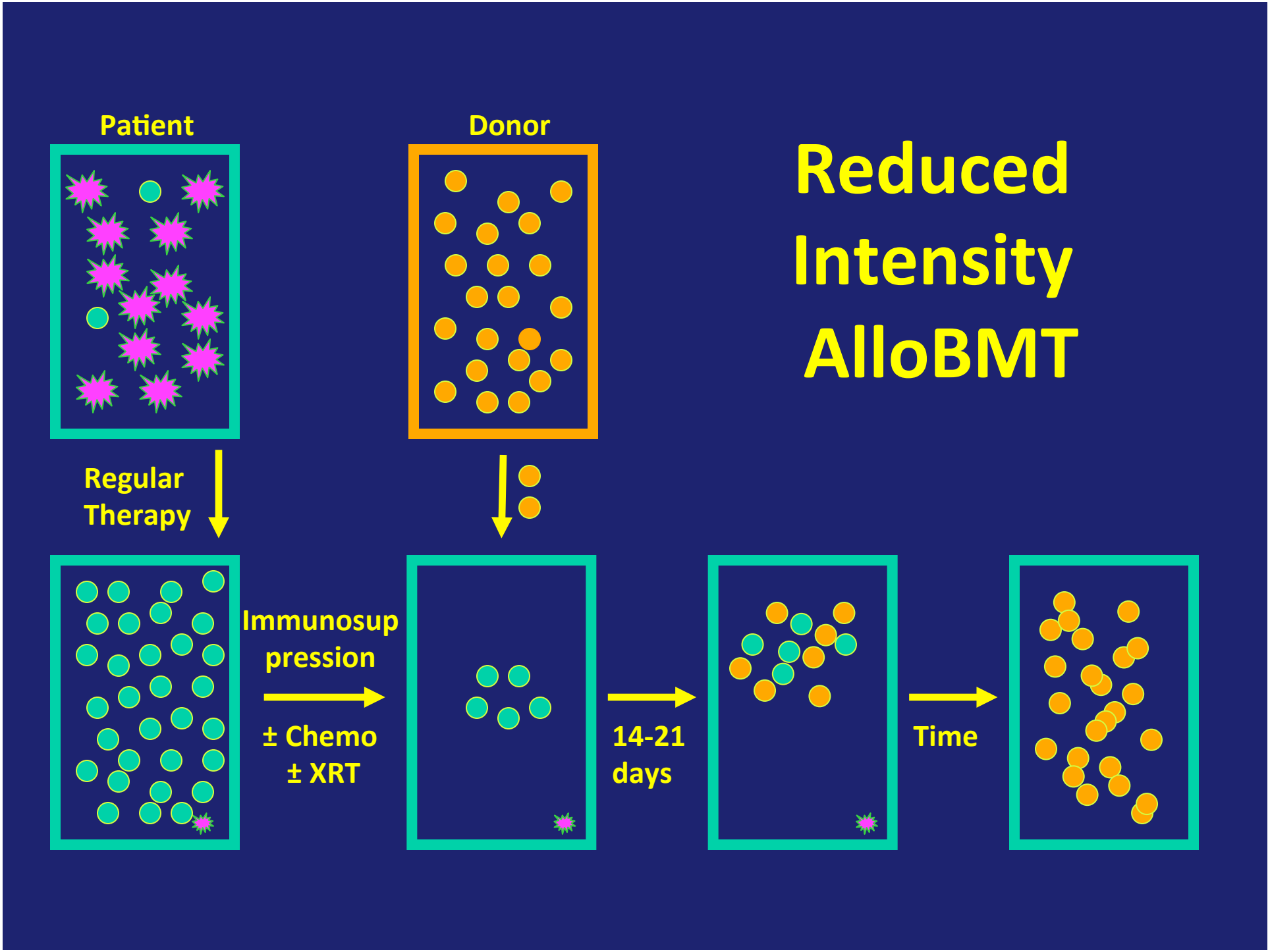
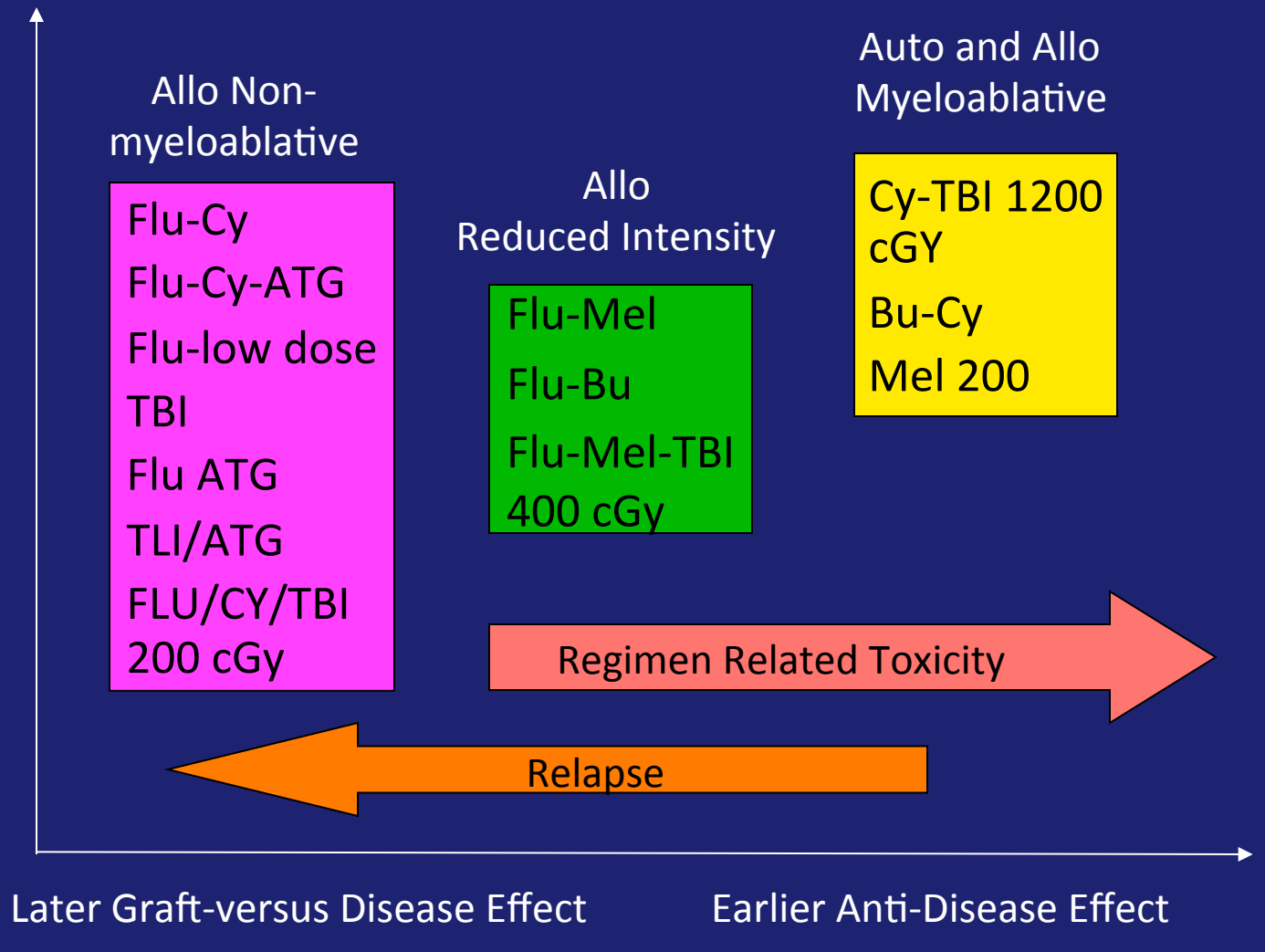
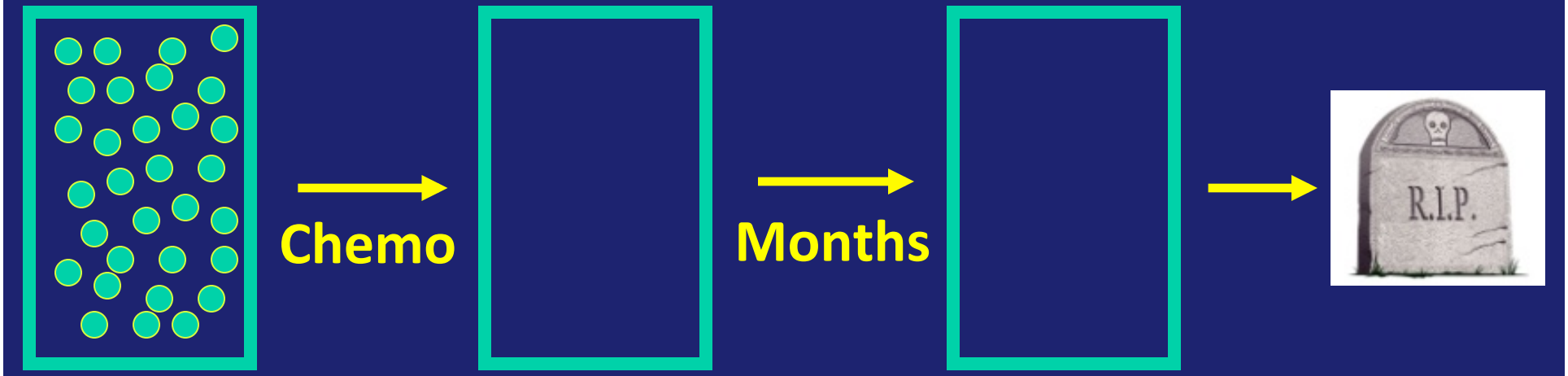

Patient
Donor
Reduced Intensity AlloBMT
Regular Therapy
Immunosuppression
± Chemo
± XRT
14-21 days
Time

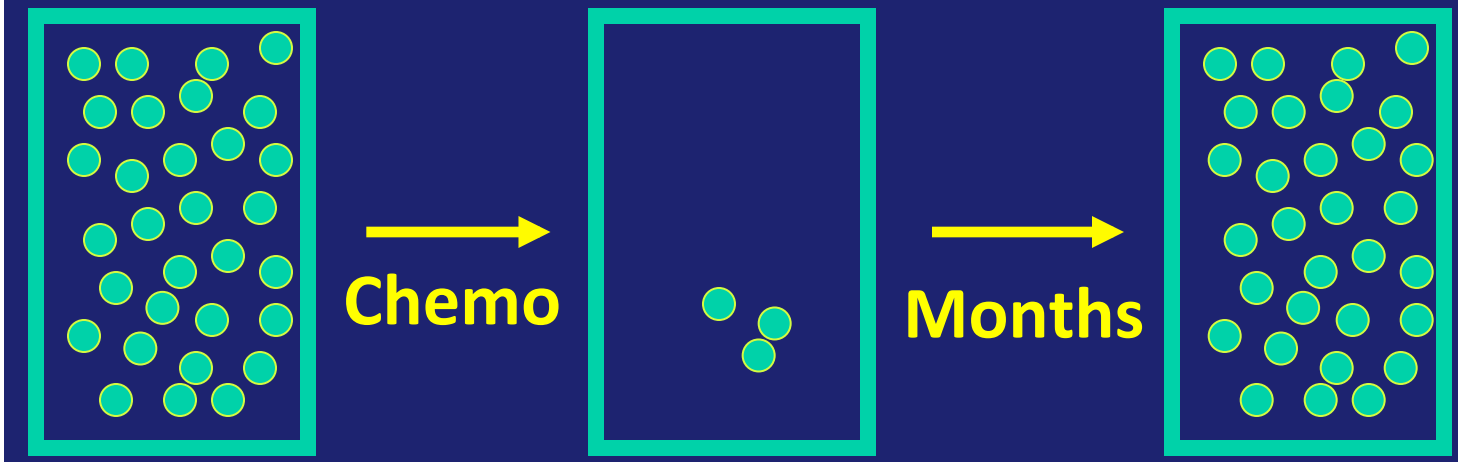
Transplant regimens



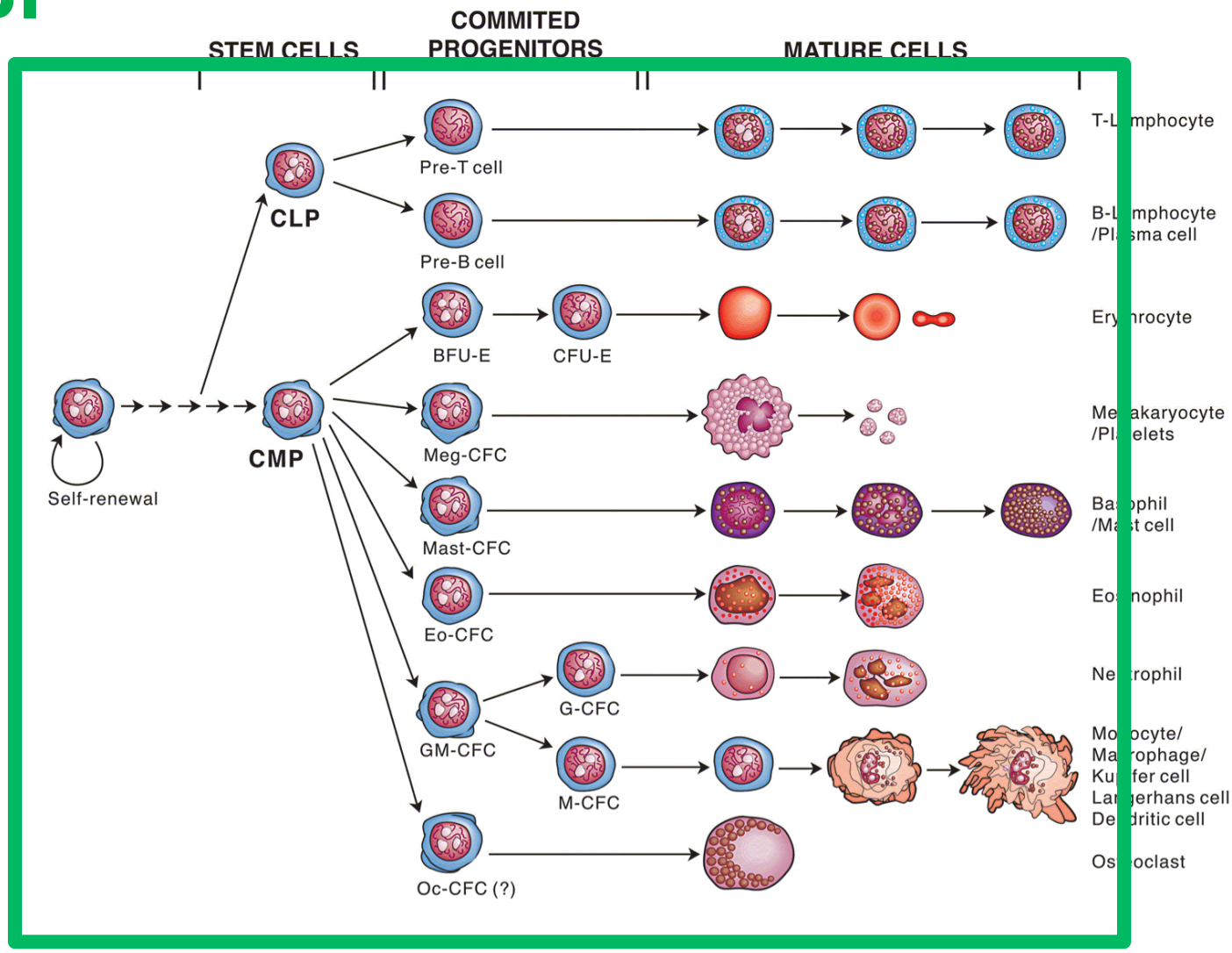
Myeloablation



Reduced intensity



Bu, Mel, TBI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Basophil
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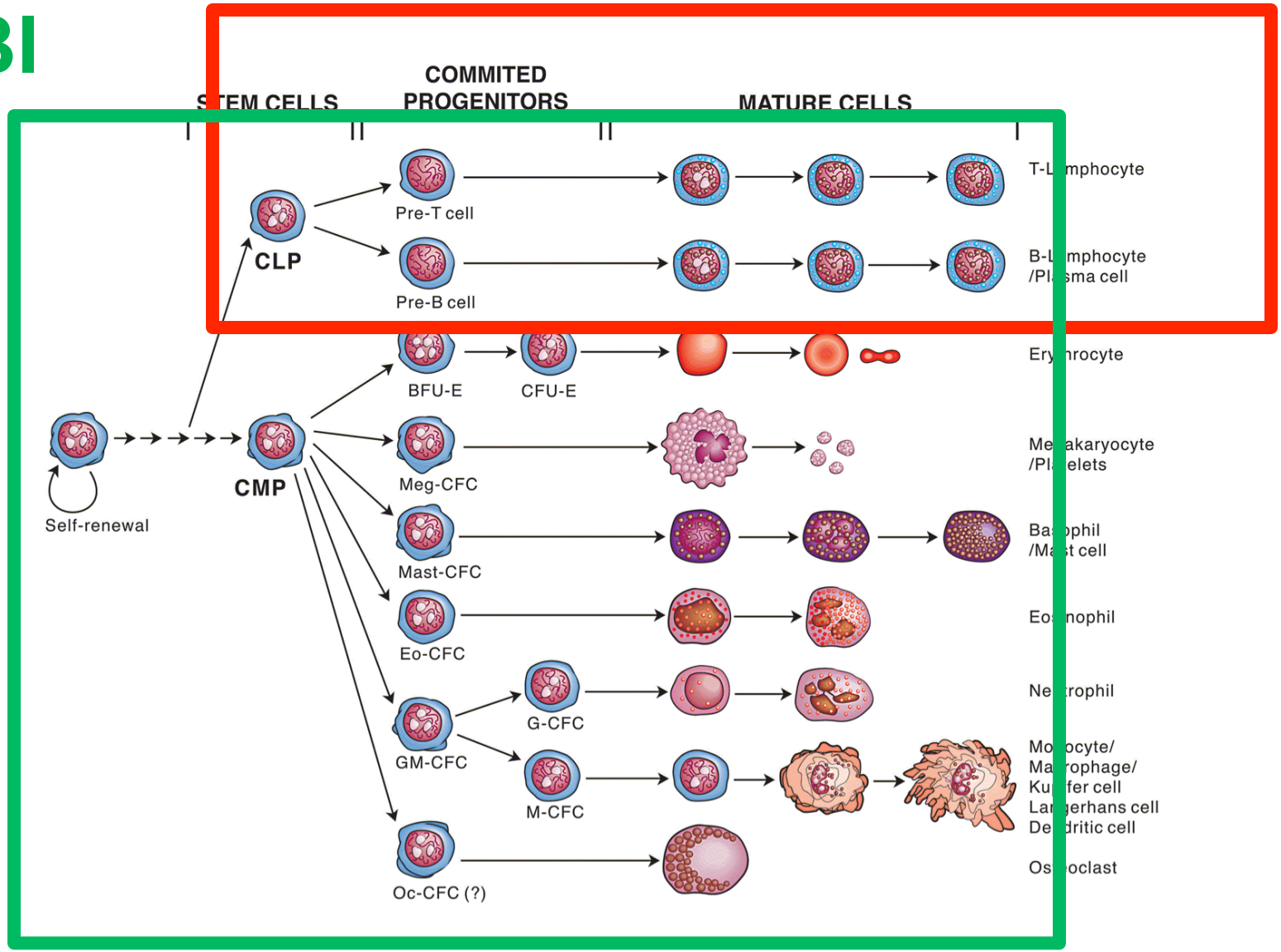
Monocyte/
Macrophage/
Kupffer cell
Langerhans cell
Dendritic cell
Osteoclast

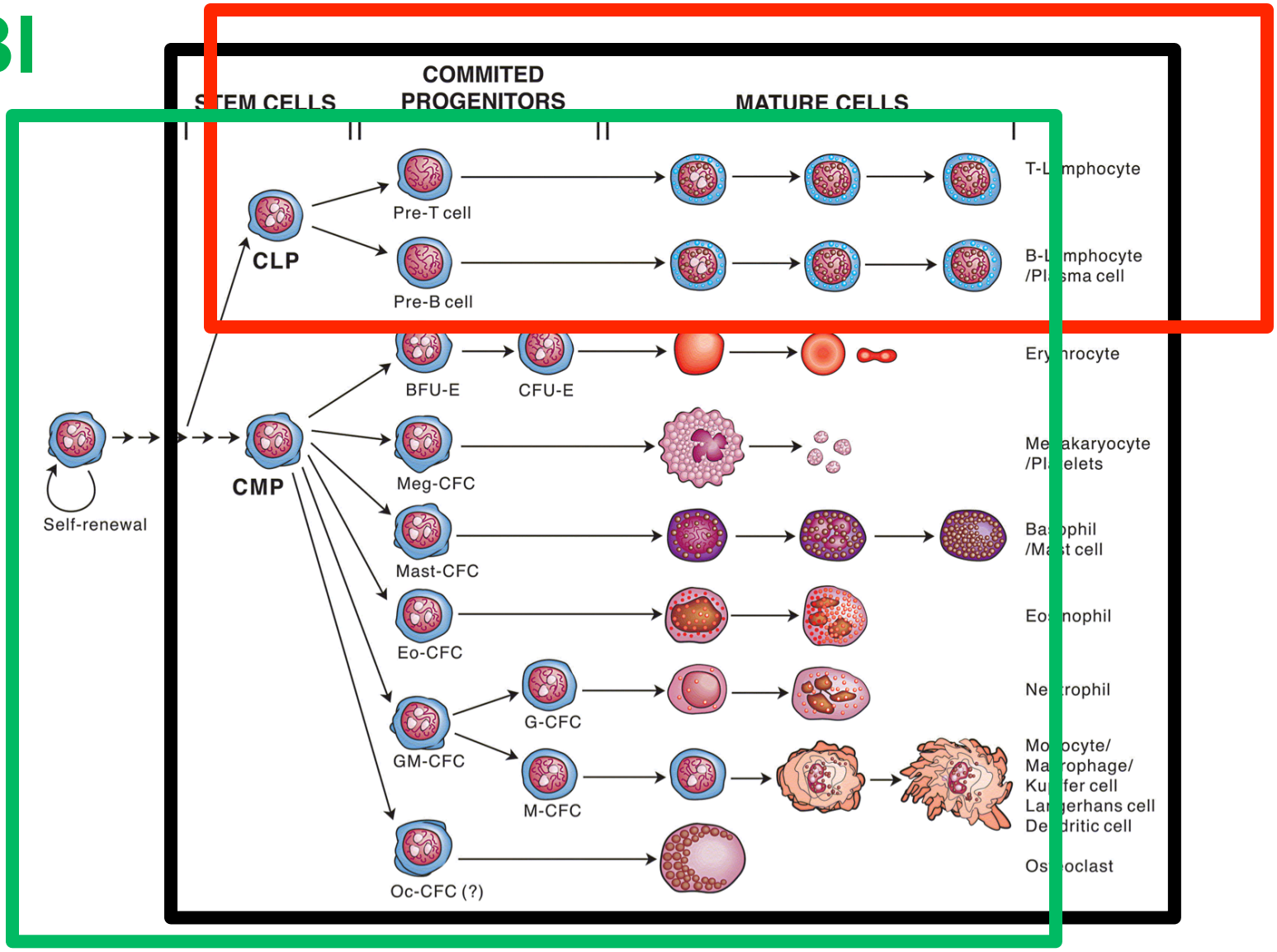
Bu, Mel, TBI

Fludarabine

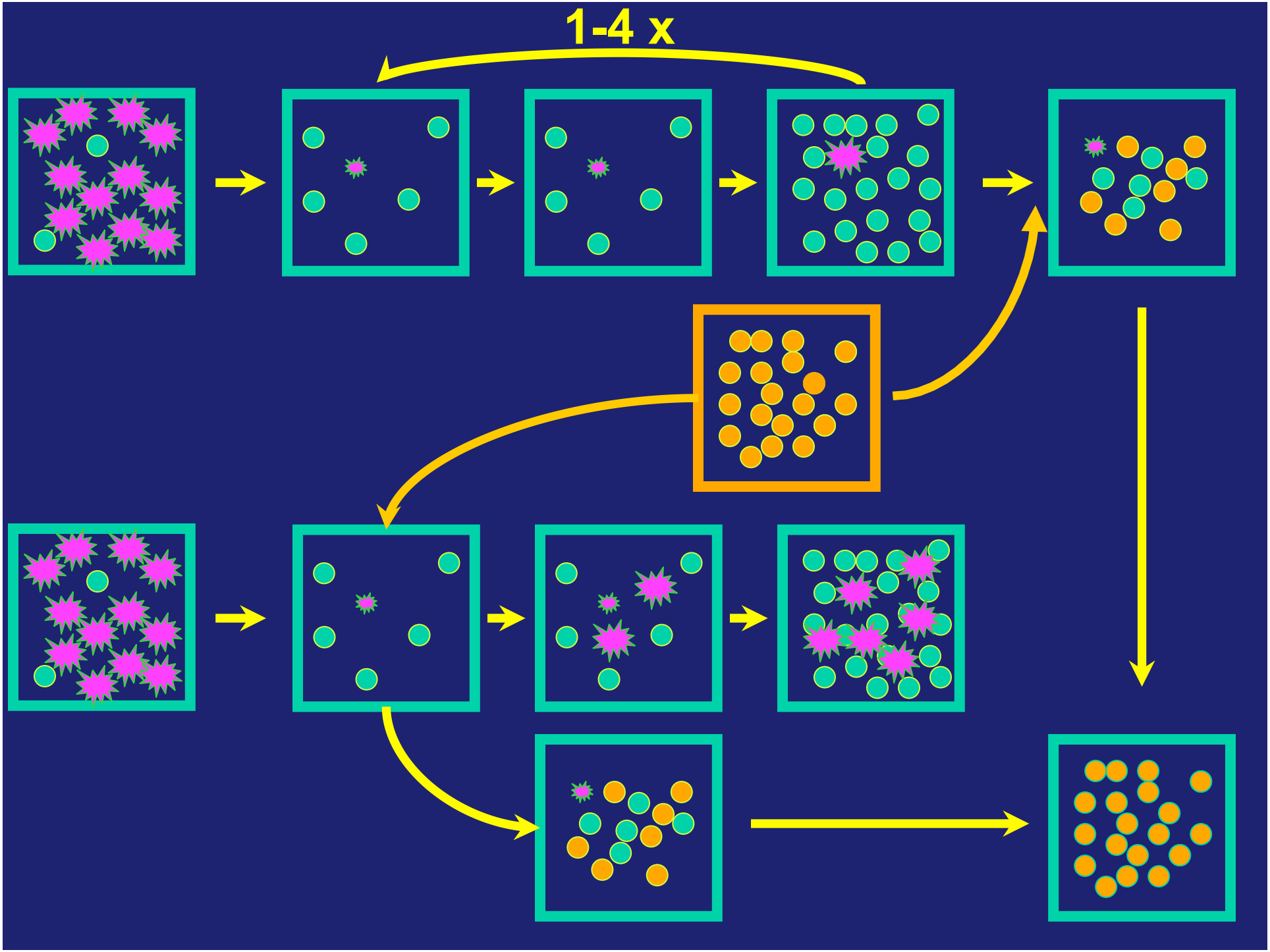


Bu, Mel, TBI

Fludarabine



Cyclophosphamide


1-4 x

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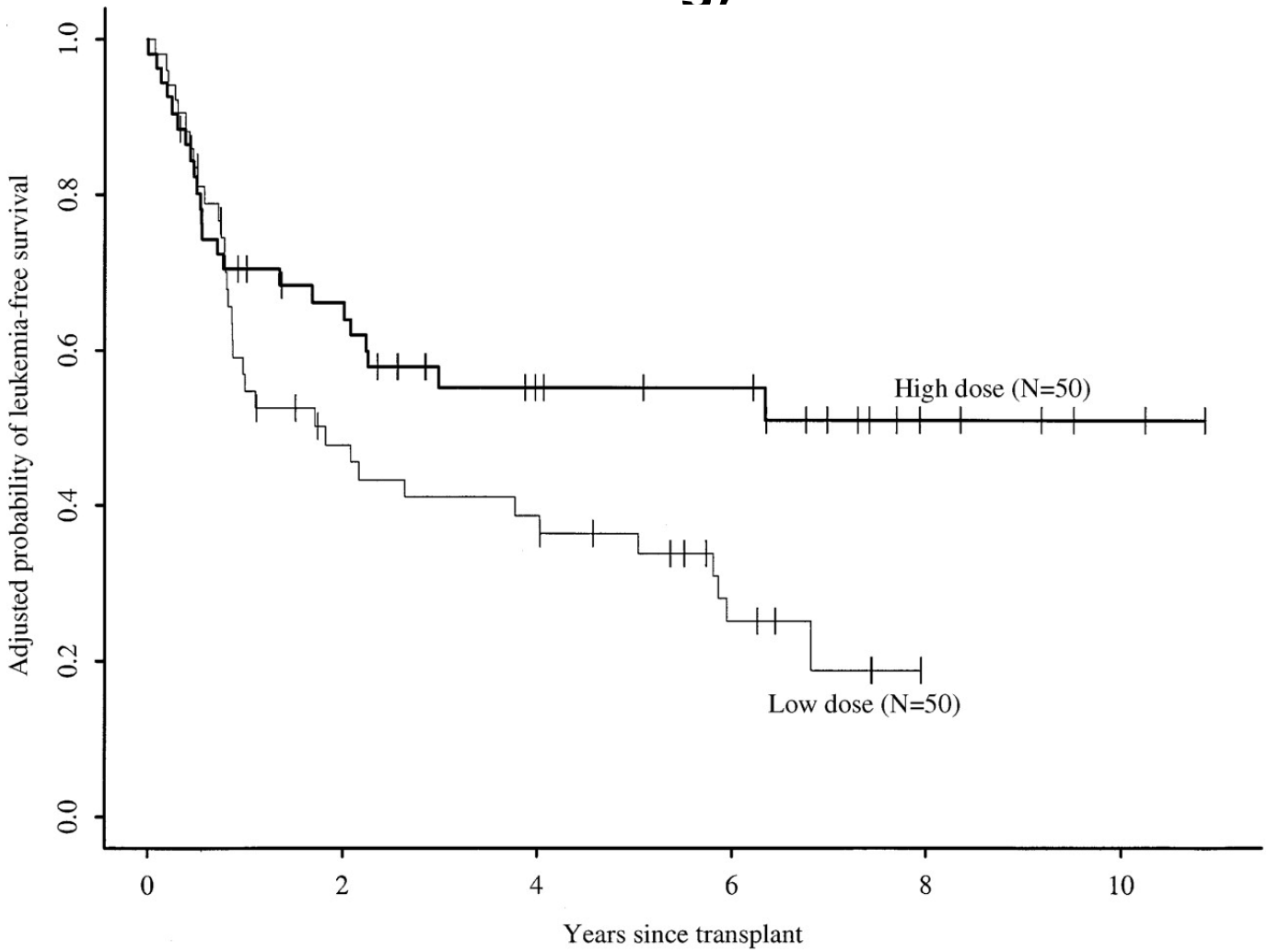
Donor source reflects purpose

	Rescue hematopoiesis	Immune therapy
Autologous	**XXX**	**X**
Allogeneic	**XXX**	**XXX**

Adjusted probabilities of leukemia-free survival rates after identical twin bone marrow transplantations with high (more than 3 × 108 cells/kg) versus low (less than or equal to 3 × 108 cells/kg) cell doses.

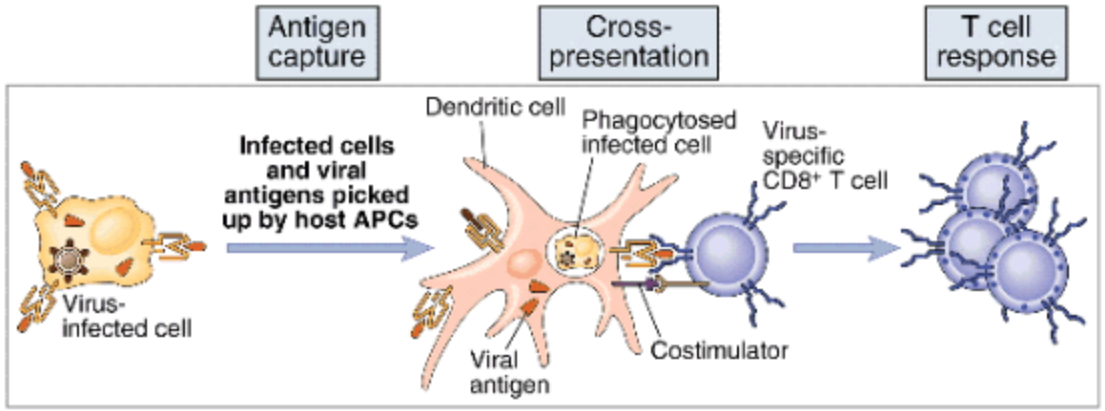


Barrett A J et al. Blood 2000;95:3323-3327

blood

HLA (aka MHC)

- On surface of most body cells
- The most important proteins in transplant
- Normal function is to present antigen to T cells.
- Responsible for graft rejection and GvHD

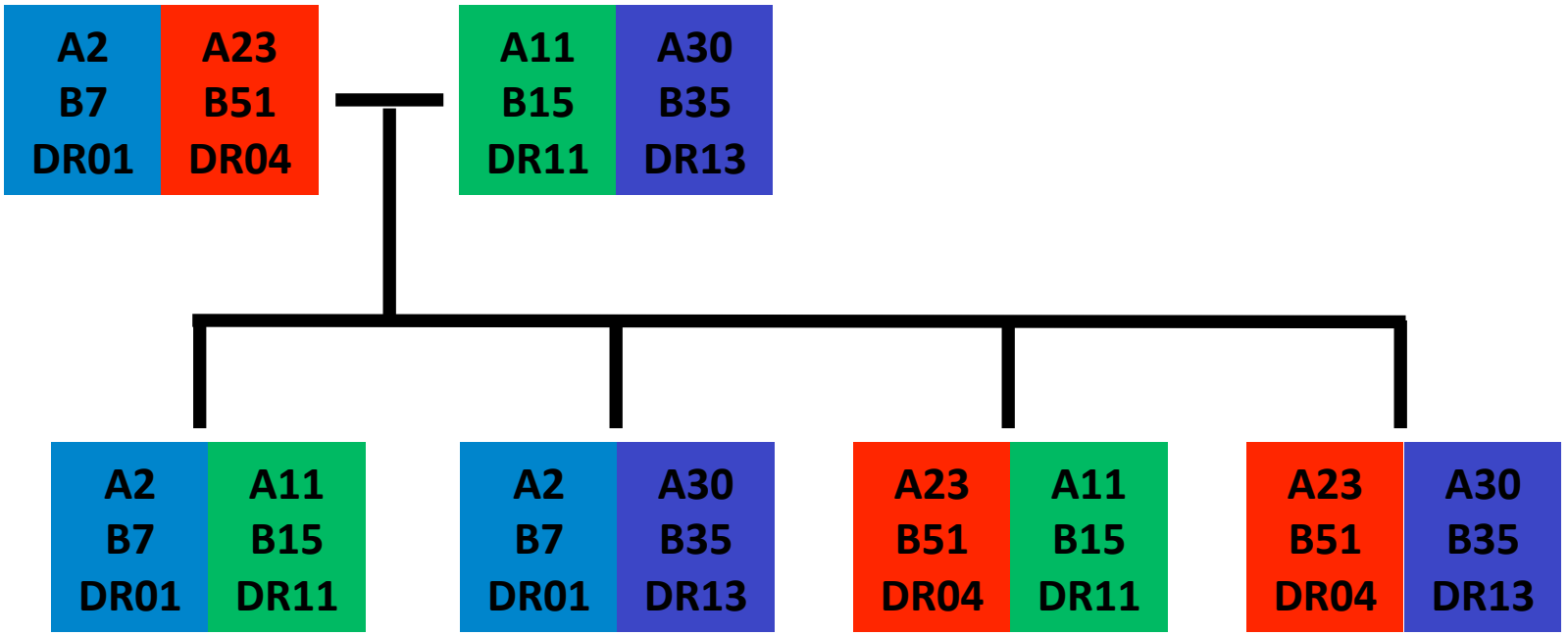


HLA (aka MHC)

HLA	DRB1	A	B	C	DQB1
Alleles	400	370	660	190	62

- $(>1 * 10^{12}$ haplotypes$)^2 = > 1 * 10^{24}$ combinations
- Not all alleles have been identified
- Frequencies are not equally distributed

HLA (aka MHC) Inheritance



Chance of a matched sibling = $1 - 0.75^{\text{\# of siblings}}$

Genetic Differences Between Donors

DNR	Maternal Haplotype					Paternal Haplotype					mMHC
	DR	B	A	C	DQ	DR	B	A	C	DQ	
MUD	X	X	X	X	X	X	X	X	X	X	NO
MRD	X	X	X	#	#	X	X	X	#	#	SOME
Haplo	X	X	X			*	*	*			HALF
Synge	X	X	X	#	#	X	X	X	#	#	ALL
Auto	X	X	X	#	#	X	X	X	#	#	ALL

Donor Selection

- Human leukocyte antigen (HLA) matching
- Relatedness
- Cytomegalovirus status
- Age
- Gender (parity)
- Not blood ABO type (so far)

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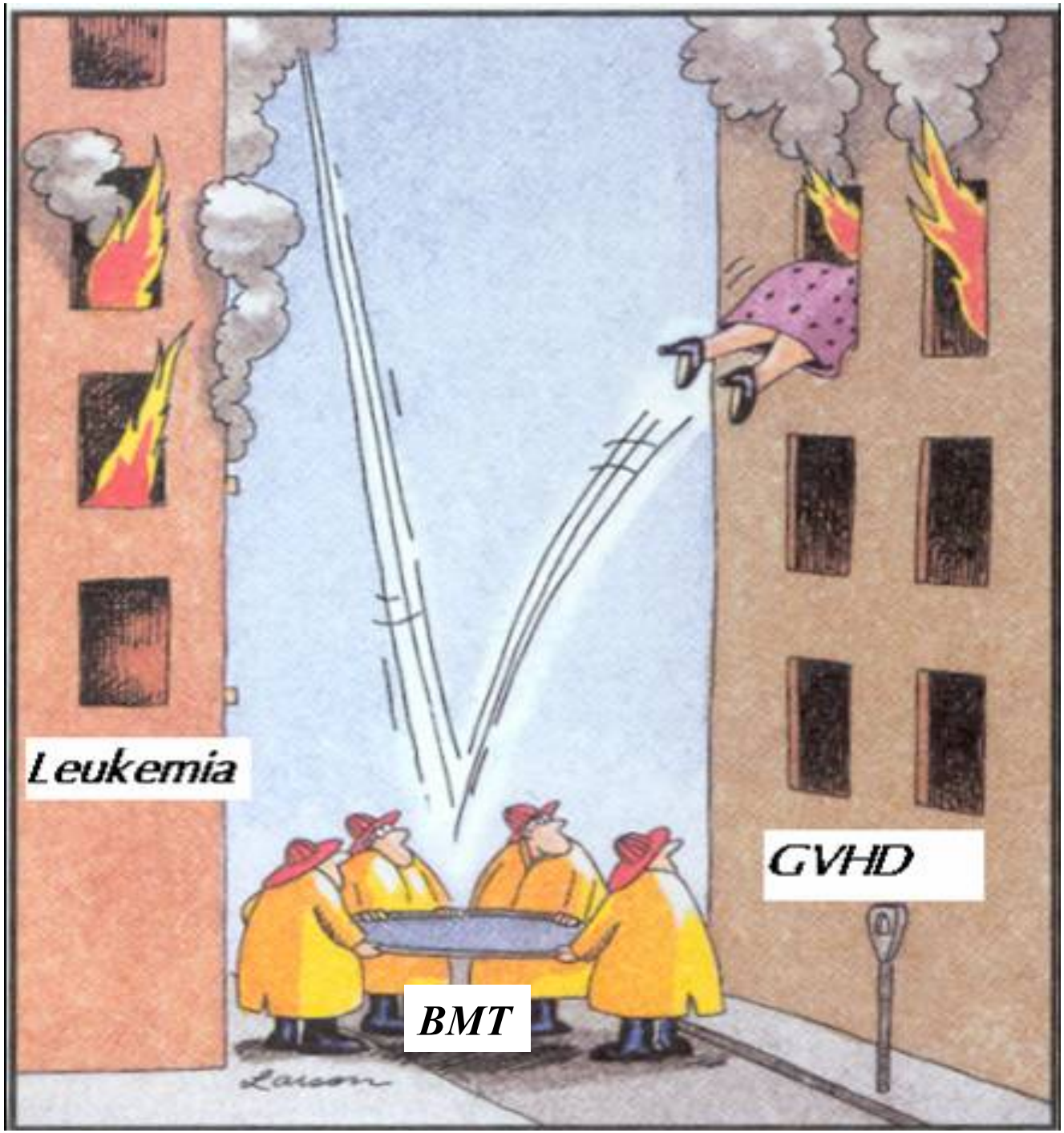
Leukemia
GVHD
BMT
Larson

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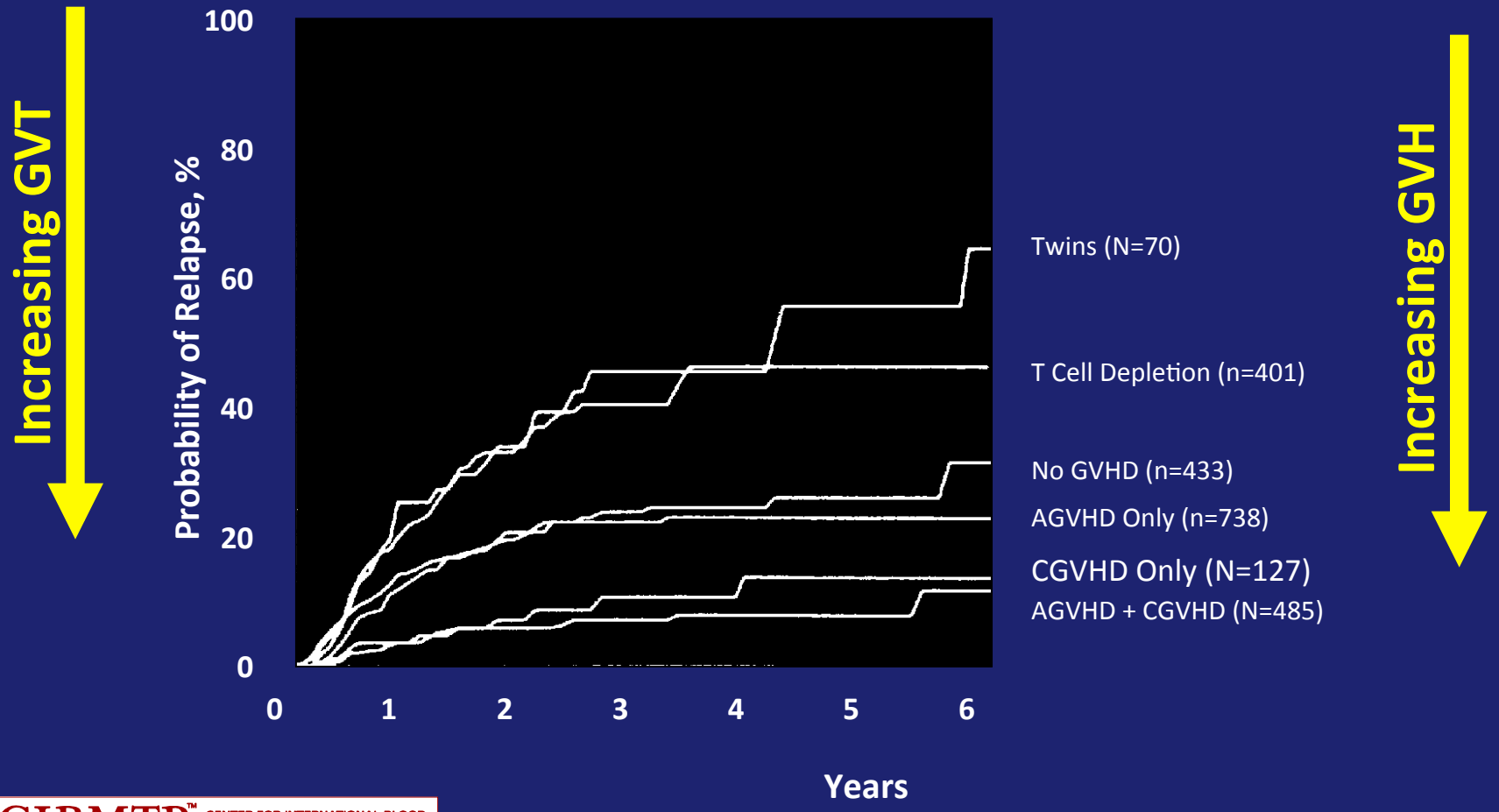

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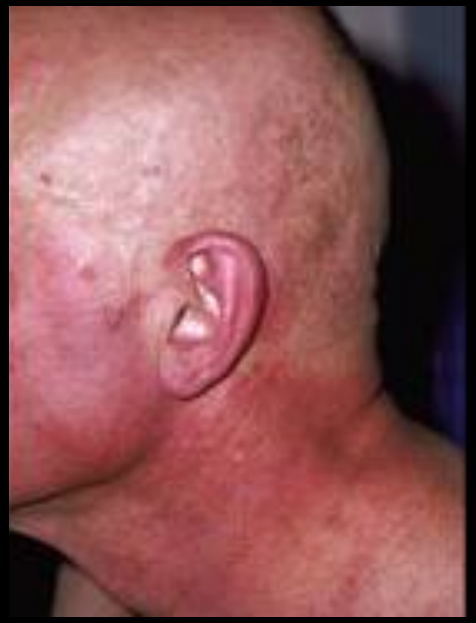
Billingham Criteria (1966)

- The graft must contain immunologically competent cells
- The host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft, and is, therefore, capable of stimulating it antigenically
- The host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities; that is, it (the graft) must have the security of tenure

Acute GvHD

- **Reaction of donor's immune system against the recipient's body tissues**
- **Manifests as diarrhea, skin rash, liver test abnormalities usually within the first 100 days.**
- **~20-50% of allogeneic transplants will develop some aGvHD**
- **Associated with a 15-20% mortality**



Acute GvHD Therapy

- **Prophylaxis – Attempts to prevent aGvHD development**
- **Treatment – For therapy of aGvHD once it occurs**

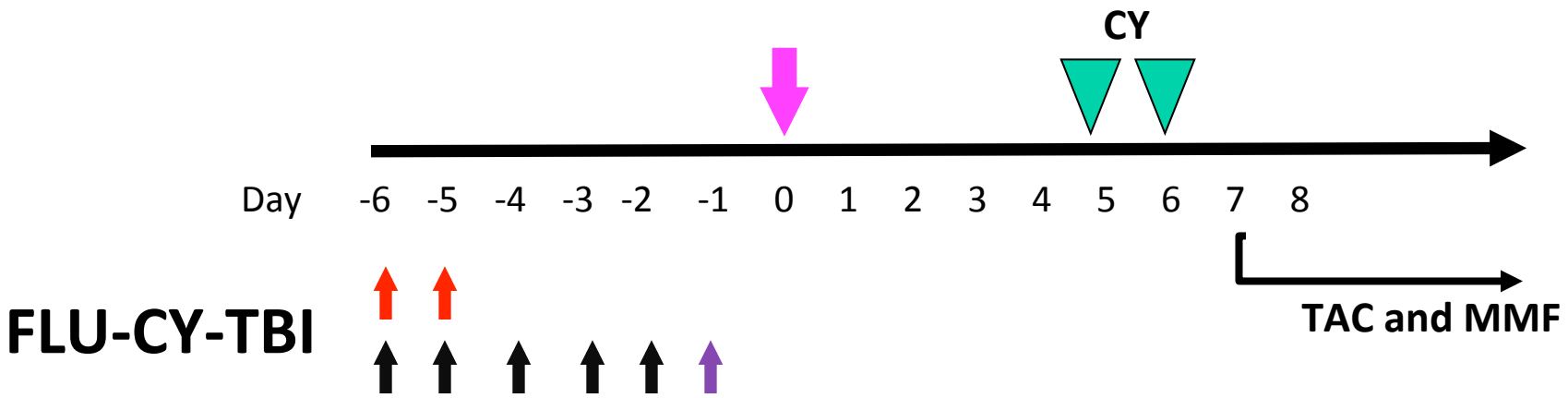
Prophylaxis

- **Pharmacologic – Calcineurin inhibitor and methotrexate after transplant**
- **T cell depletion**
  - ***Ex vivo* CD34 selection or T cell depletion of the graft**
  - ***In vivo* anti-thymocyte globulin or anti-CD52**
- **Post transplant high dose cyclophosphamide**

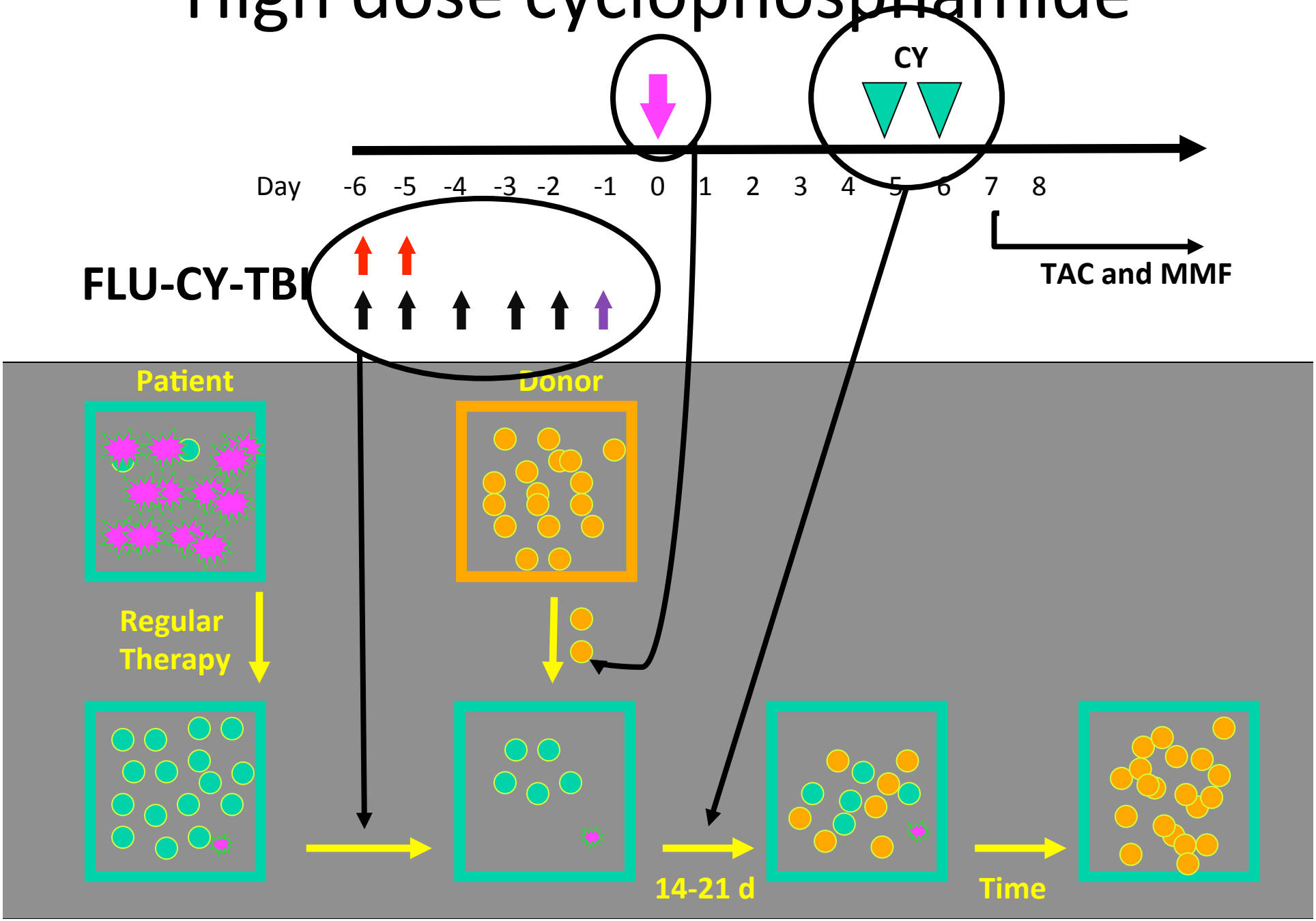
T Cell Depletion vs. Pharmacologic Approaches

	N	Acute GvHD	Long term
TCD vs. CSA/ MTX	48	23% vs. 12%	LFS: 42 vs 44% @ 3 yrs
Partial TCD/ CSA vs. CSA/ MTX	400	18% vs. 37%	cGvHD: 18 vs. 37% DFS @ 3 years the same
TLI/ATG	37	1/37 (3%)	cGvHD: 27% of patients surviving >100d

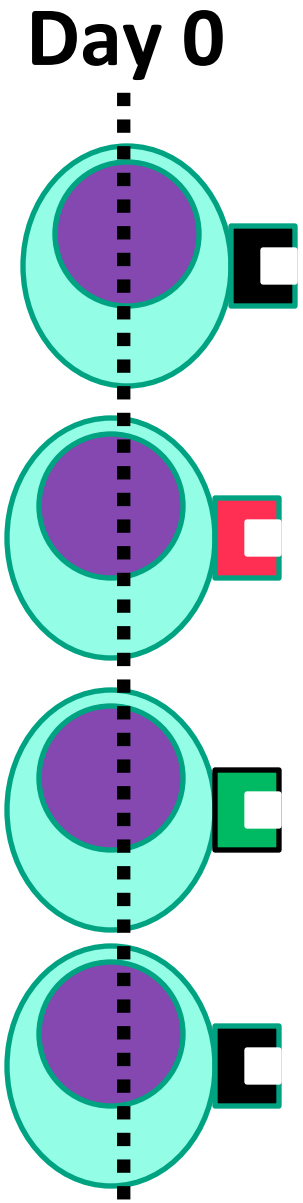
High dose cyclophosphamide



High dose cyclophosphamide



Post HCT cyclophosphamide (Cy) for GvHD



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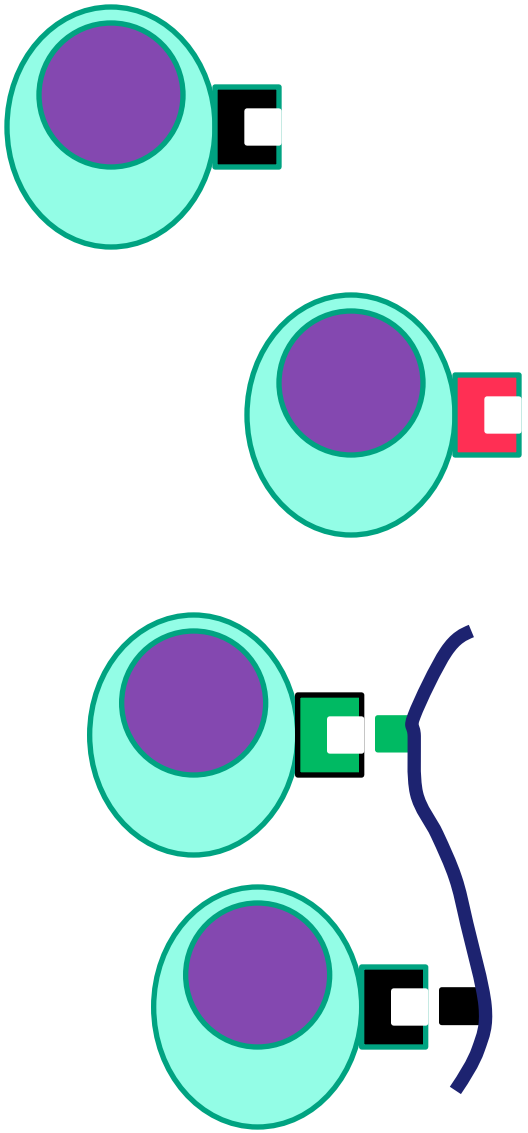

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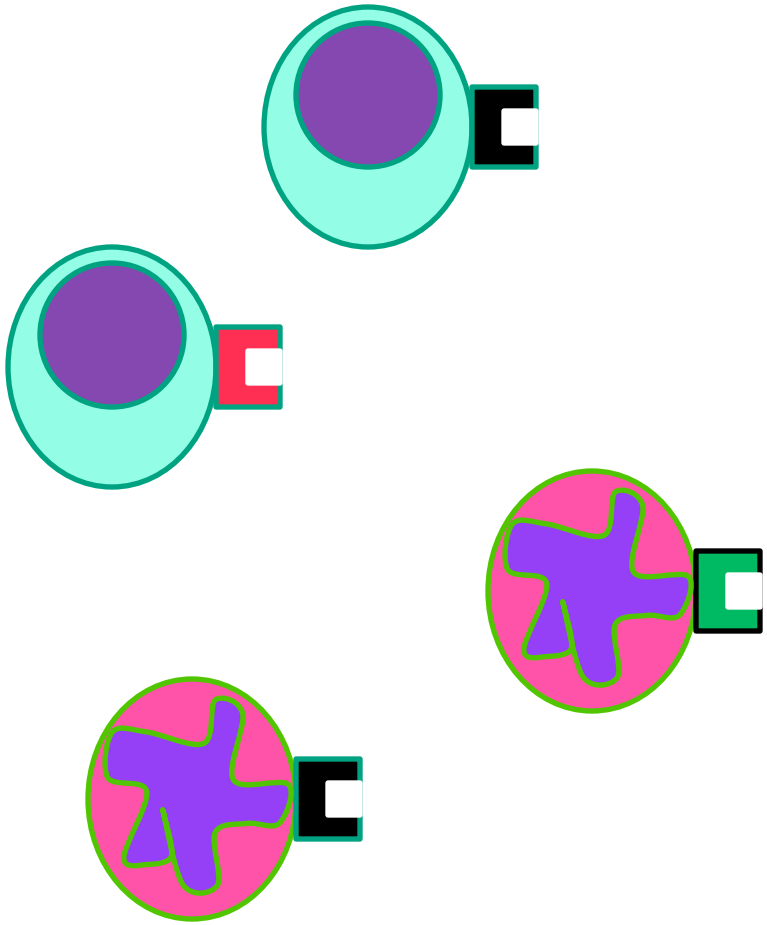

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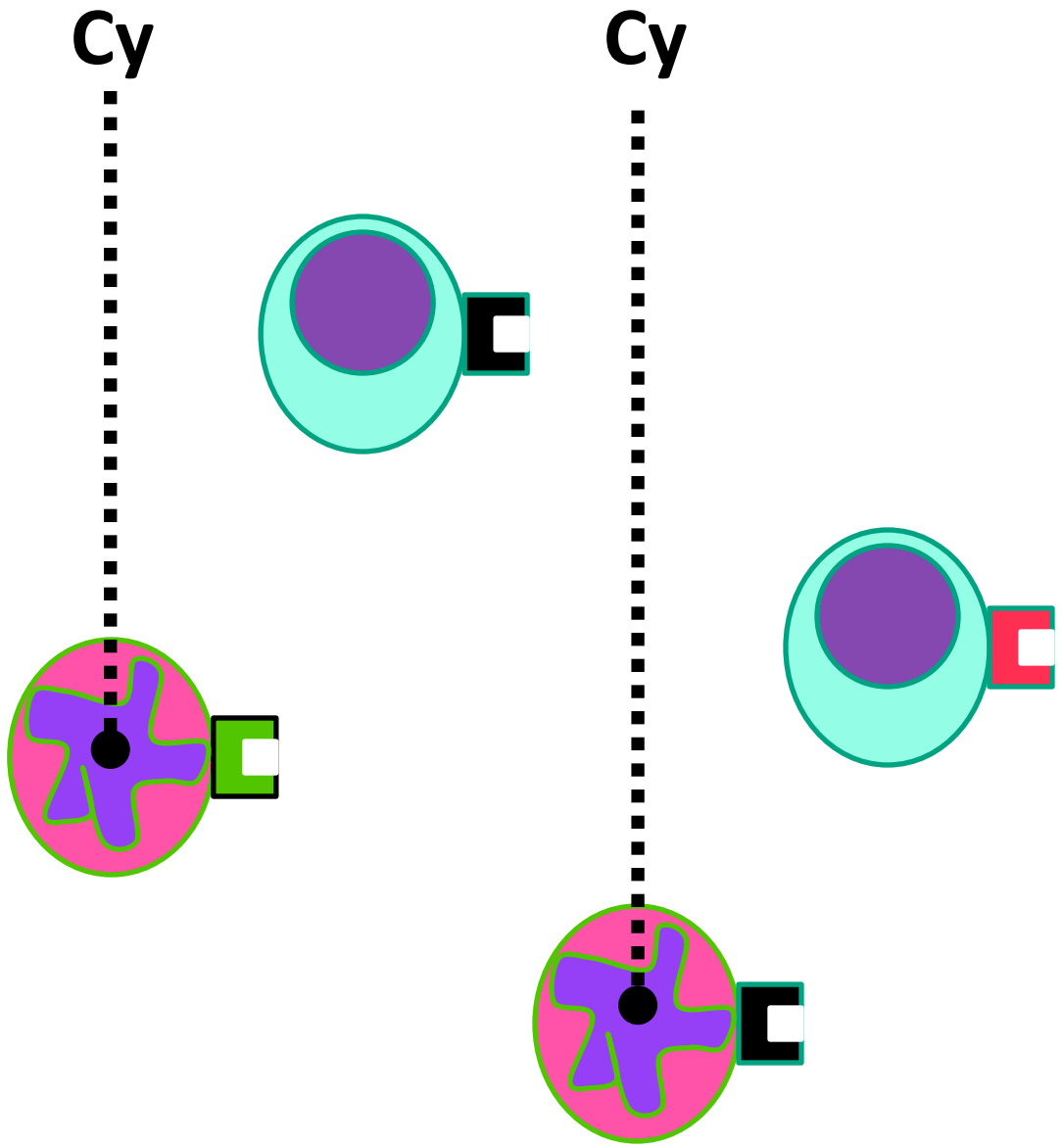

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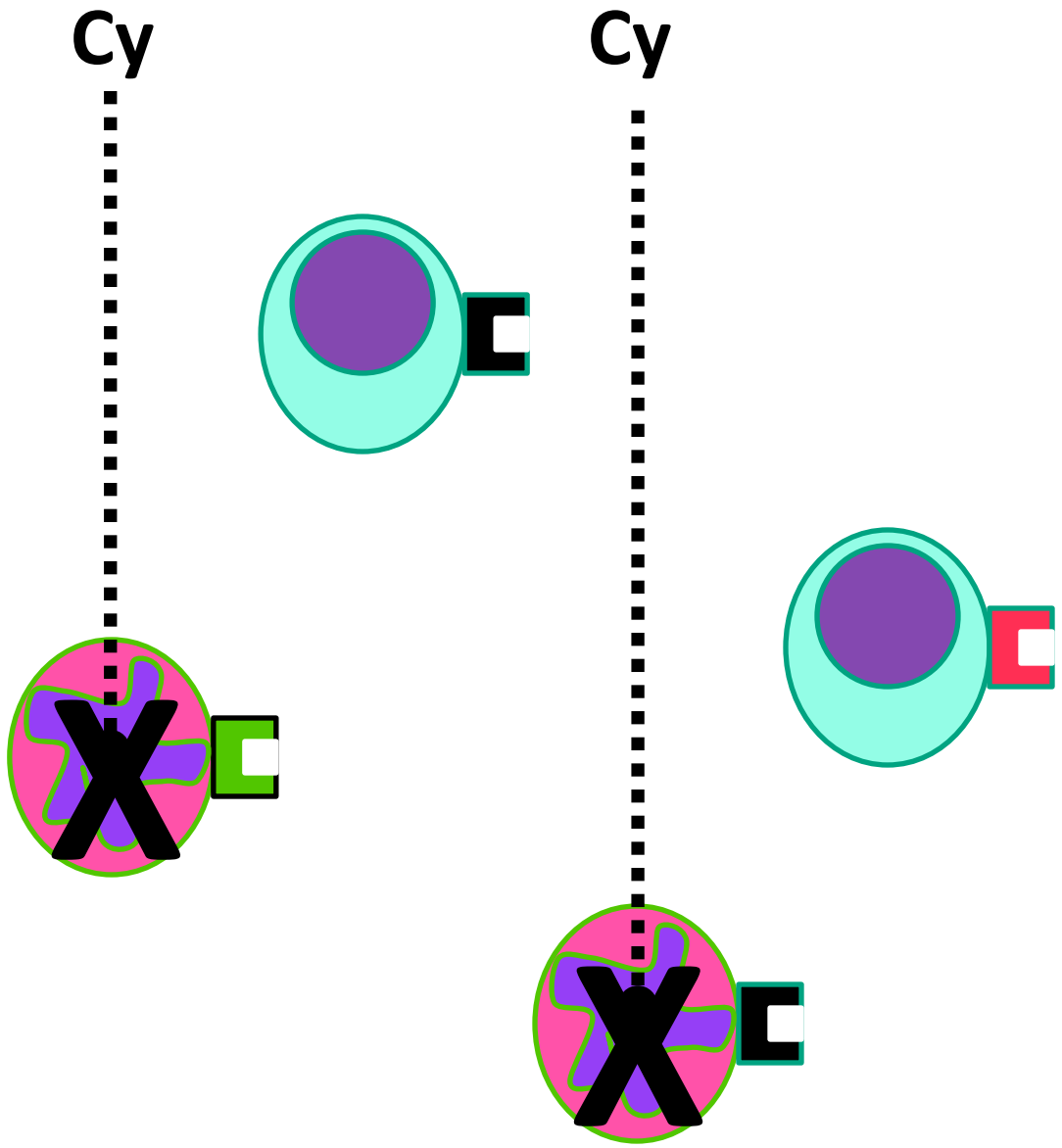

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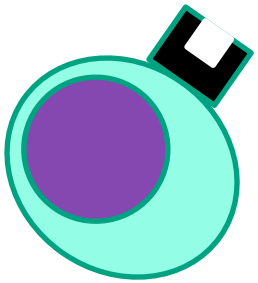
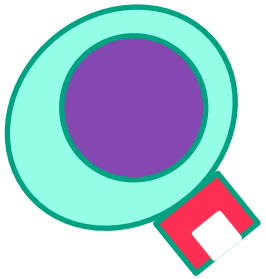




Post HCT cyclophosphamide (Cy) for GvHD

HCT for hematologic malignancy

	Haplo*	Standard#
Conditioning	Flu/Cy/TBI	Flu/Mel/TBI
aGvHD prophylaxis	Cy/Tac/MMF	uMTX/Tac/ MMF
Graft failure	13%	0%
aGvHD Gr. III-IV	6% (day 200)	27% (day 100)
Progression free survival	26% (2 years)	44% (2 years)
Overall survival	36% (2 years)	47% (2 years)

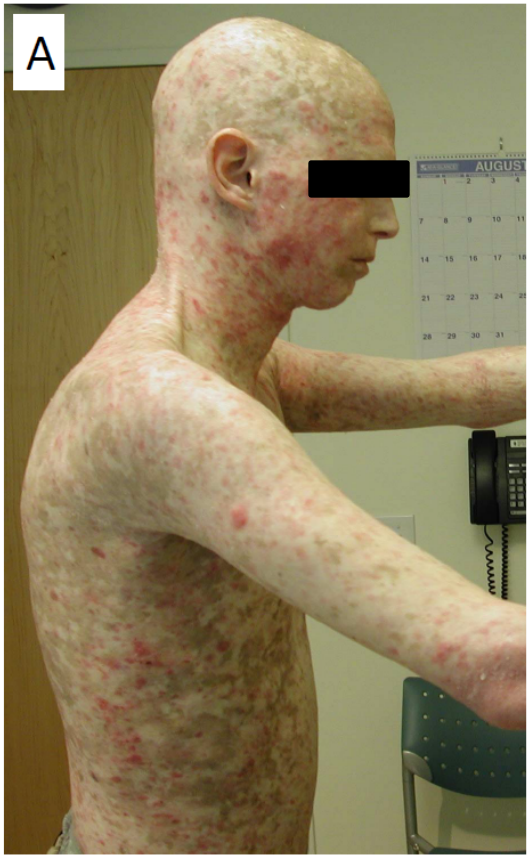
* Luznik, et al. BBMT 14:641 2008, # RPCI unpublished data

Something to think about

- **How does Billingham's hypothesis explain how post-transplant cyclophosphamide prevents acute graft-versus-host disease?**
- **What property does cyclophosphamide have that enables its use after transplant without endangering the graft?**

Chronic Graft-versus-Host Disease

- Post transplant complication usually occurring > 100 days characterized by
  - Fibrotic skin disease
  - Dry and gritty mouth eyes due to glandular destruction
  - Gastrointestinal fibrosis with malnutrition
- 50% of long term survivors will develop some form of cGvHD
- Chronic GvHD is the major cause of long term mortality other than relapse after transplant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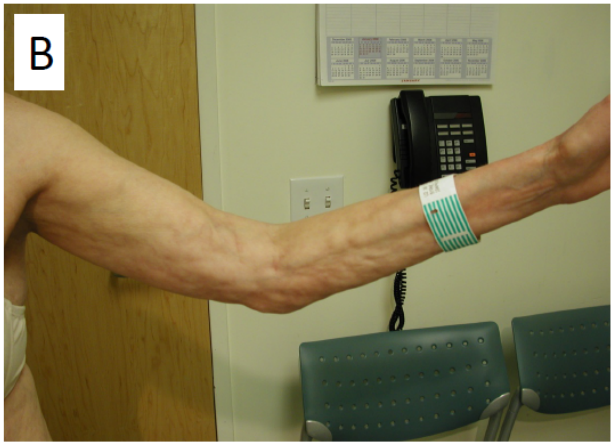
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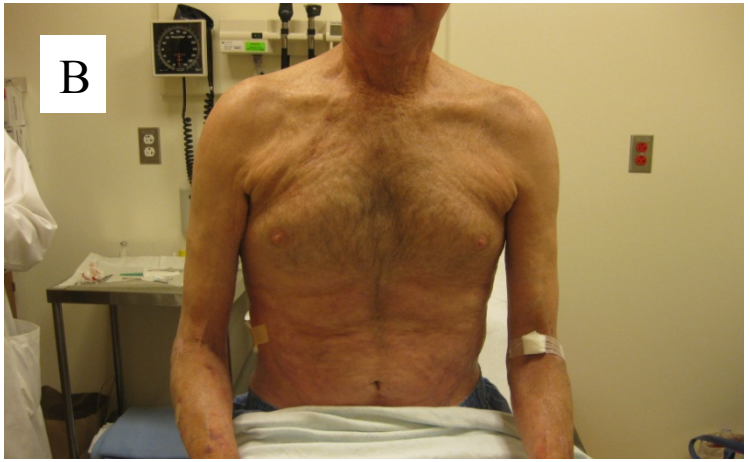
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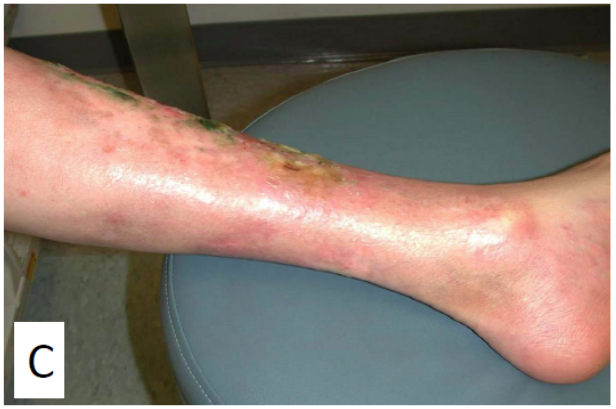
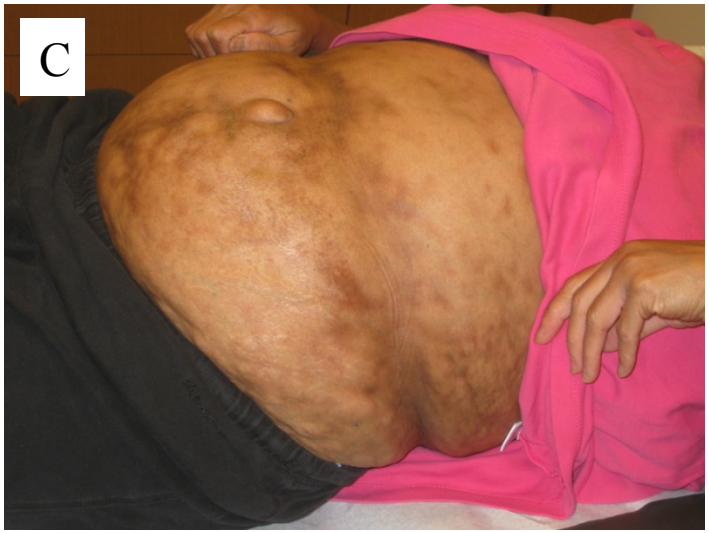

C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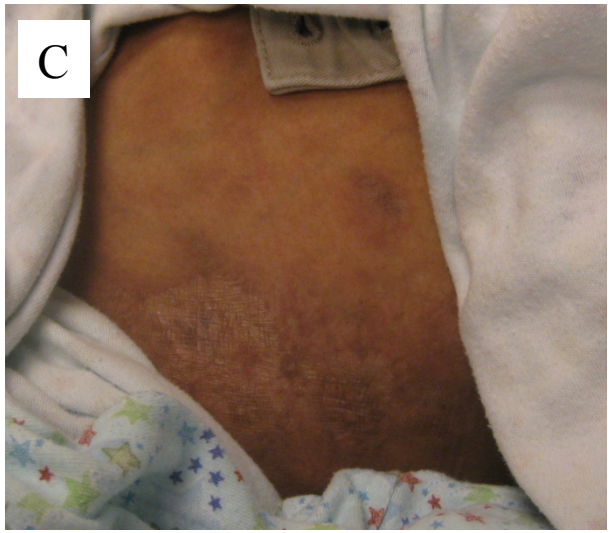
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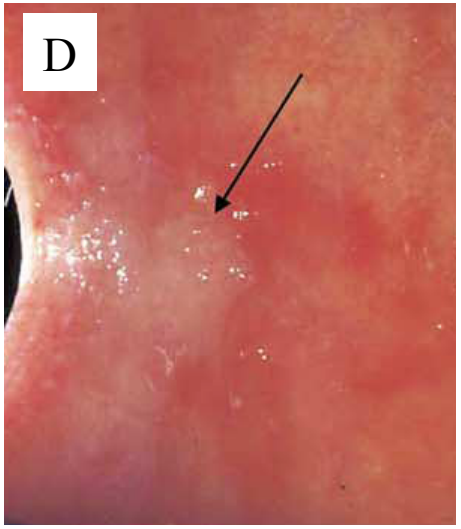
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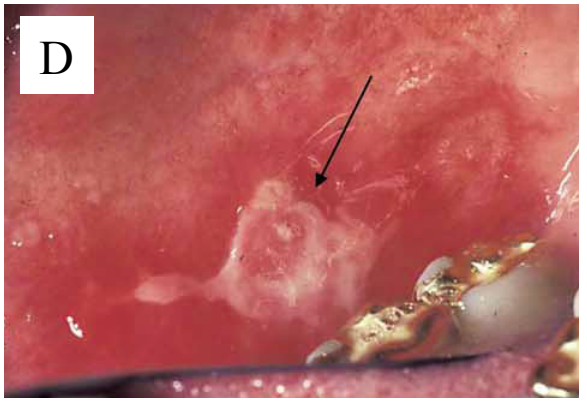
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Important Concepts

- **Autologous vs allogeneic HCT**
- **Myeloablative vs reduced intensity conditioning regimens**
- **Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors**
- **Acute vs. chronic graft versus host disease**
- **Donor chimerism**

Chimera

KHIMAIRA (Greek) was a three headed, fire-breathing creature with the fore-parts of a lion, the hindquarters of a goat, and the tail of a serpent. The Chimera was slain by Bellerophon astride Pegasus.

http://www.theoi.com/Tartaros/Khimaira.html

Donor Chimerism