

Introduction to Clinical Hematopoietic Cell Transplantation (HCT)

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Friday, May 12, 17

Goals for Today

- **What is HCT?**
- **How is HCT done and how is it tailored to fit the patient's disease and circumstances?**
- **What are some of the clinical problems in HCT?**

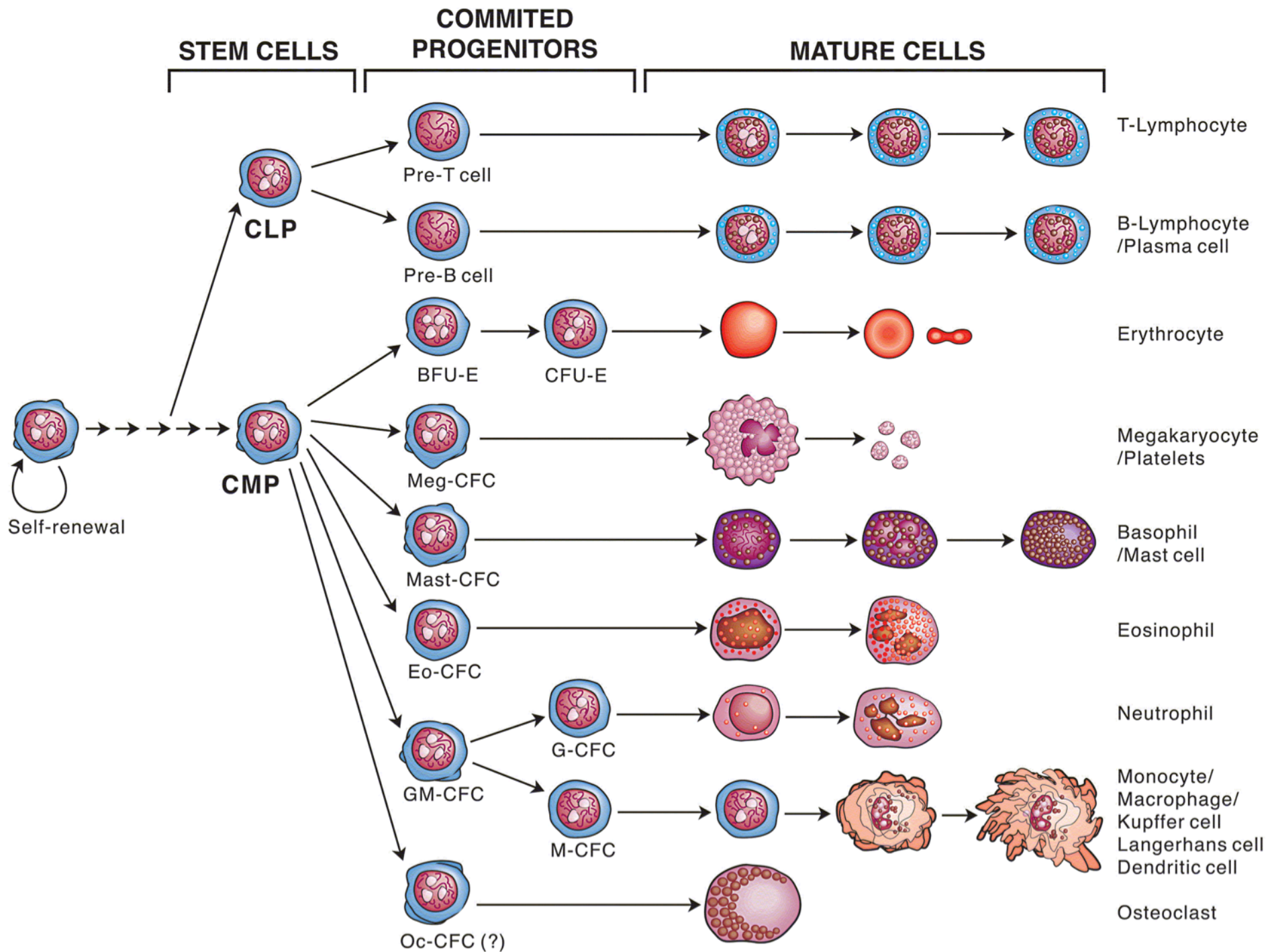
Important Concepts

- **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**



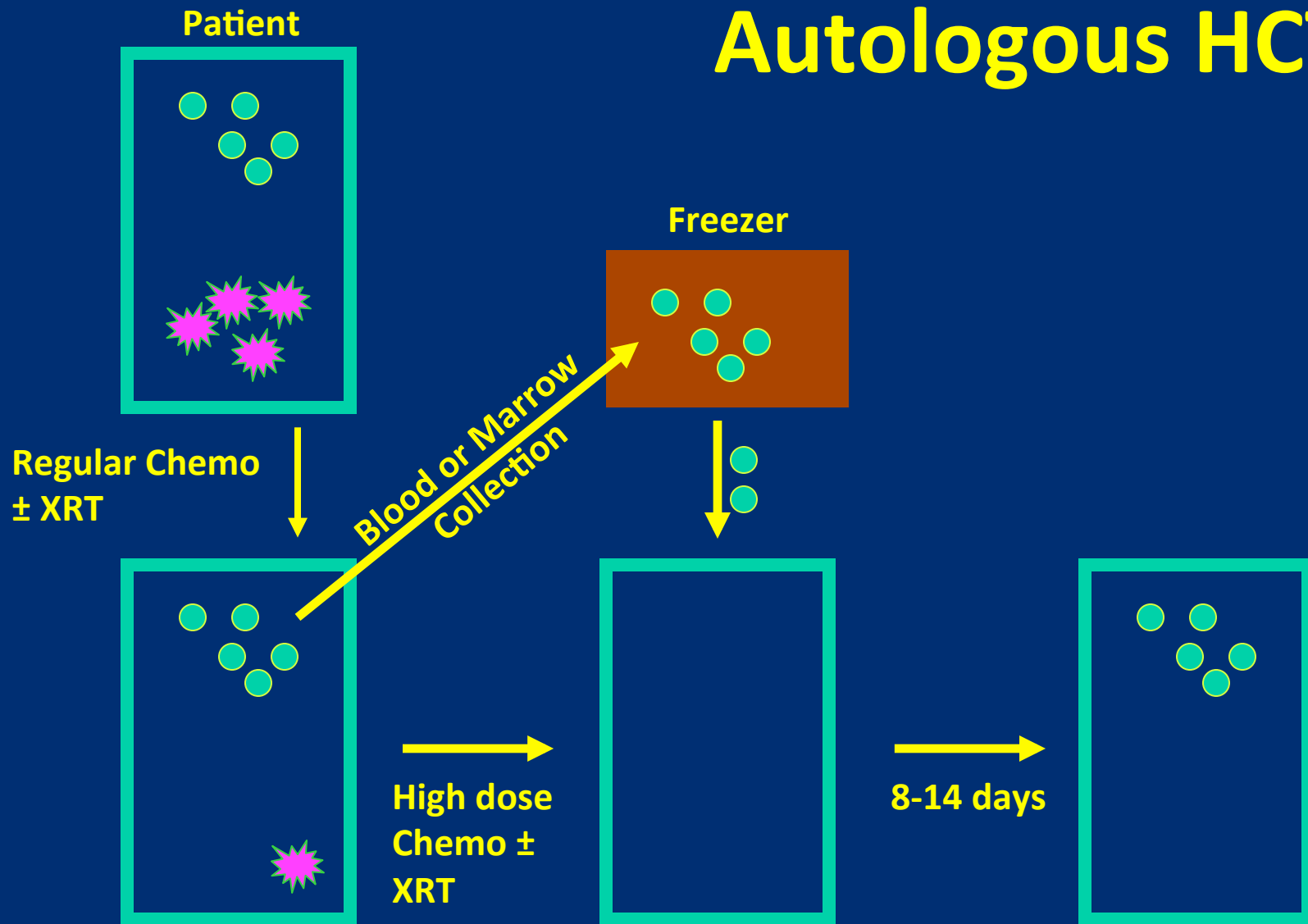
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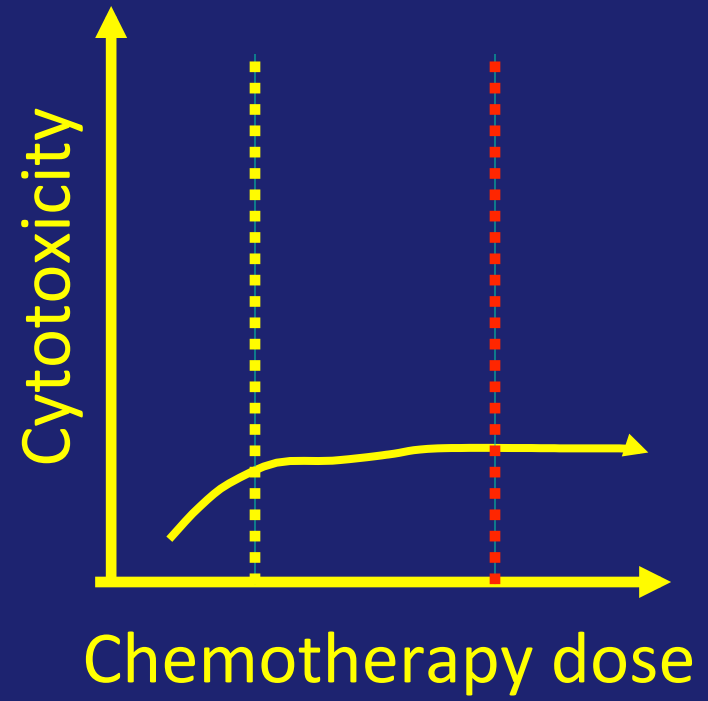
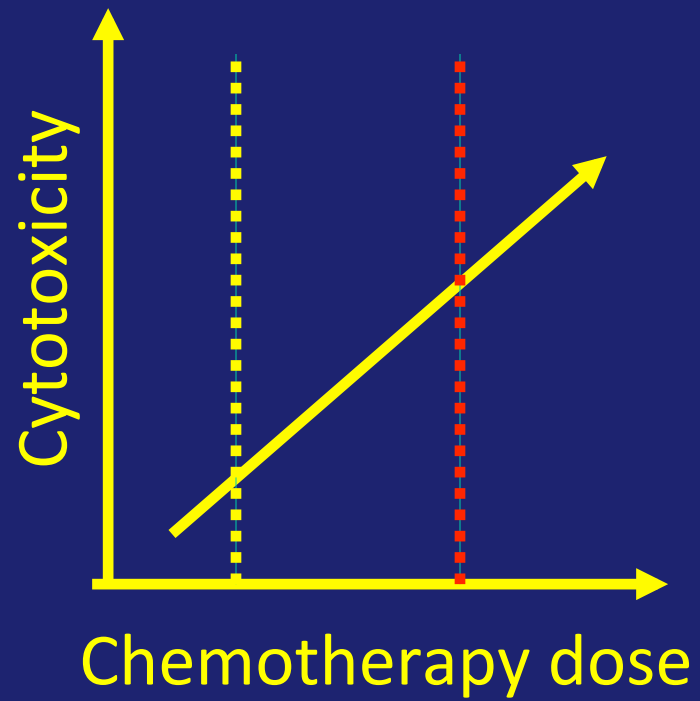
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Basic Definitions

- **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

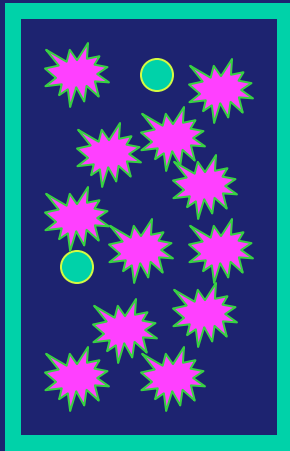




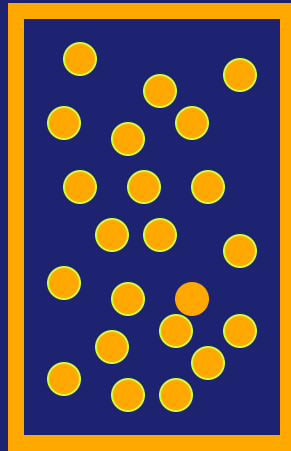
Indications for autoHCT

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

Patient

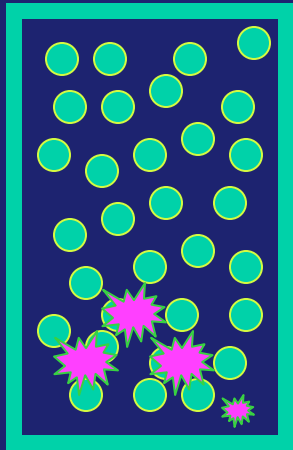


Donor

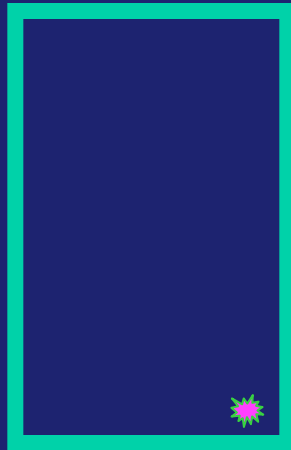


Allogeneic HCT

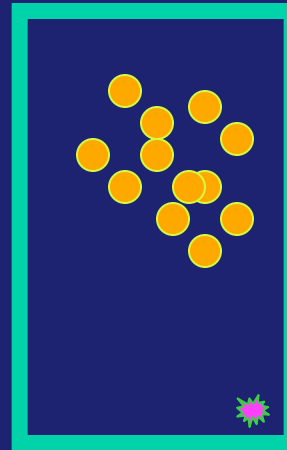
Regular Chemo
± XRT



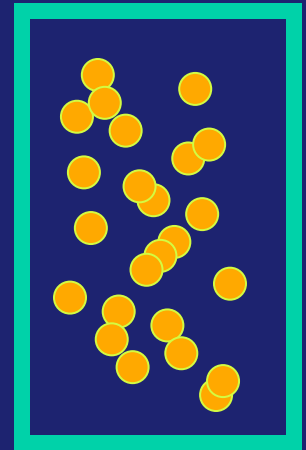
High dose
Chemo ±
XRT



14-21
days



Time



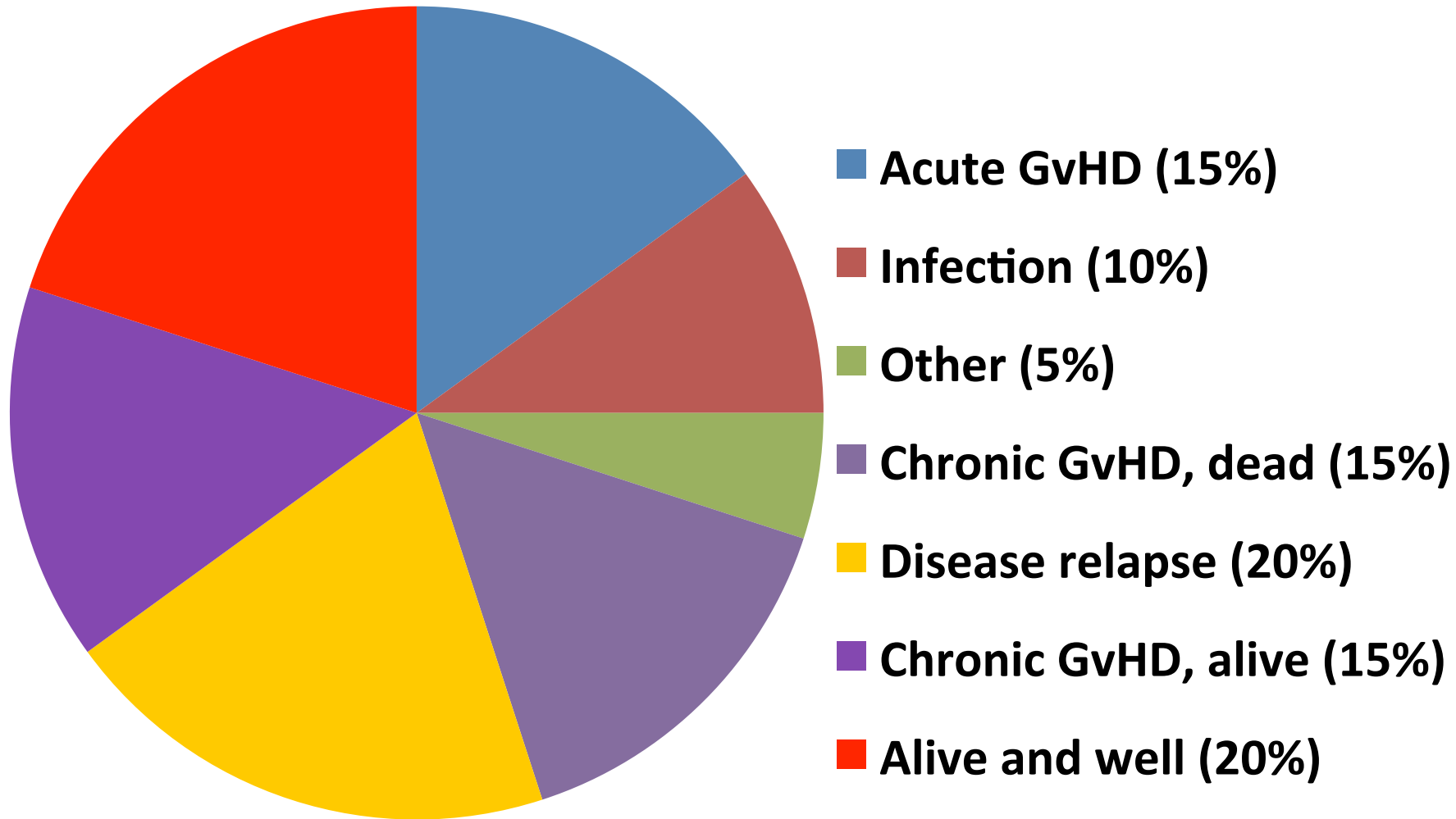
Indications for alloHCT

- **Replacement of hematopoiesis**
 - **Aplastic anemia**
- **Immune mediated effect against the underlying malignancy**
- **Prevention of relapse**
 - **Acute and chronic leukemia**
 - **Myelodysplastic syndrome**
 - **Indolent lymphomas**

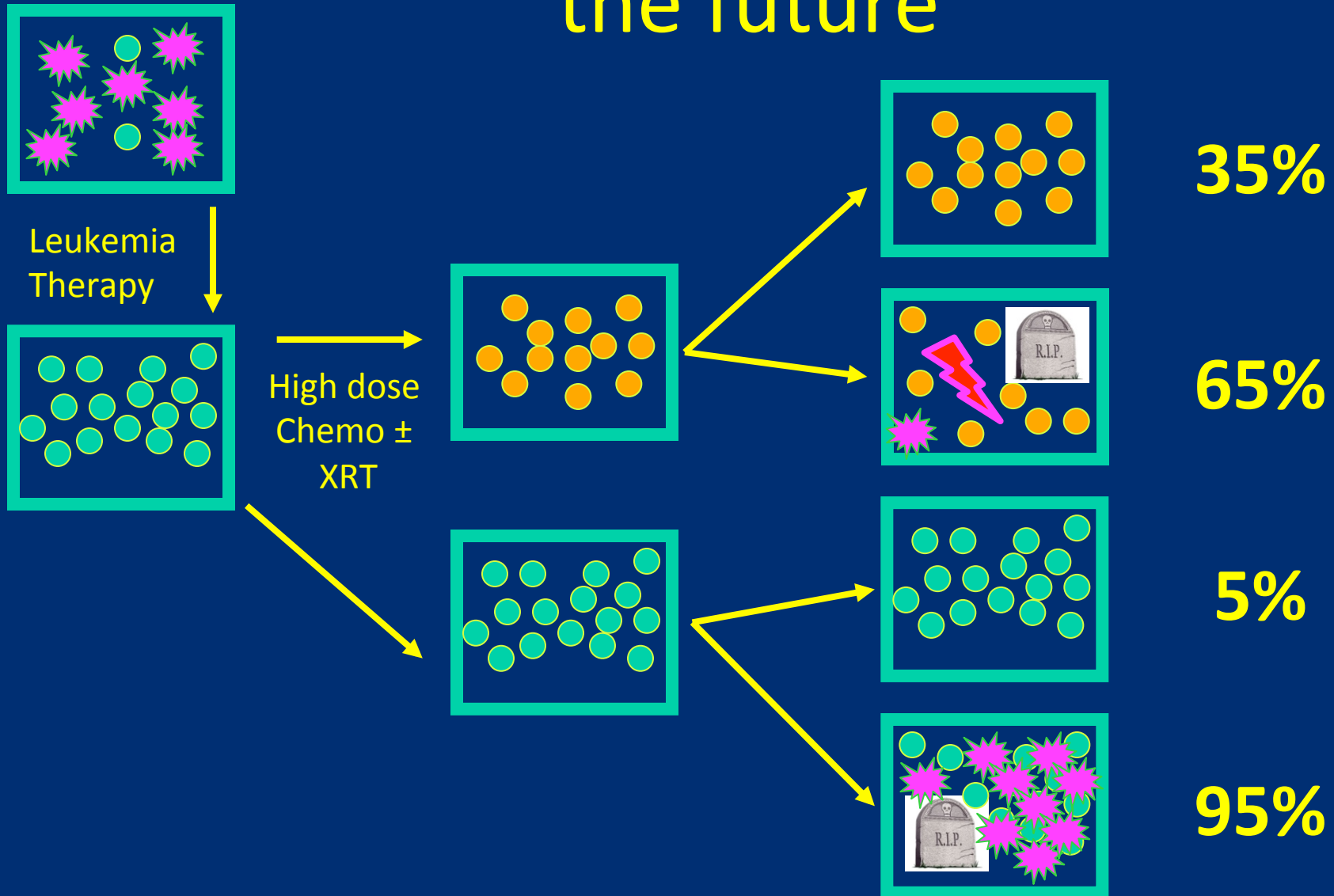
Something to think about

- What tumor characteristics are amenable to autologous versus allogeneic transplantation?
- For later: What tumor characteristics lend themselves to myeloablative versus reduced intensity conditioning?

Allogeneic BMT Survival Outcomes (AML)

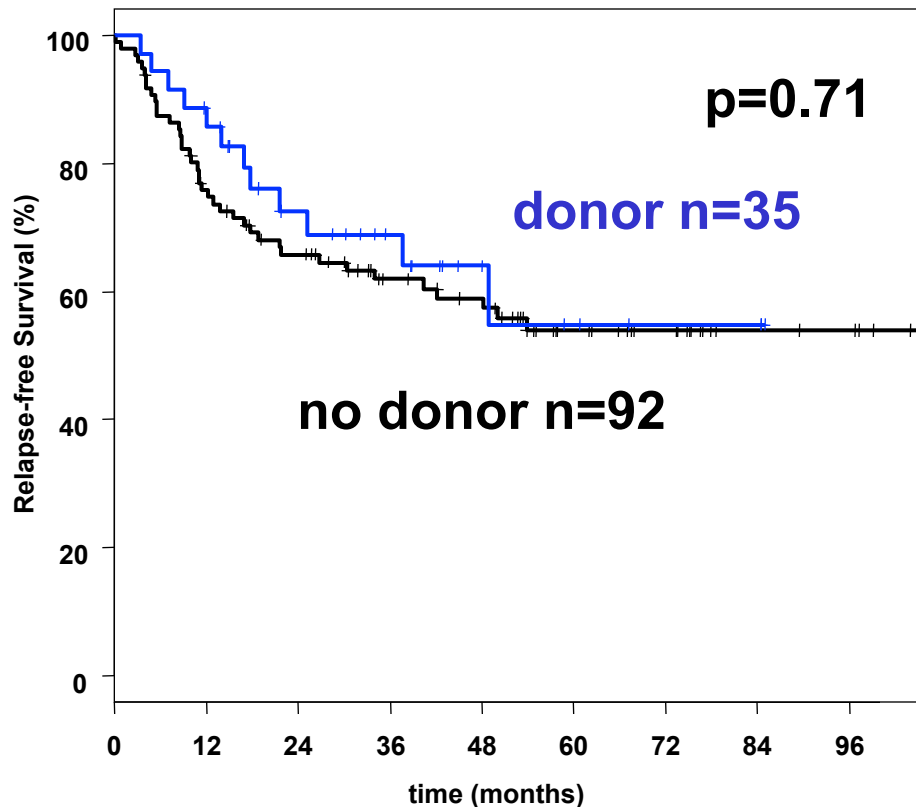


A transplant is a bet against the future

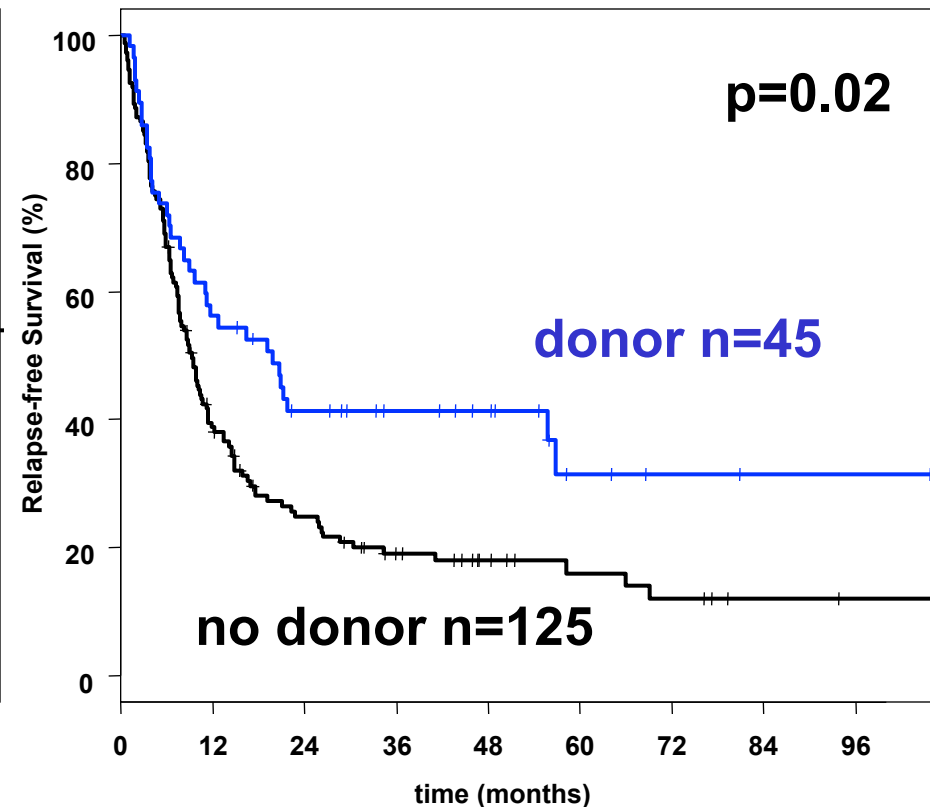


Genetic Subgroup Analysis: RFS

NPM1+/*FLT3* ITD-

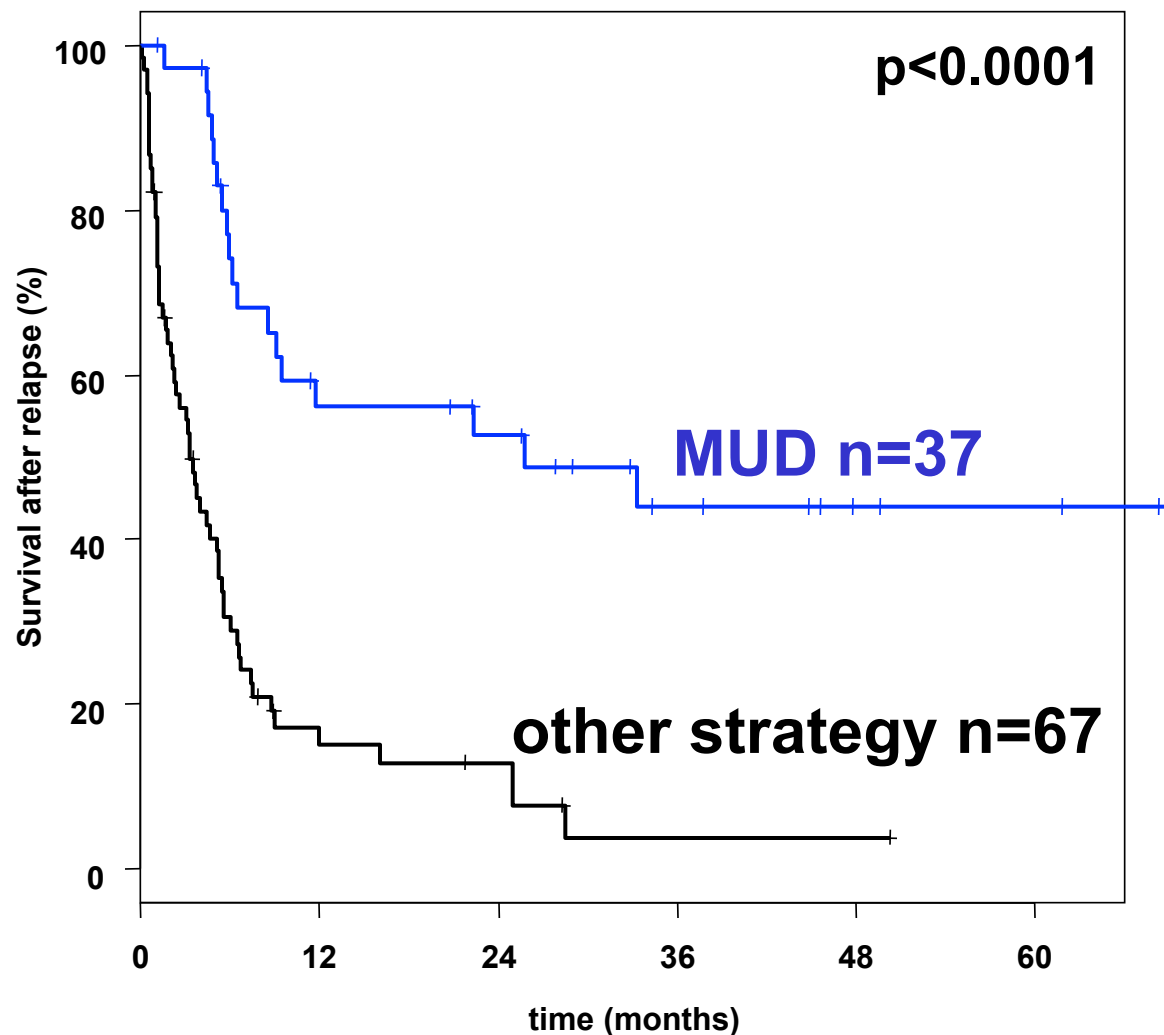


Others



Courtesy of Schlenk R et al, NEJM 2008

MUD Transplantation in Relapsed Patients with Unfavorable Genotype



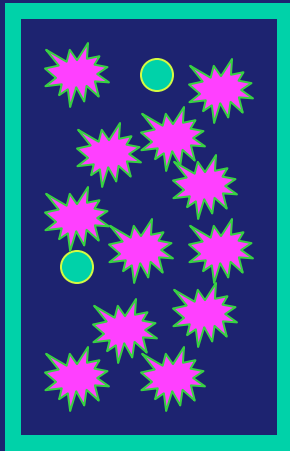
Prognostic categories for AML

- Good
 - t(8:21), t(9:22), inv16, t(15:17)
 - NPM1
 - CEPB
- Medium
 - Normal karyotype
- Poor
 - Multiple karyotypic abnormalities
 - Flt3 ITD or TDK
- Clinical factors indicating a poor prognosis
 - Induction failure
 - Prior hematologic disorder

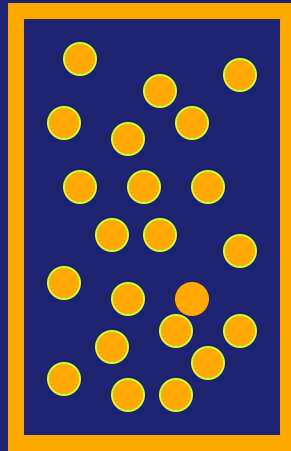
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Patient

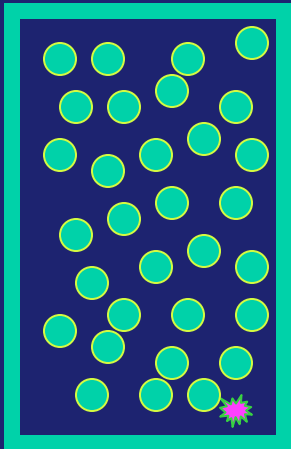


Donor

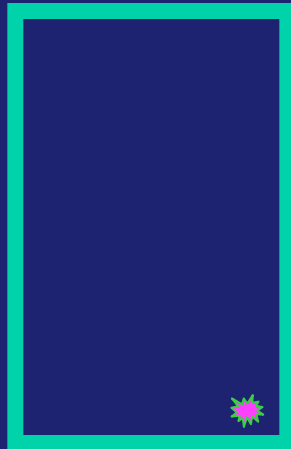


Allogeneic BMT

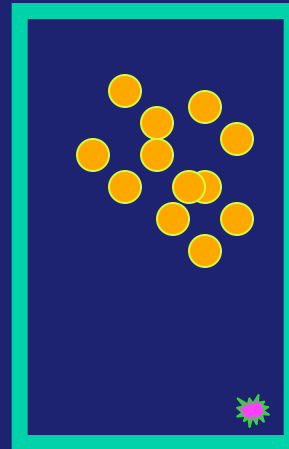
Regular Chemo
± XRT



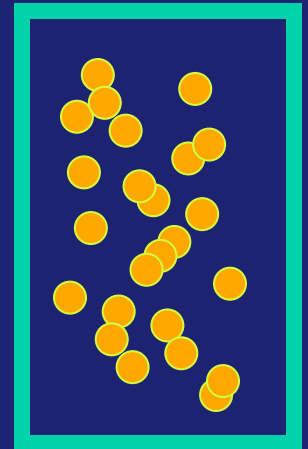
High dose
Chemo ±
XRT



14-21
days



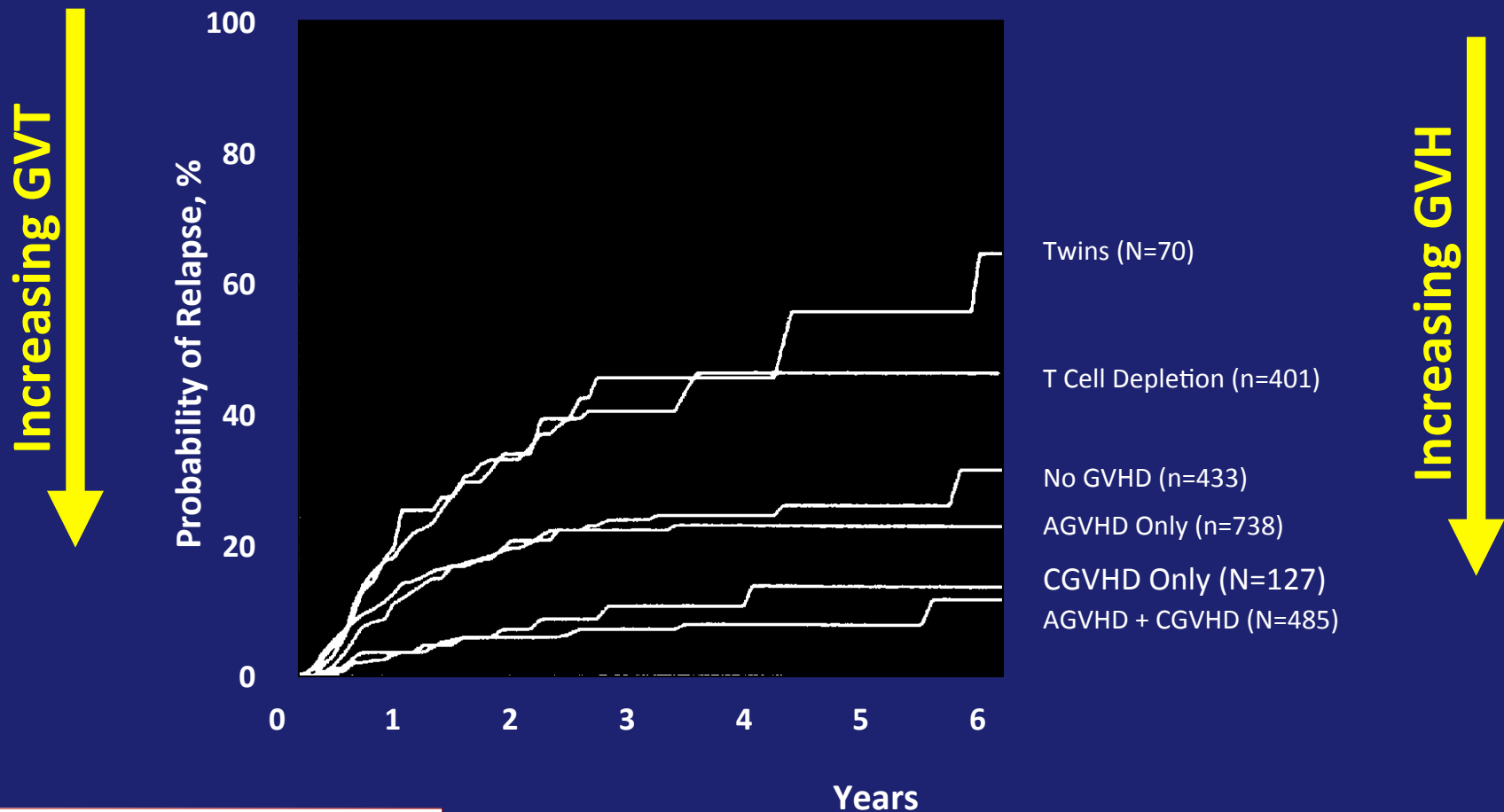
Time

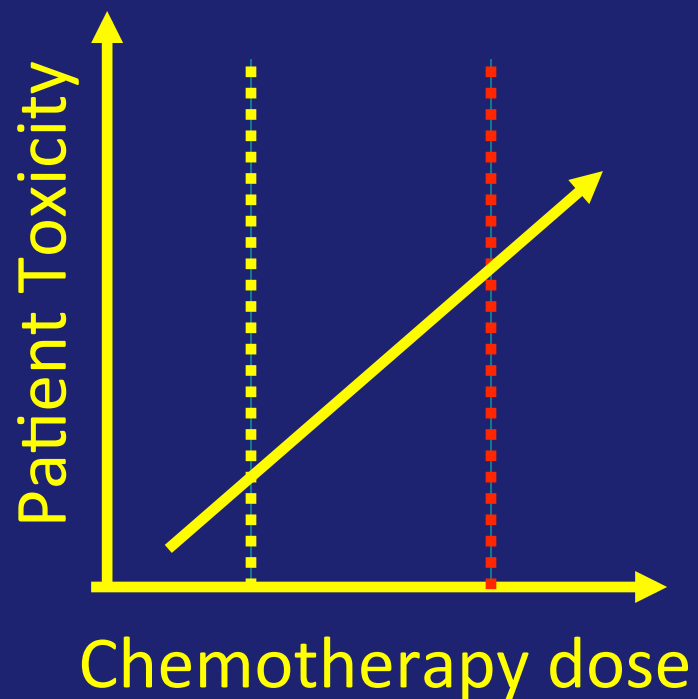
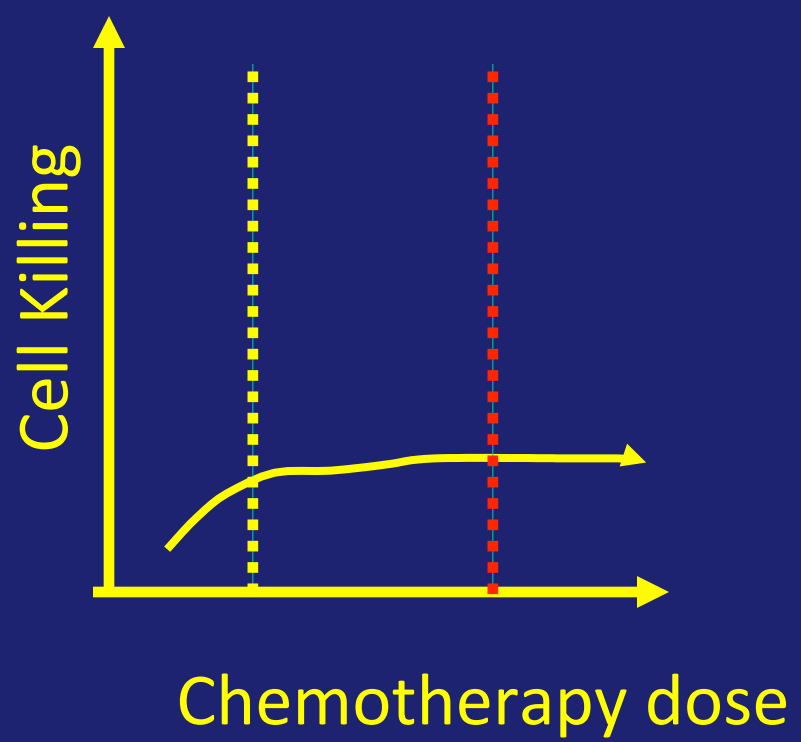
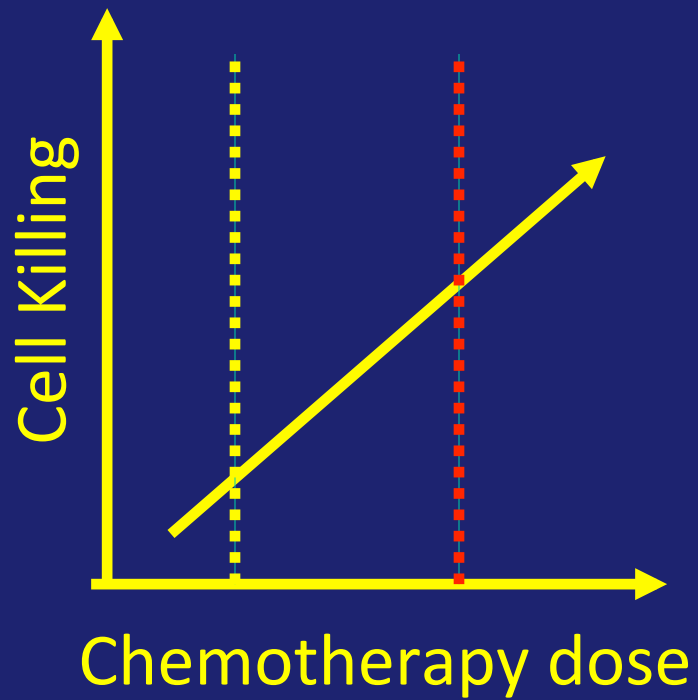


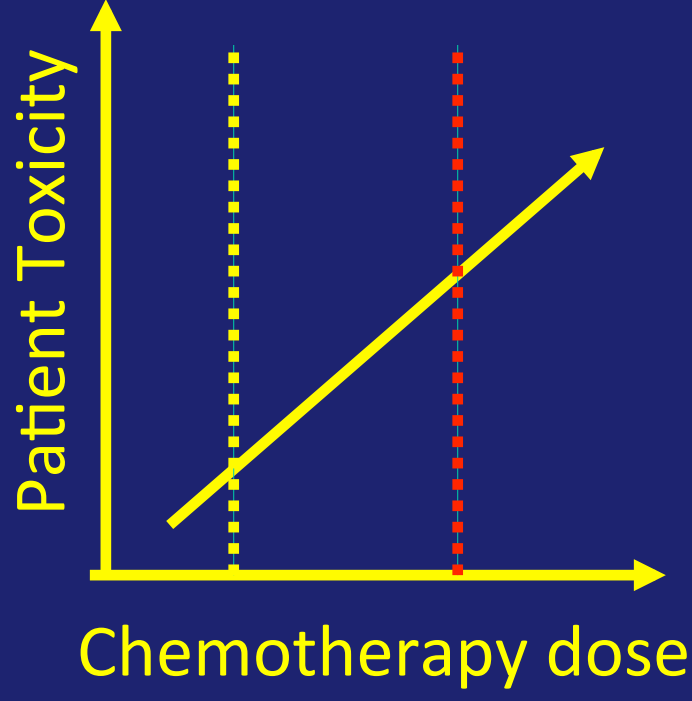
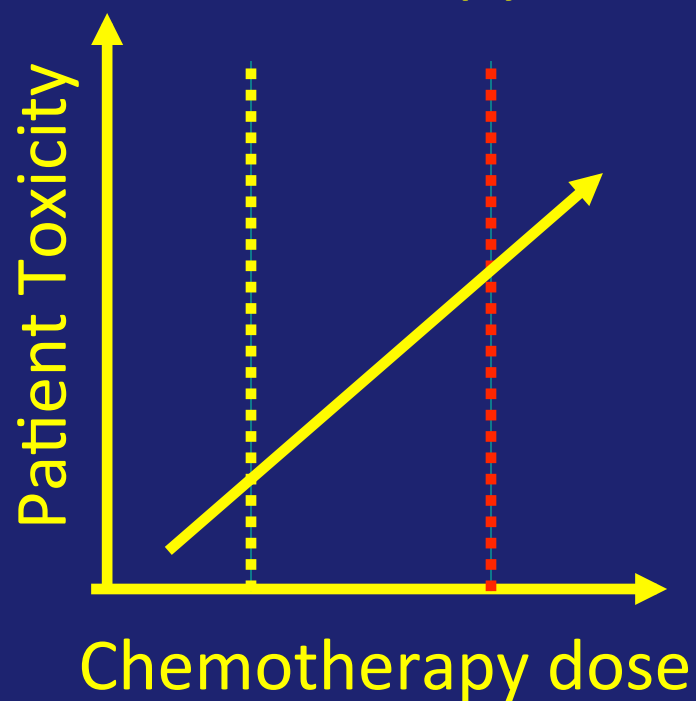
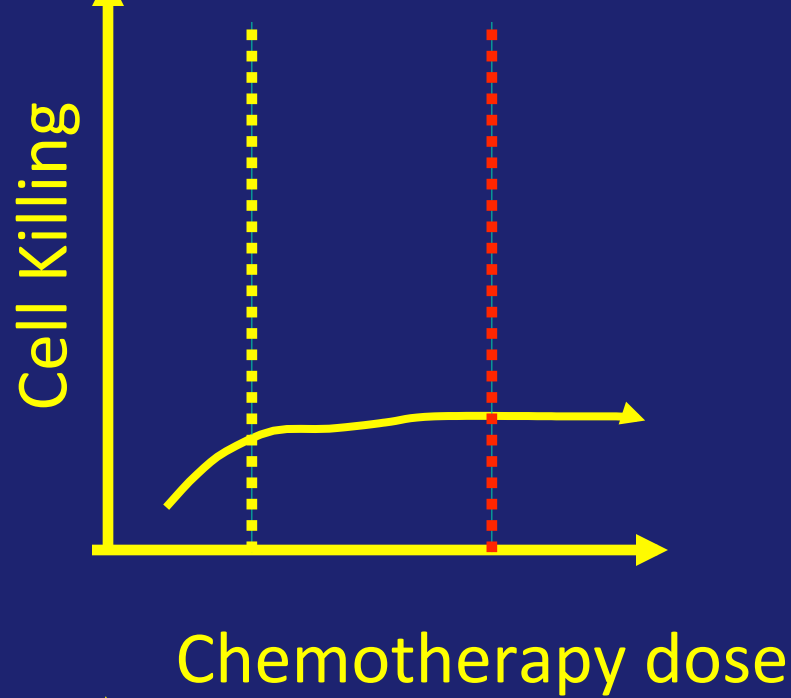
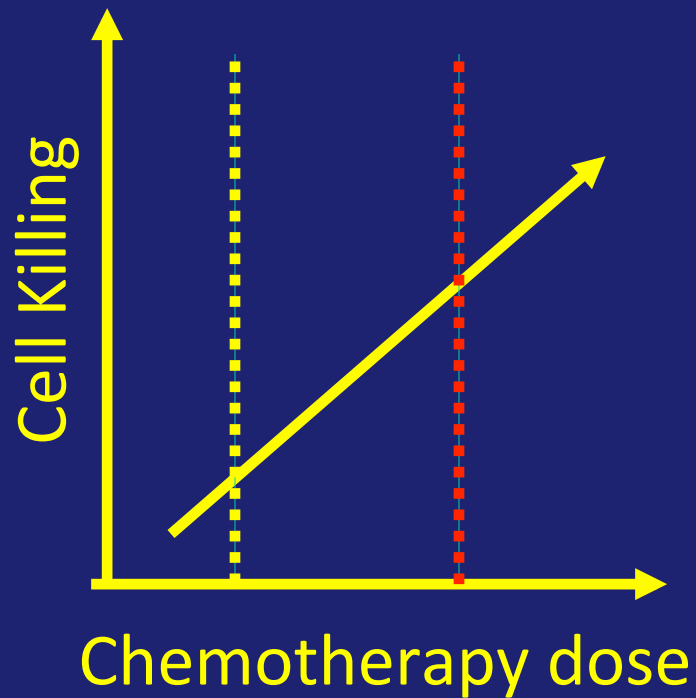
Immunologic Effects of Allogeneic Grafts

- **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







Patient

Donor

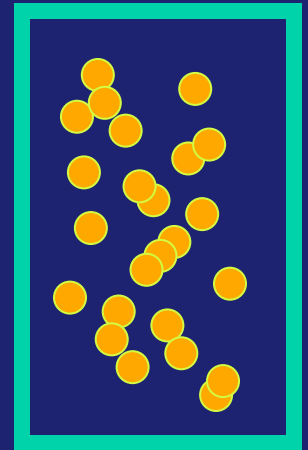
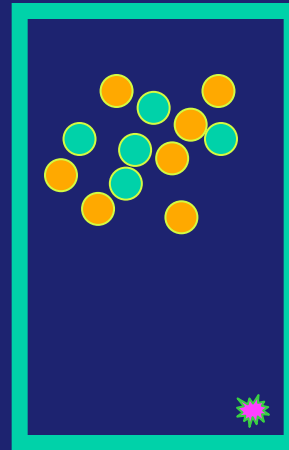
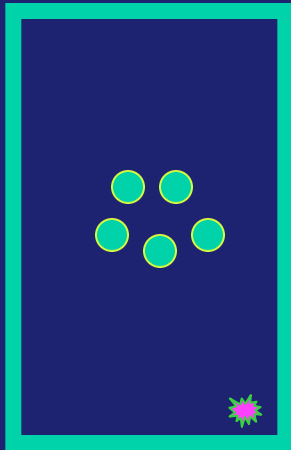
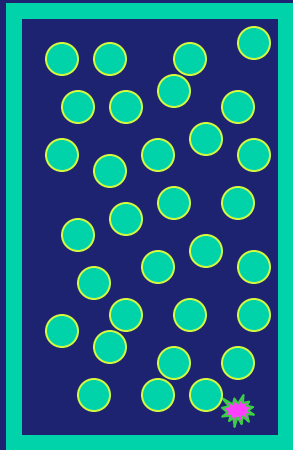
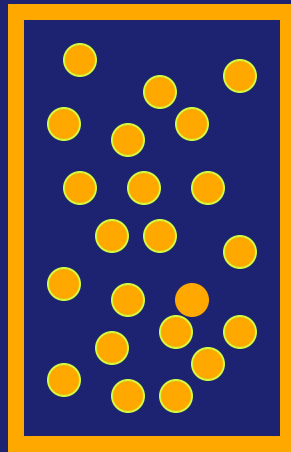
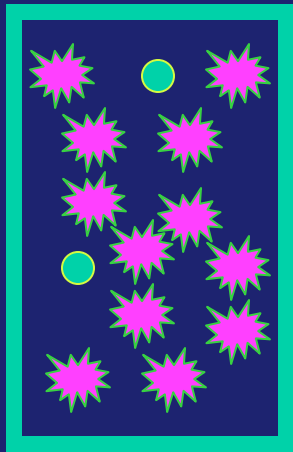
Reduced Intensity AlloBMT

Regular
Therapy

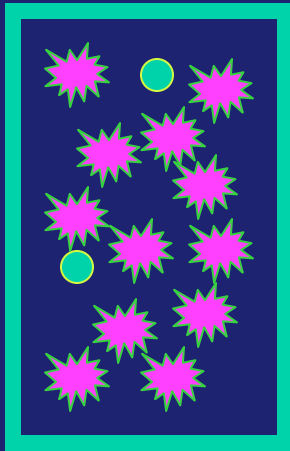
Immunosup
pression
→
± Chemo
± XRT

14-21
days

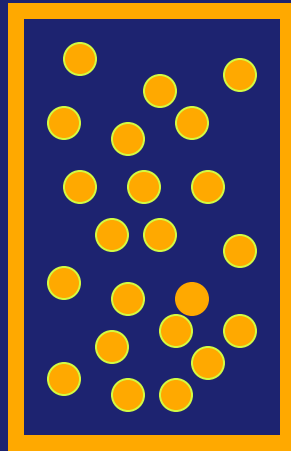
Time



Patient

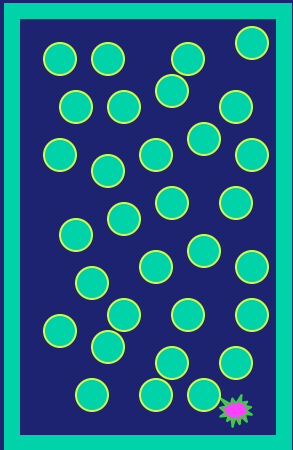


Donor

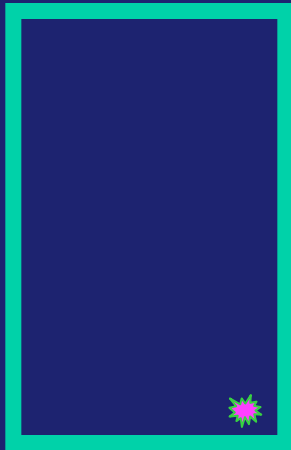


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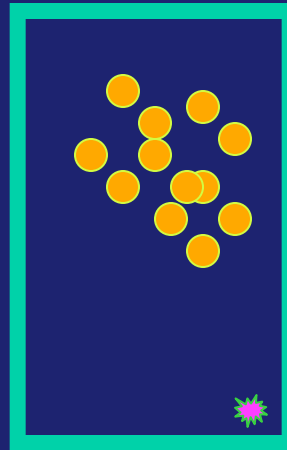
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± XRT



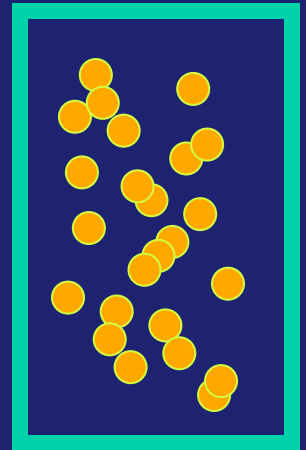
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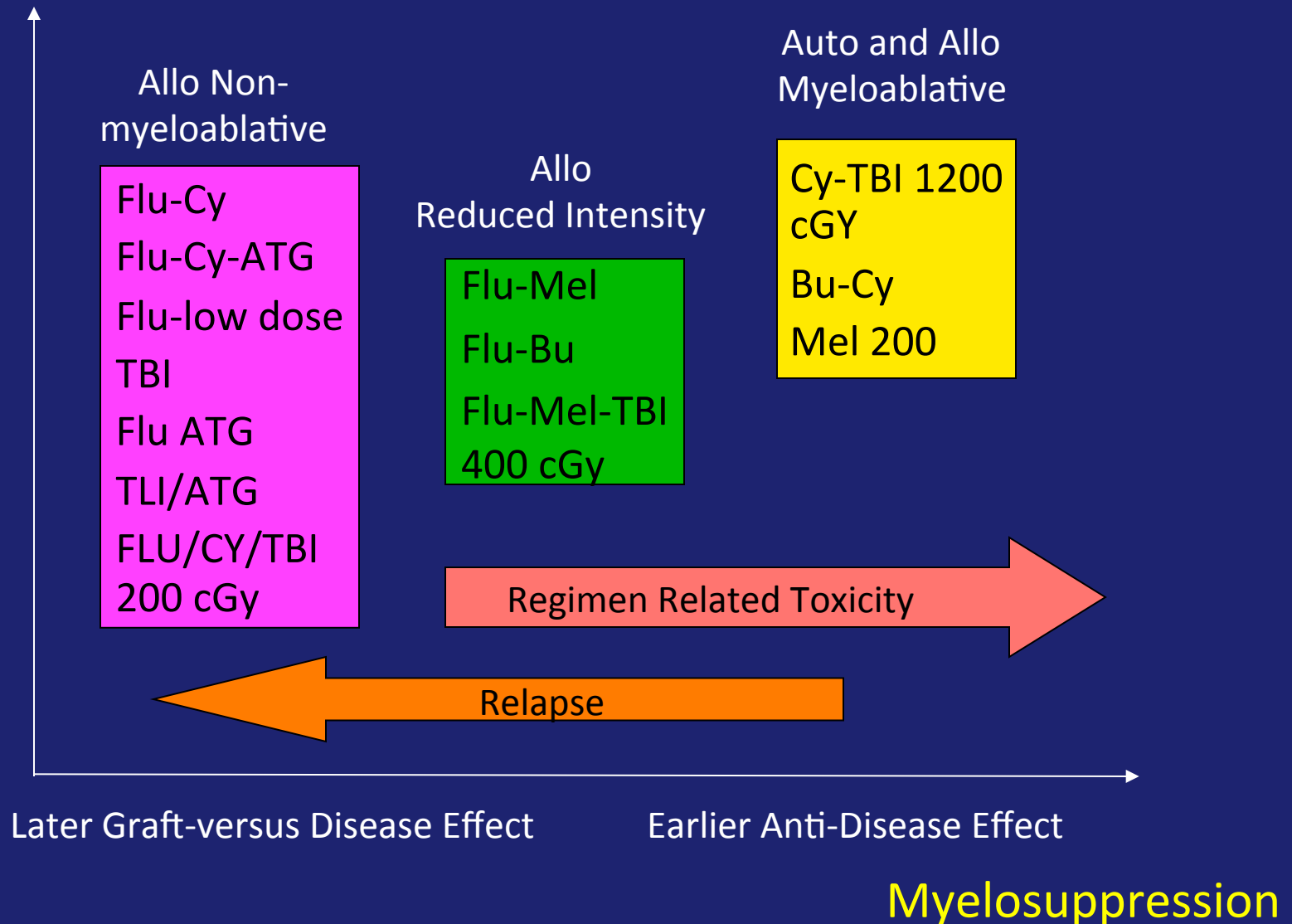
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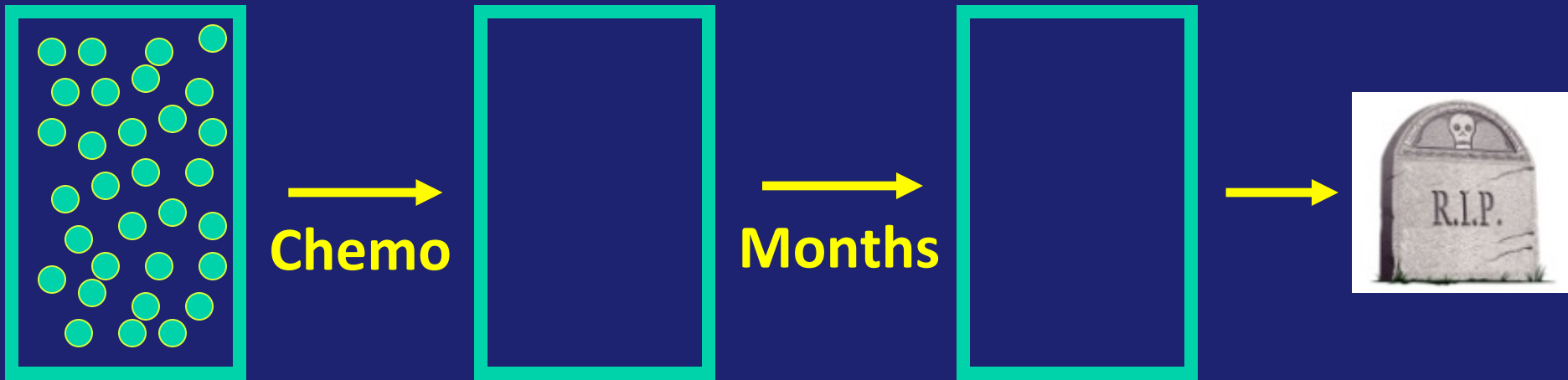
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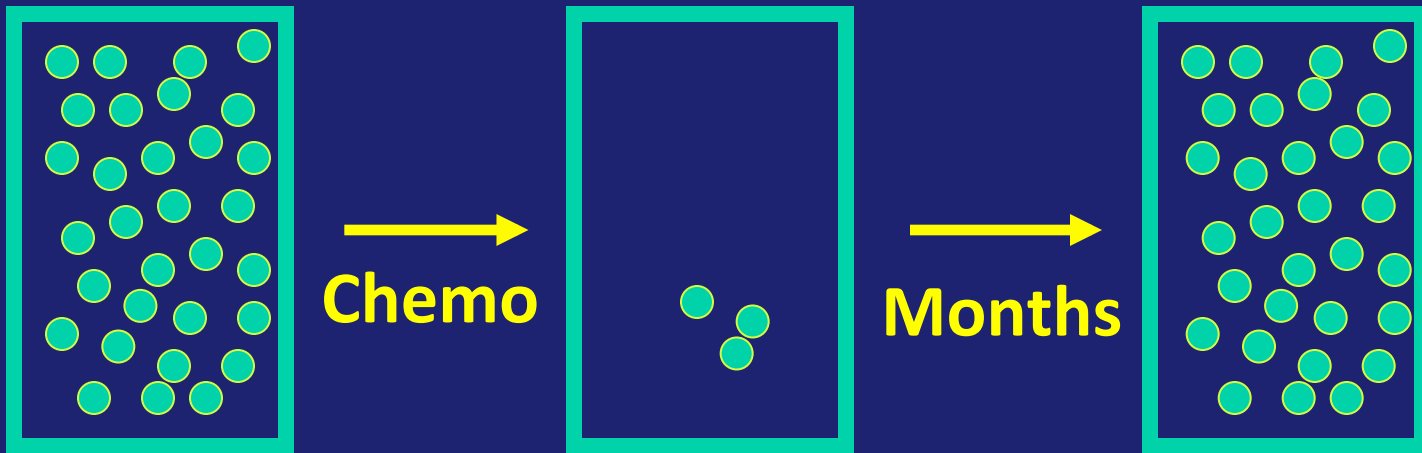
Transplant regimens

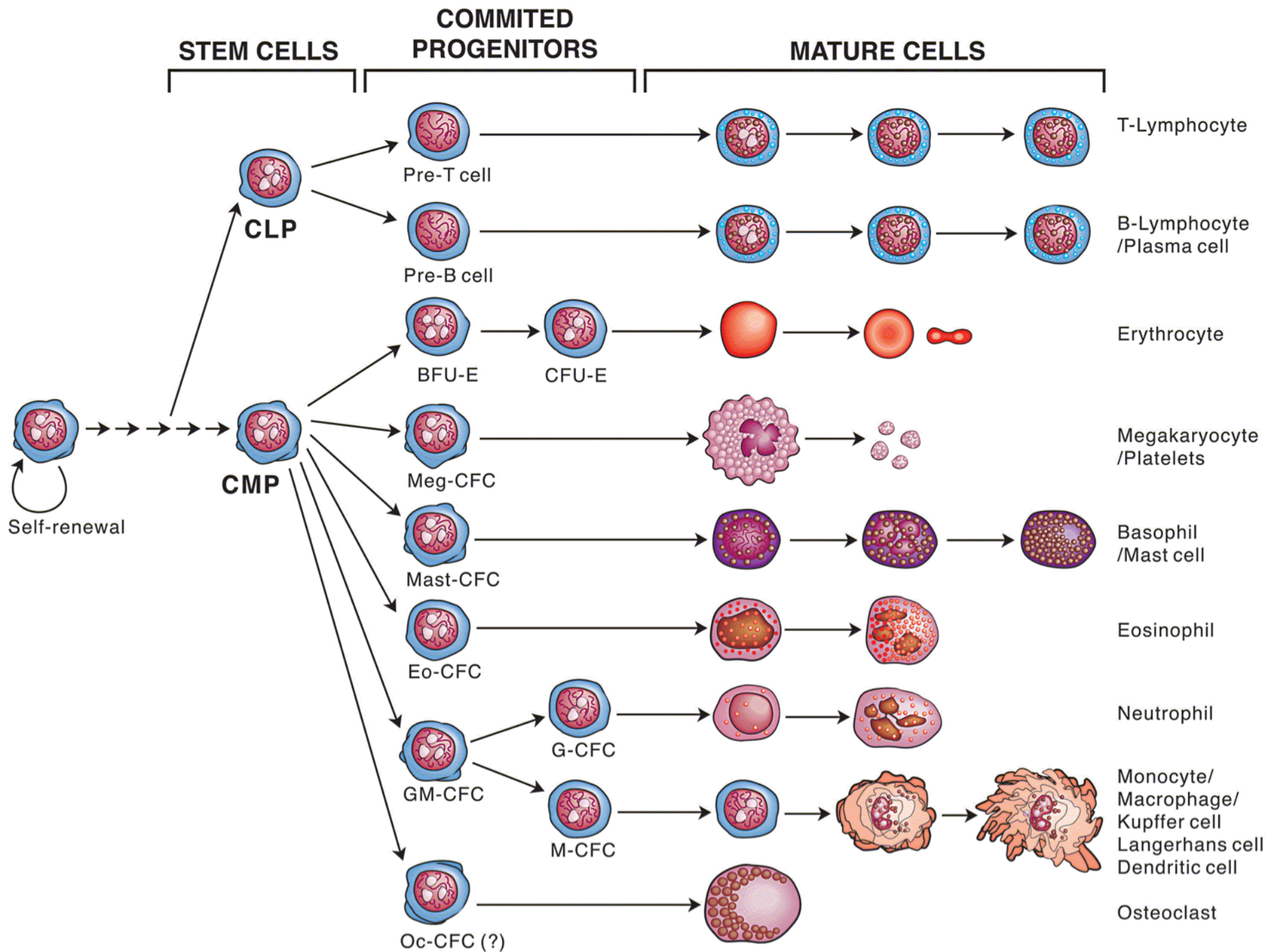


Myeloablation

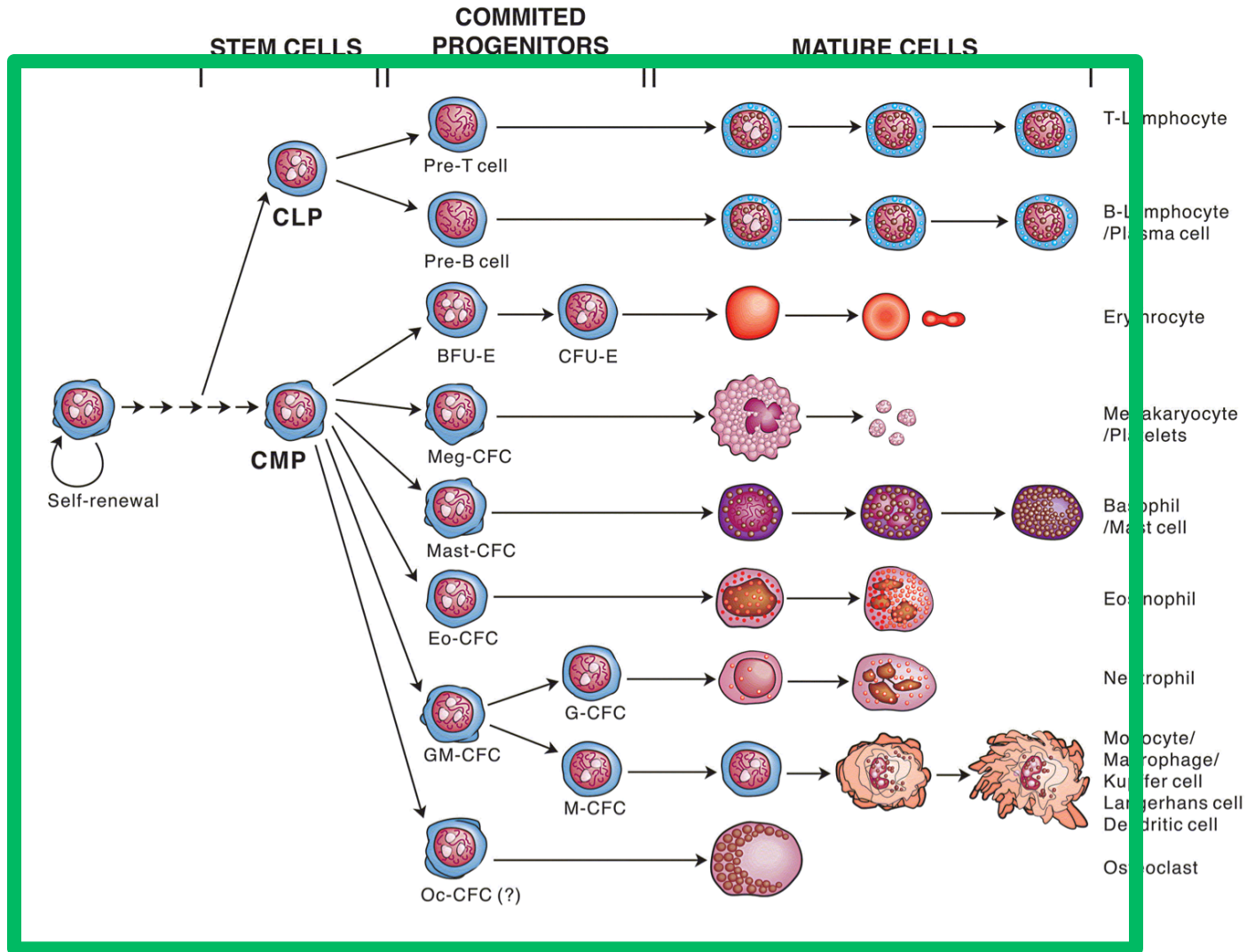


Reduced intensity



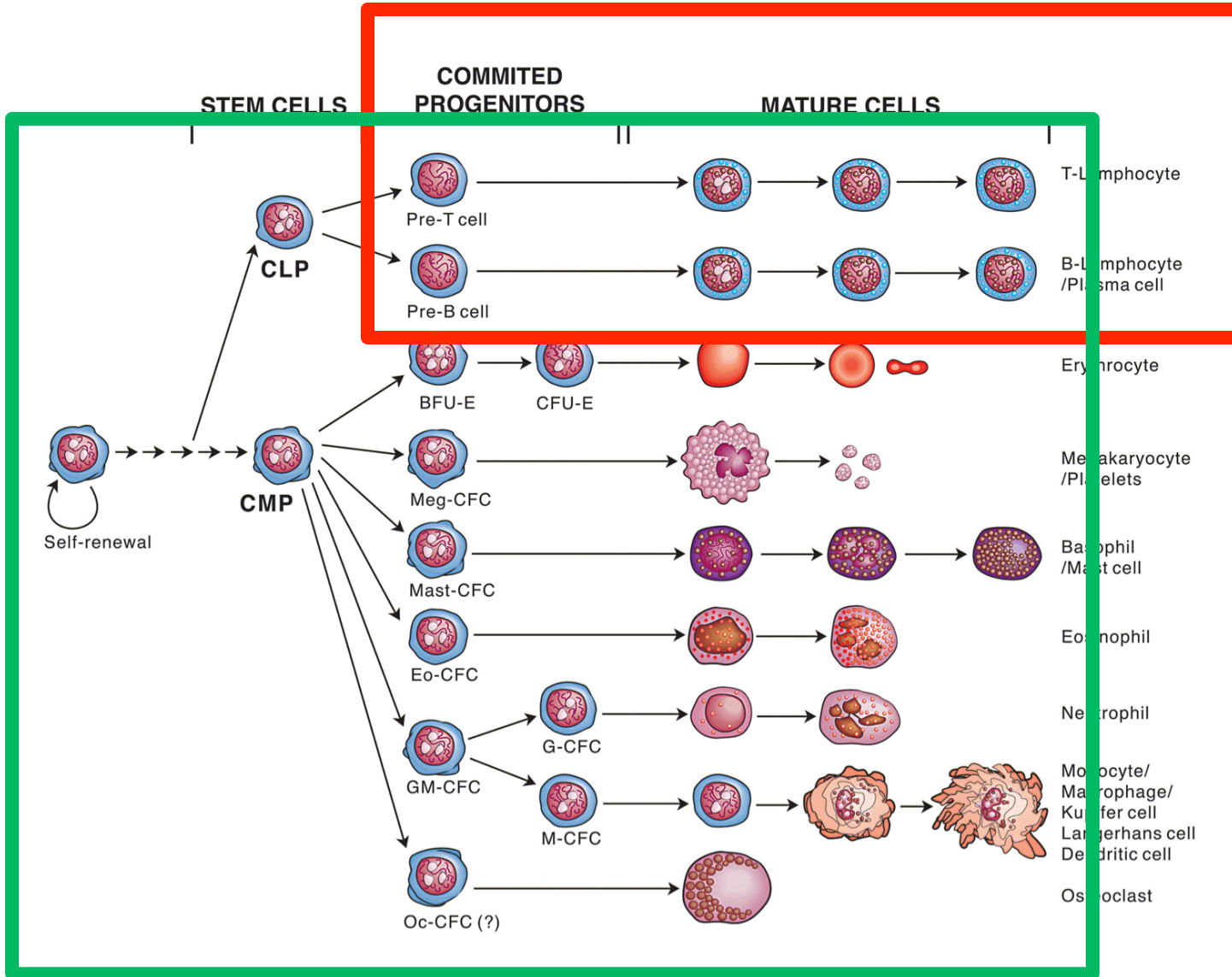


Bu, Mel, full dose TBI



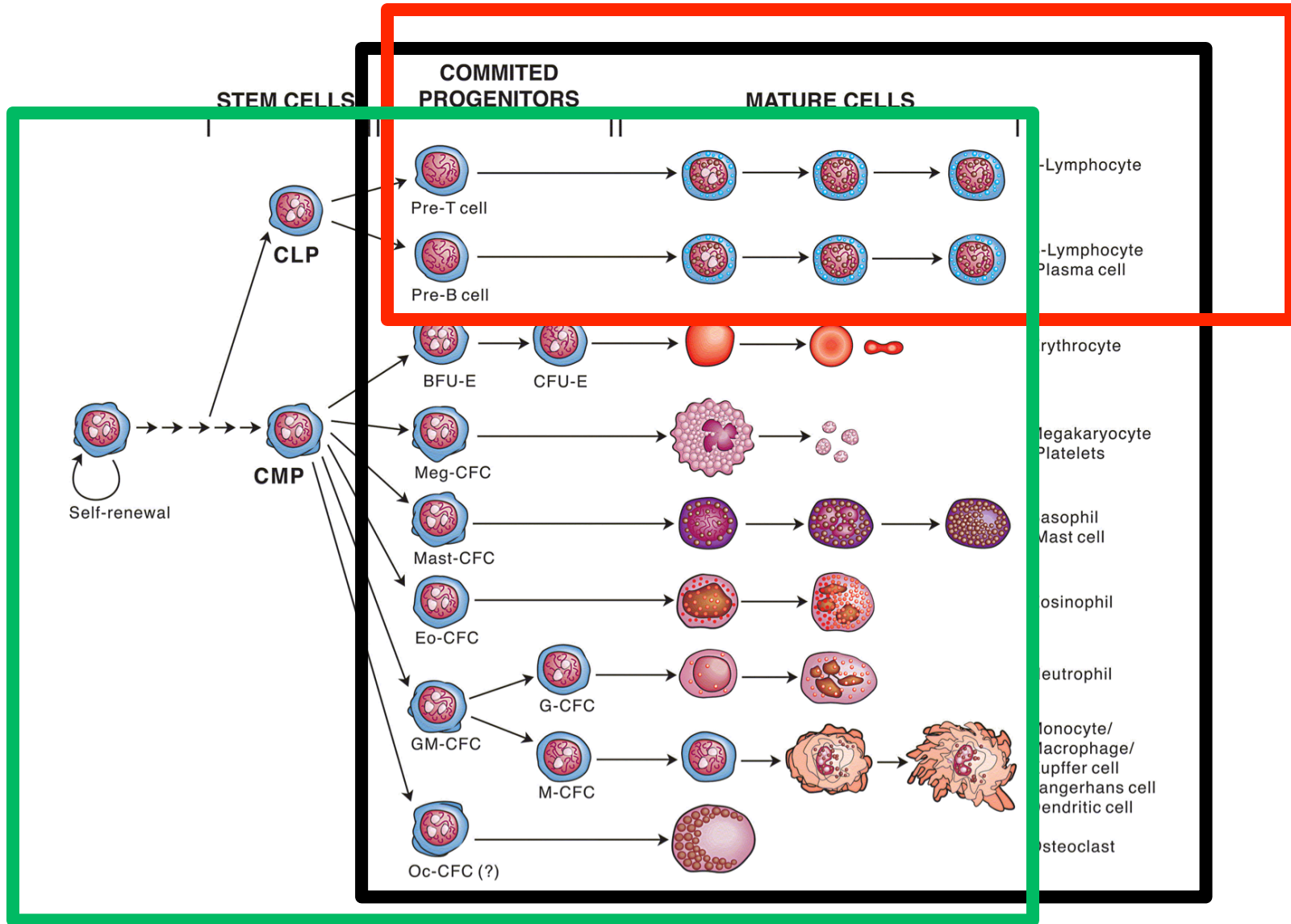
Bu, Mel, full dose TBI

Fludarabine



Bu, Mel, full dose TBI

Fludarabine



Cyclophosphamide

Cyclophosphamide



Cytochrome
P450

4-hydroxy-cyclophosphamide

Tautomer-
ization



Aldehyde
dehydrogenase

Aldophosphamide

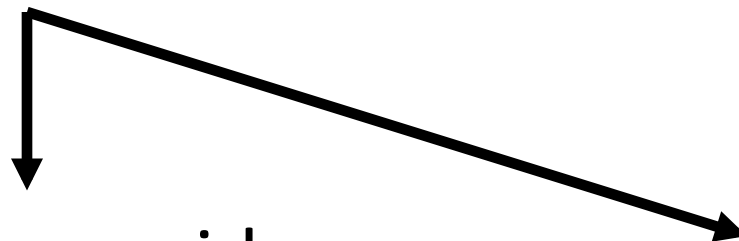


Carboxy
phosphamide
(inactive)



Phosphoramidate
mustard
(active)

Acrolein
(active)



Cyclophosphamide



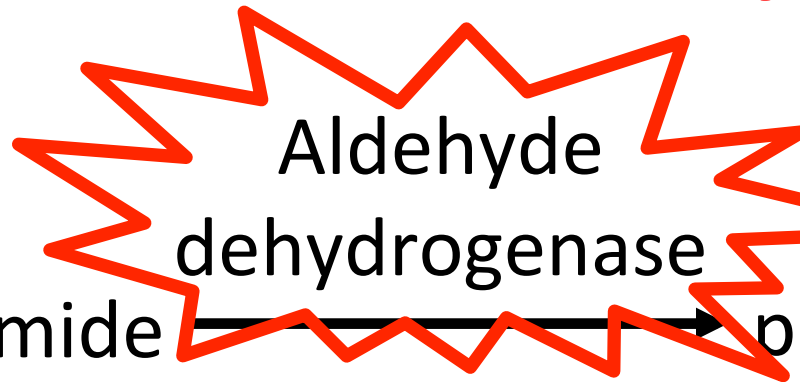
Cytochrome
P450

*Elevated in stem cells
Higher in resting
lymphocytes versus
activated lymphocytes*

4-hydroxy-cyclophosphamide



Tautomer-
ization



Aldehyde

dehydrogenase

Aldophosphamide

Carboxy

phosphamide

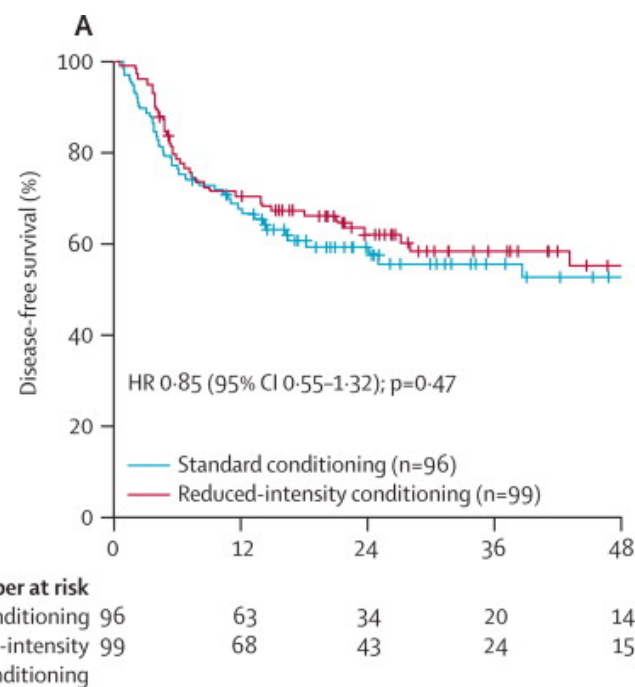
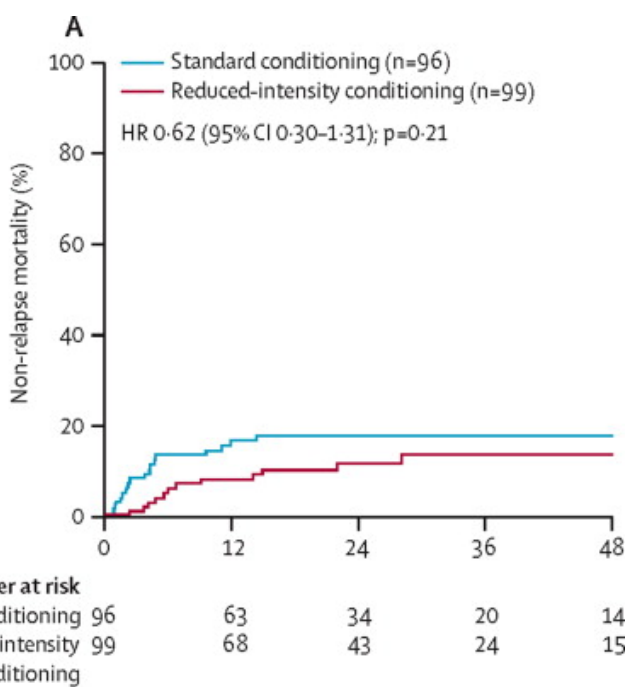
(inactive)



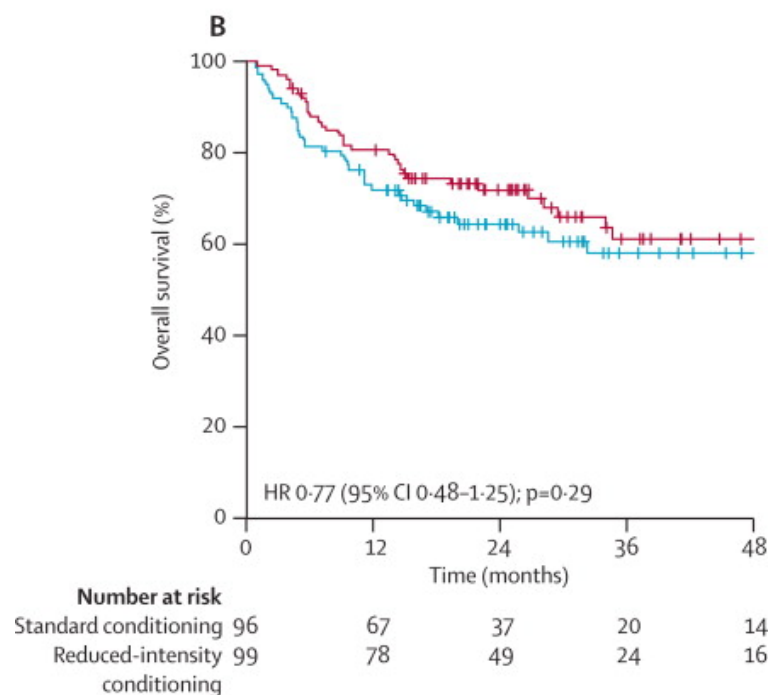
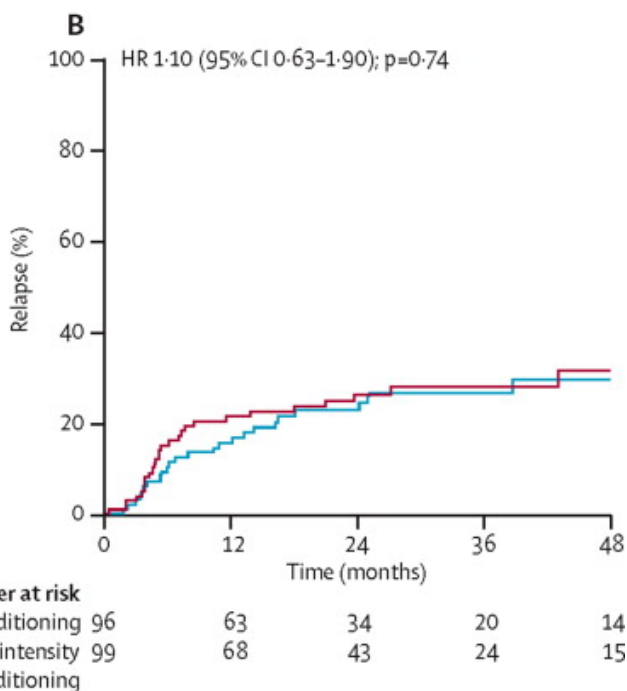
Phosphoramidate
mustard
(active)

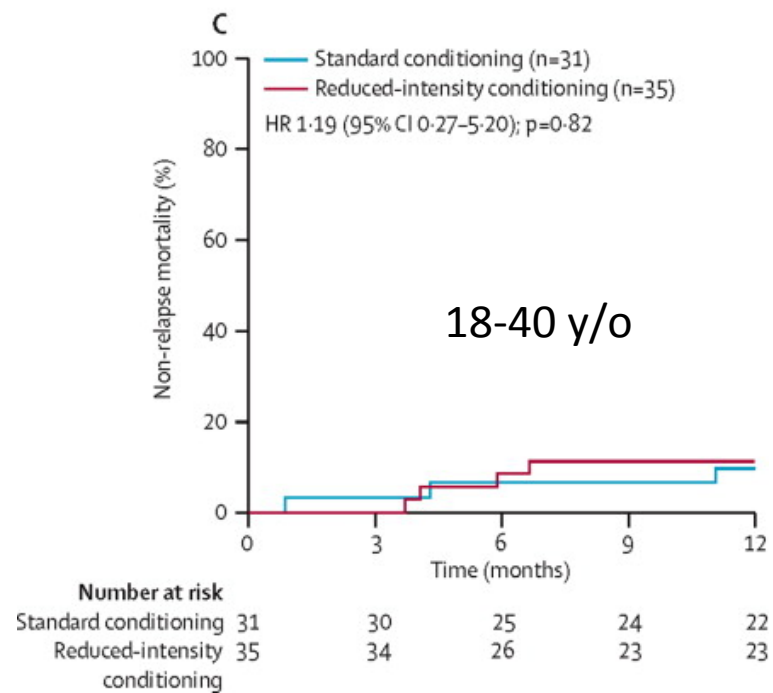
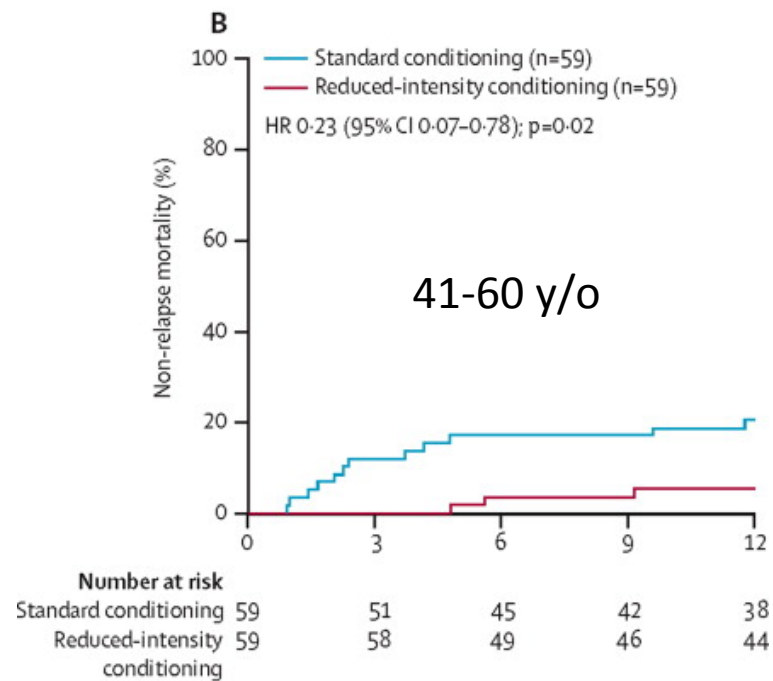
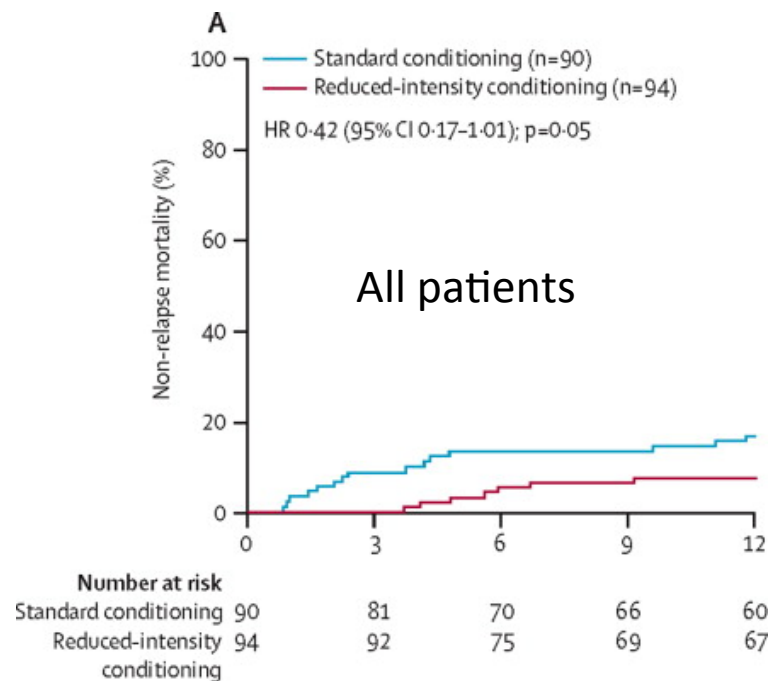
Acrolein
(active)





1st CR
MRD
9/10 MUD





Something to think about

- What tumor characteristics are amenable to myeloablative versus reduced intensity conditioning allogeneic transplantation?

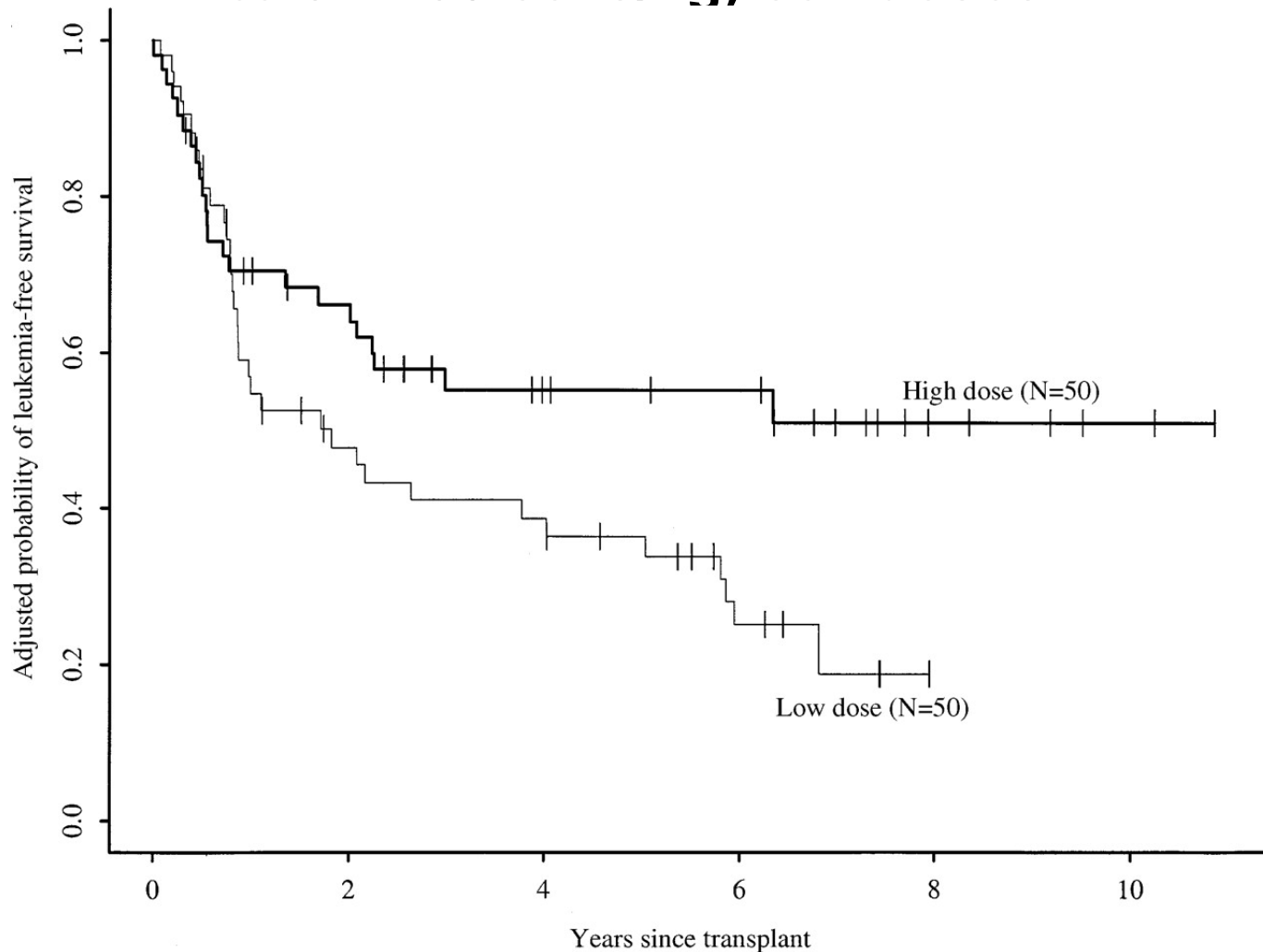
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Donor source reflects purpose

	Rescue hematopoiesis	Immune therapy
Autologous	XXX	?
Allogeneic	XXX	XXX

Adjusted probabilities of leukemia-free survival rates after identical twin bone marrow transplantations with high (more than 3×10^8 cells/kg) versus low (less than or equal to 3×10^8 cells/kg) cell doses.

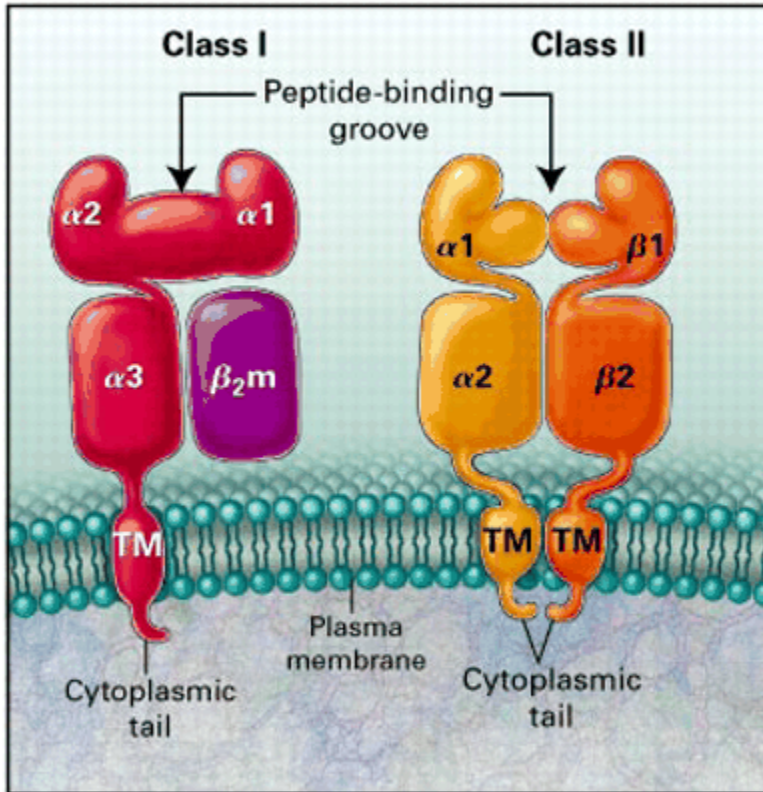


Barrett A J et al. Blood 2000;95:3323-3327

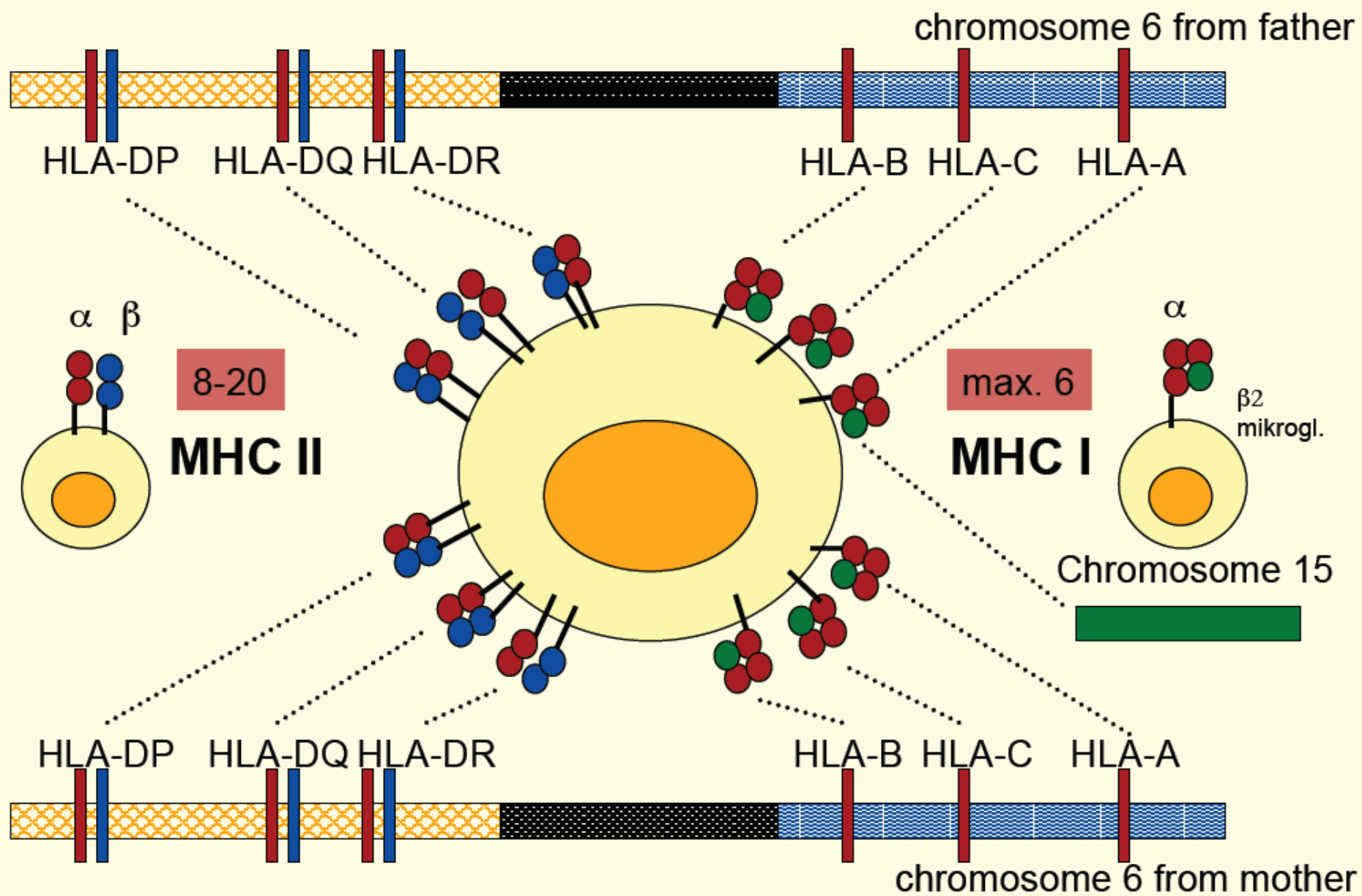
Human Leukocyte Antigen (HLA)

- Proteins which present antigenic peptides to T cells
- On surface of most body cells
- The most important proteins in transplant
- Responsible for graft rejection and GvHD

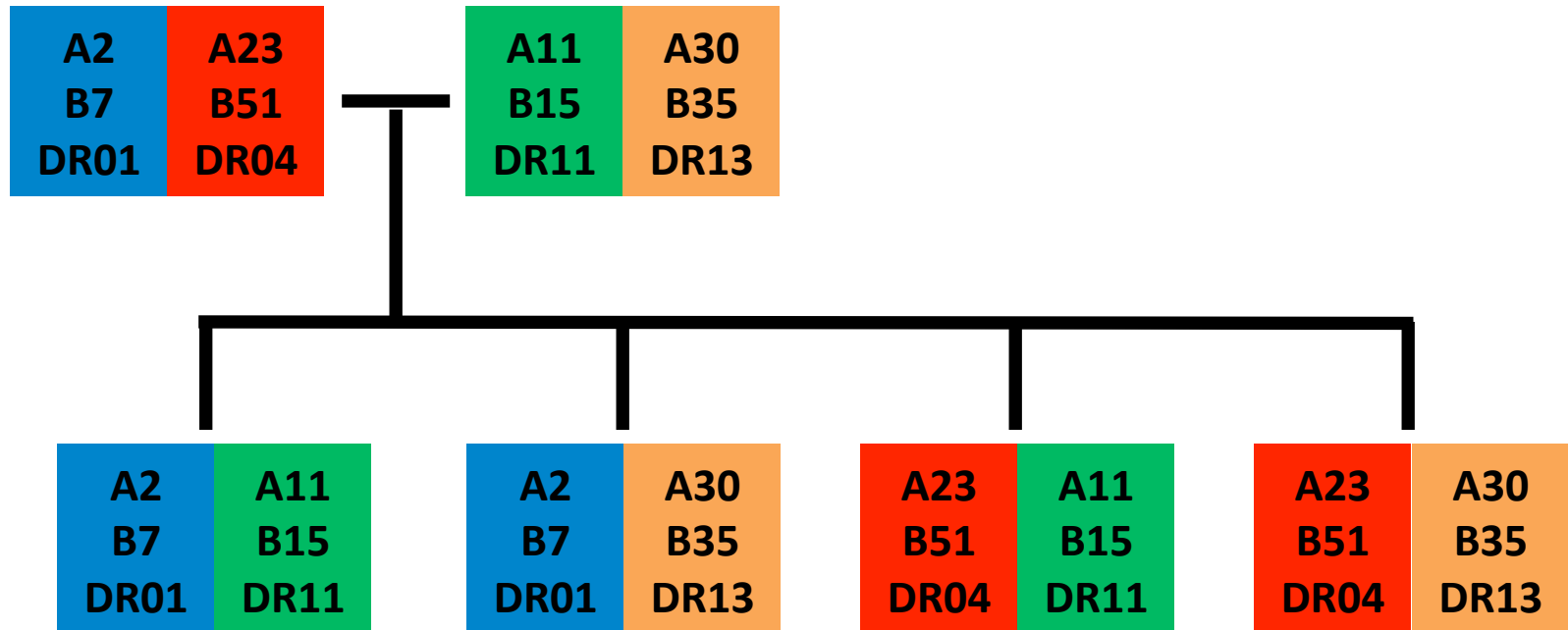
HLA



- Class I – A, B, C
- Class II – DR, DQ, DP



HLA Inheritance



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

HLA

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

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

HLA Expression Level

- High expression level (HEL) antigens –
DRB1, A, B, C
- Low expression level (LEL) antigens –
DQ, DP, DRB3-5

Relative Mismatch Between Donor Sources

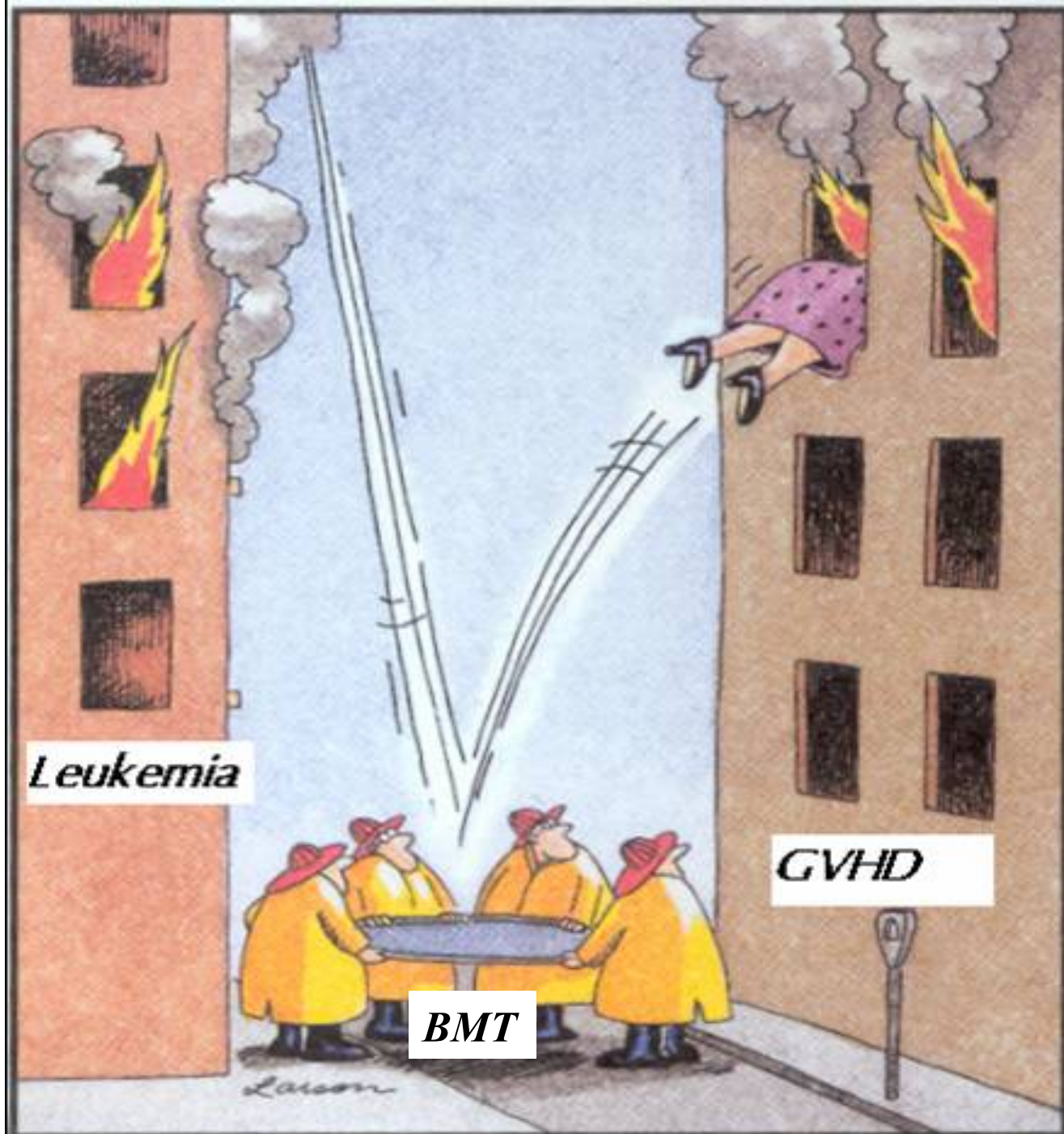
	Parent 1						Parent 2					
Donor	DR B1	B	A	C	DQ	DP	DR B1	B	A	C	DQ	DP
Related	=	=	=				=	=	=			
Unrelated	=	=	=	=	=	=	=	=	=	=	=	=
LEL-MM	=	=	=	=	≠	=	=	=	=	=	≠	≠
HEL-MM	≠	=	=	=	=	=	=	=	=	=	=	=
Haplo	=	=	=				≠	≠	≠			

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

Lalson

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



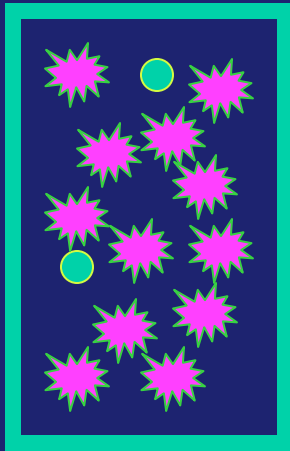
Prevention/Control of aGvHD Is Important

Acute GvHD	100 Day Survival
Grade I	78-90%
Grade II	66-92%
Grade III	29-62%
Grade IV	23-25%

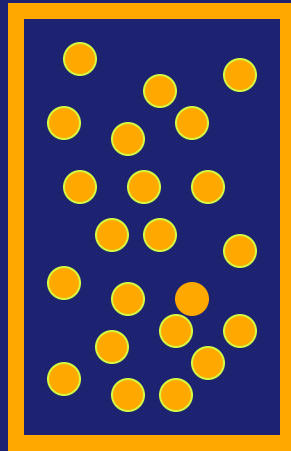
(Przepiorka et al, 1995)

- Prophylaxis – Prevention of aGvHD
- Treatment – Therapy of aGvHD

Patient

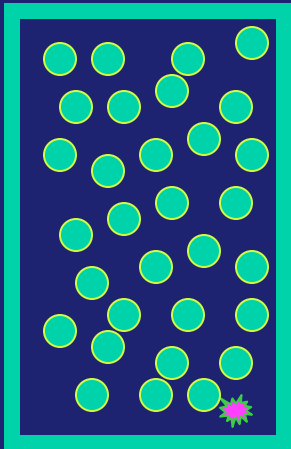


Donor



Allogeneic BMT

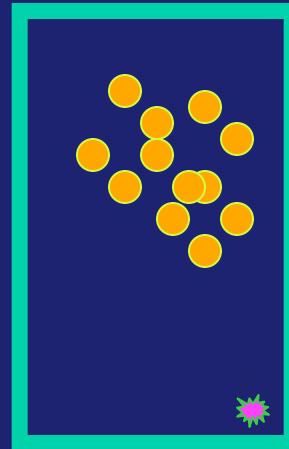
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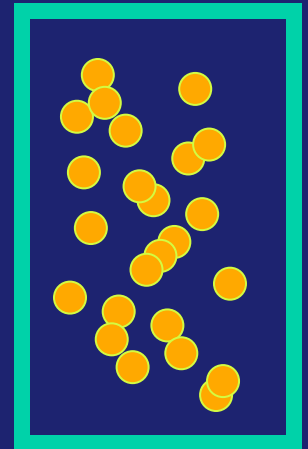
High dose
Chemo ±
XRT



14-21
days



Time

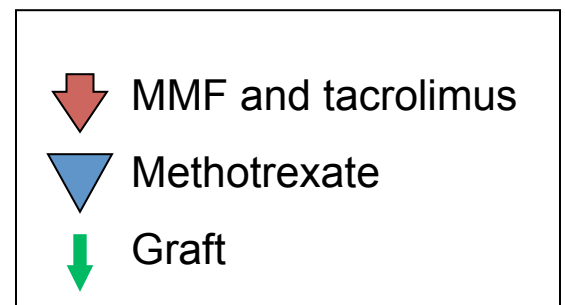
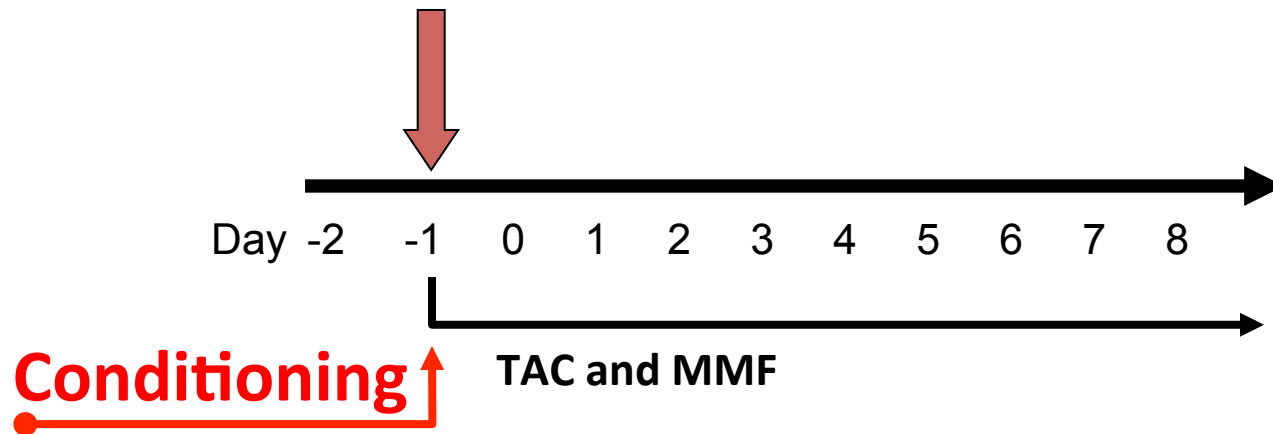


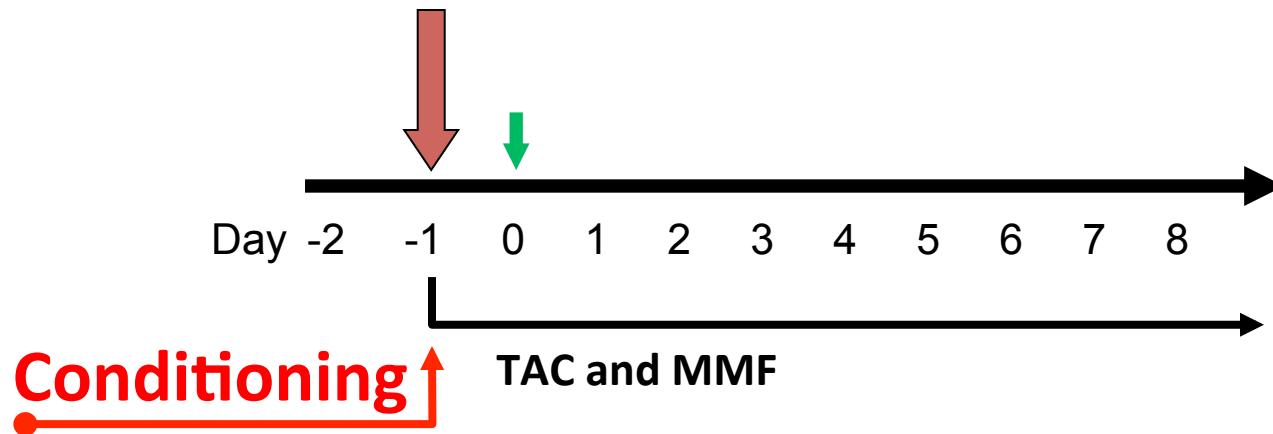
Acute GvHD Prophylaxis

- **Micro methotrexate**
- Post transplant cyclophosphamide
- Alpha beta T cell depletion and CD34 selection

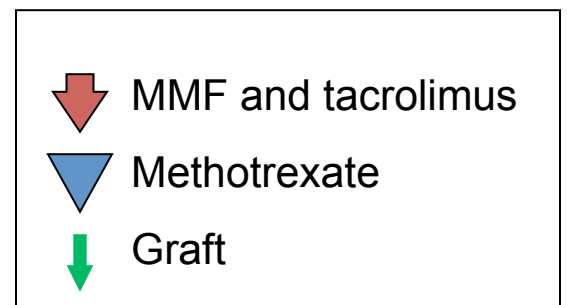
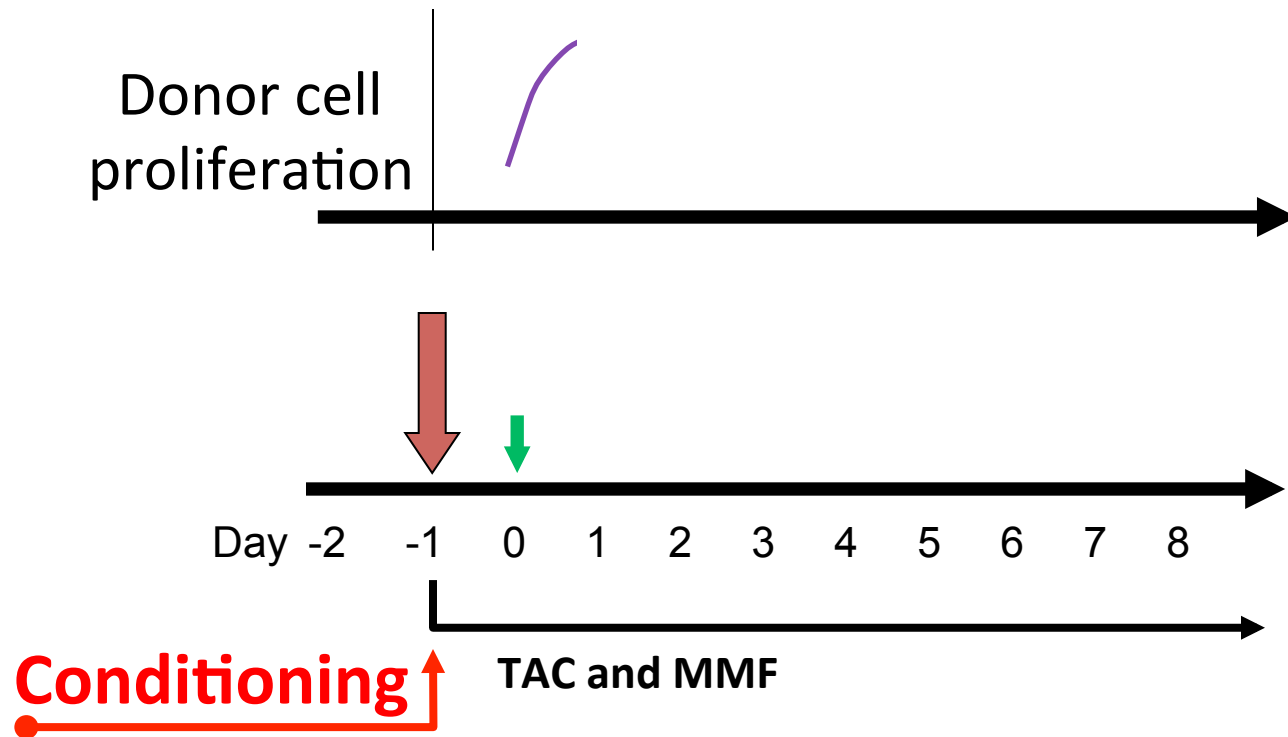
Acute GvHD Prophylaxis – μ MTX

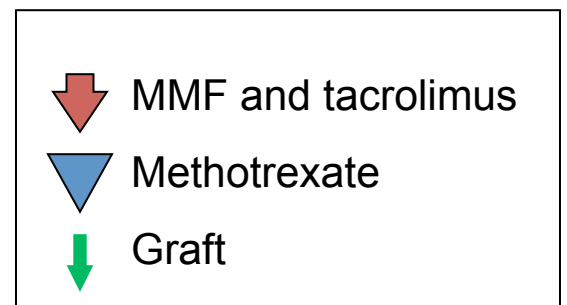
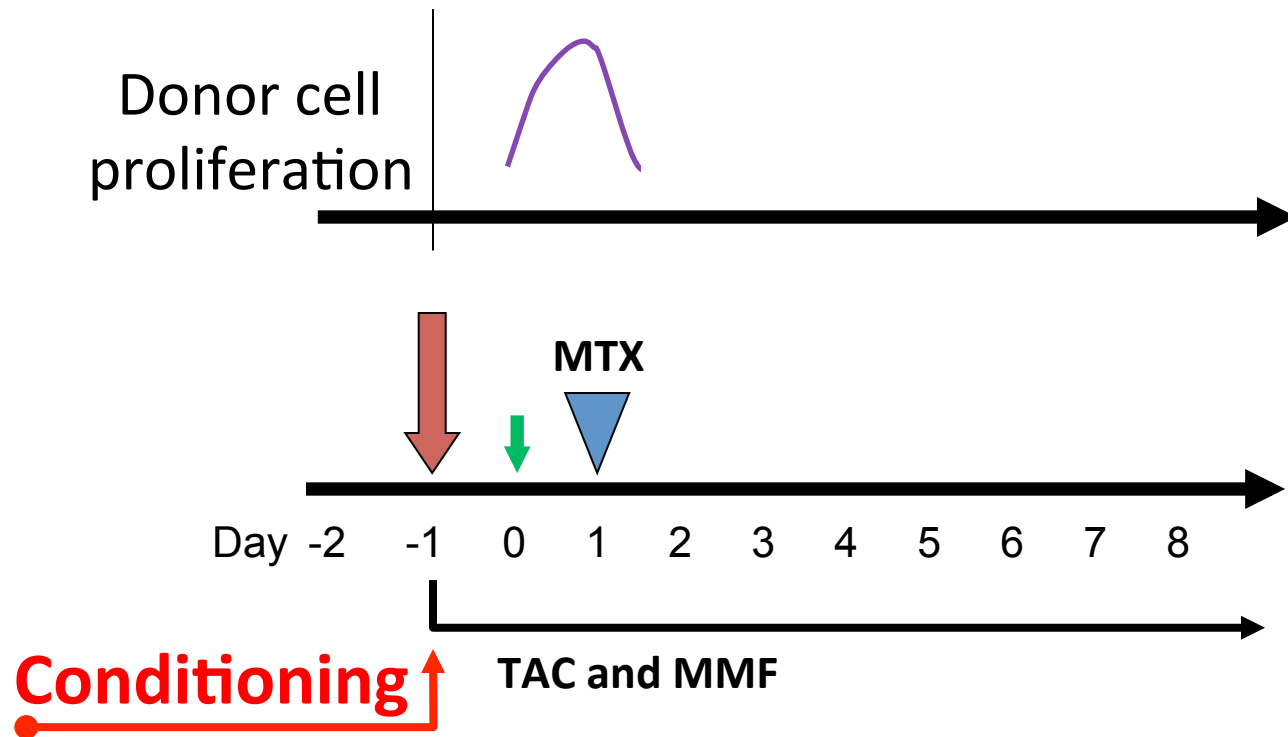
- Prophylaxis with tacrolimus (TAC), mycophenolate mofetil (MMF), and methotrexate
- Methotrexate (2.5 mg/m^2) is given on days 1, 3, 6
- MMF is given from day -1 until day 60
- TAC is given from day -1 until day 100. At day 100 tapering begins until day 180 when it is stopped.
- 21% of patients develop aGvHD despite prophylaxis

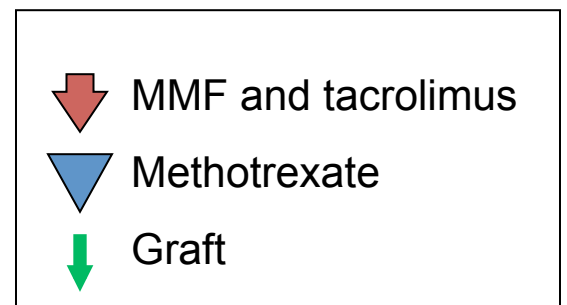
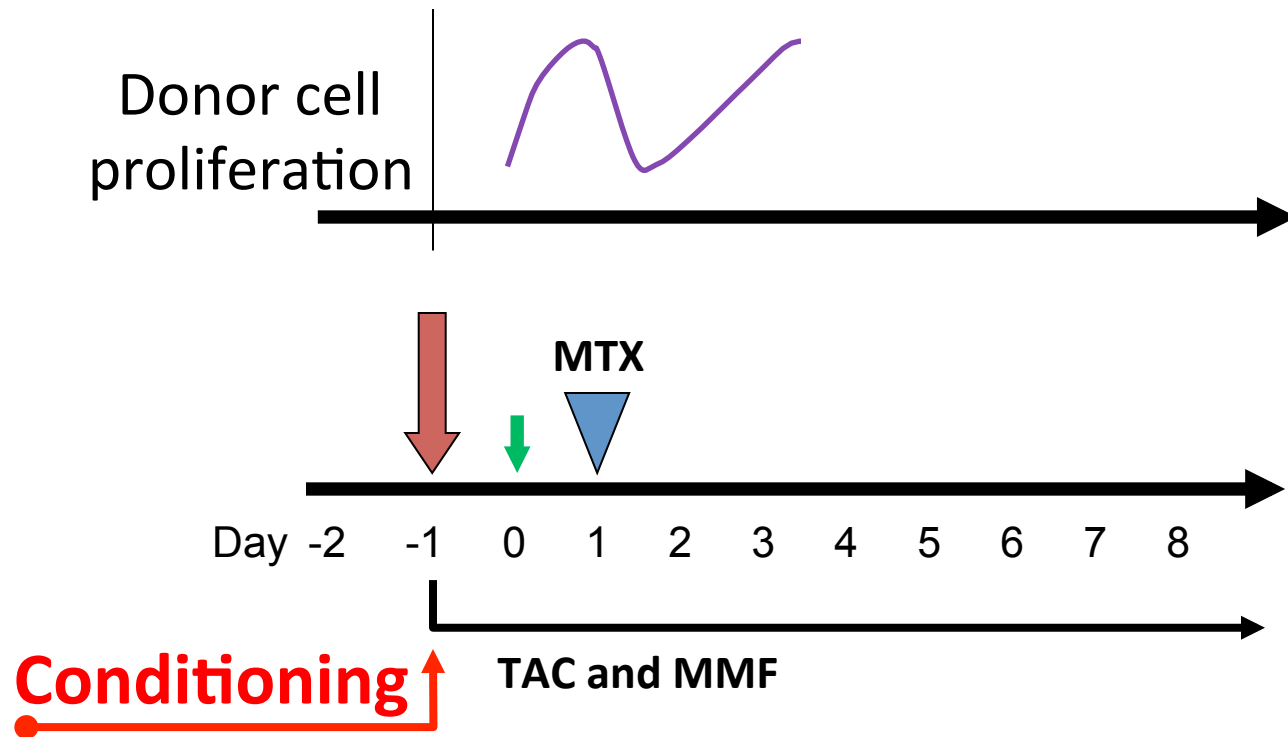


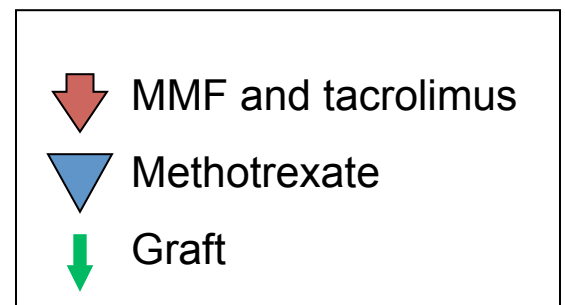
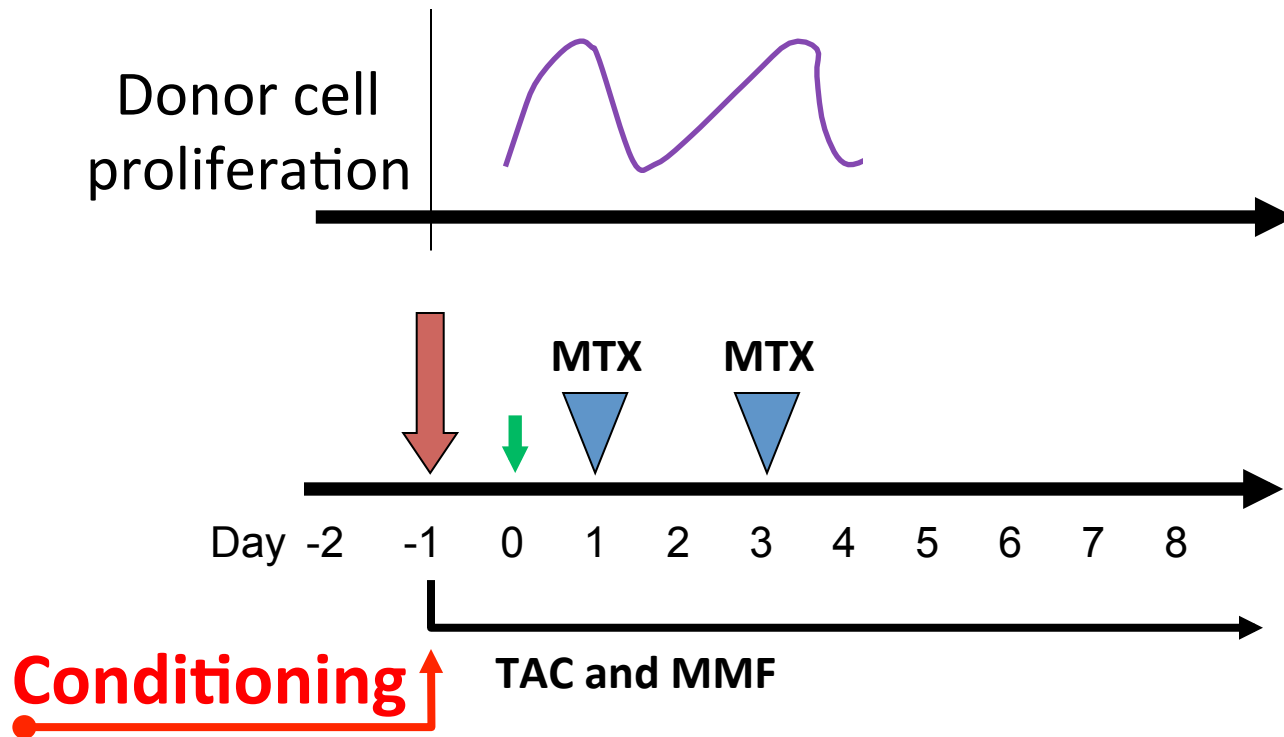


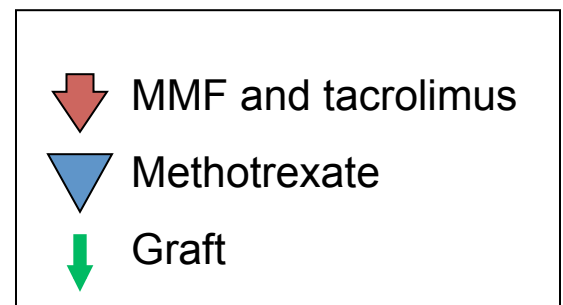
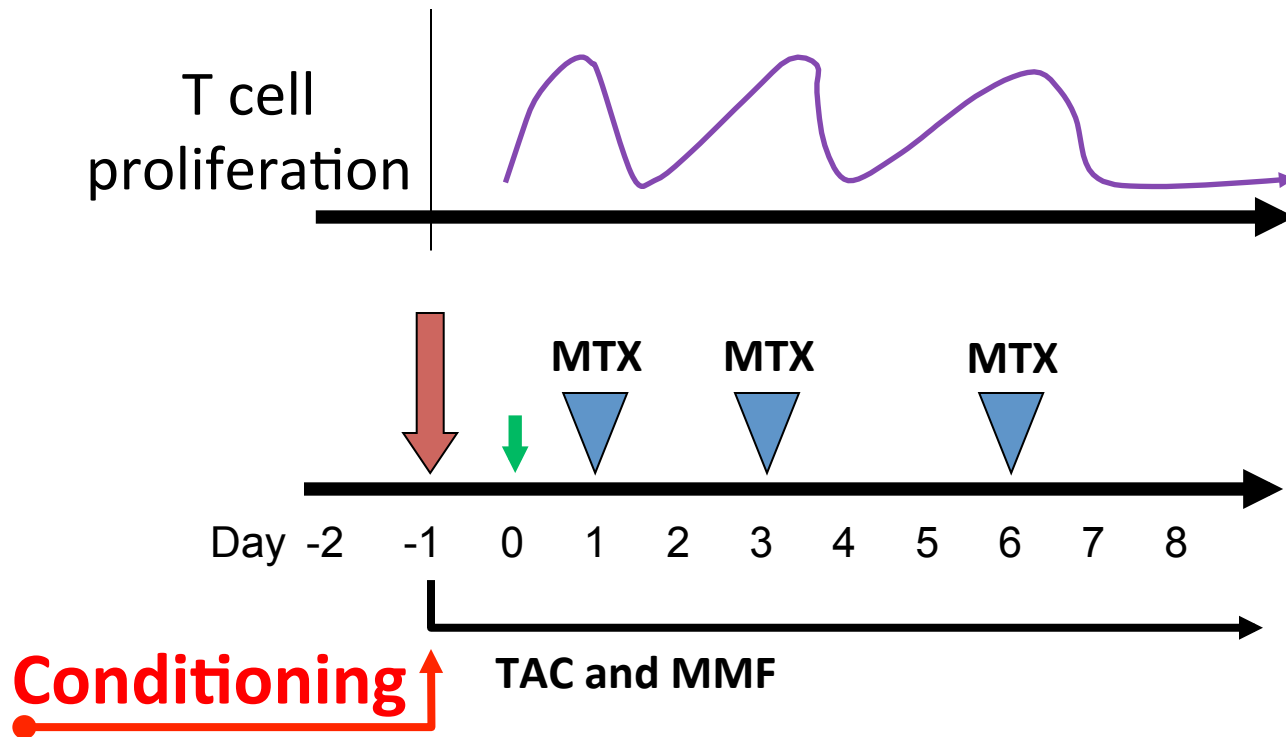
- ↓ MMF and tacrolimus
- ▼ Methotrexate
- ↓ Graft











Acute GvHD Prophylaxis

- Micro methotrexate
- **Post transplant cyclophosphamide**

Cyclophosphamide



Cytochrome
P450

*Elevated in stem cells
Higher in resting
lymphocytes versus
activated lymphocytes*

4-hydroxy-cyclophosphamide



Tautomer-
ization



Aldehyde

dehydrogenase

Carboxy

Aldophosphamide

phosphamide

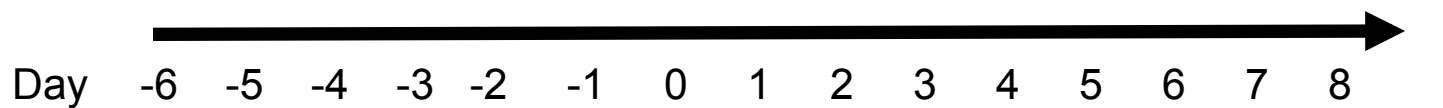
(inactive)



Phosphoramidate
mustard
(active)

Acrolein
(active)



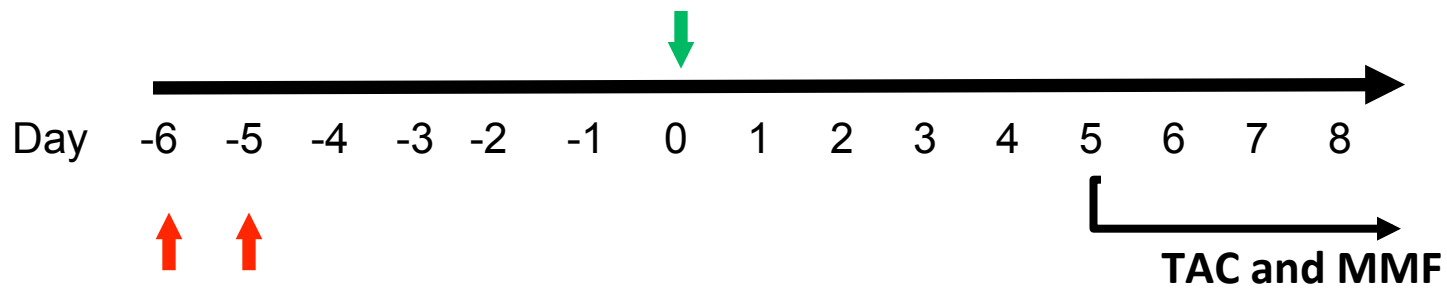


↑ ↑
↑ ↑ ↑ ↑ ↑
FLU-CY-TBI

↑ ↑ ↑ ↑ ↑

TAC and MMF

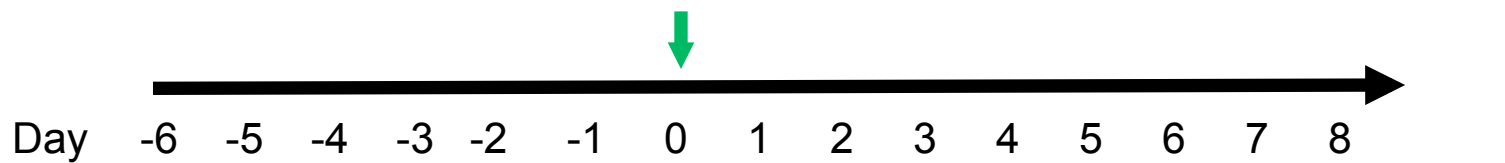
- ↓ MMF and tacrolimus
- ▽ High dose CY
- ↓ Graft



↑ ↑
↑ ↑ ↑ ↑ ↑ ↑
FLU-CY-TBI

- ↓ MMF and tacrolimus
- ▽ High dose CY
- ↓ Graft

T cell
proliferation

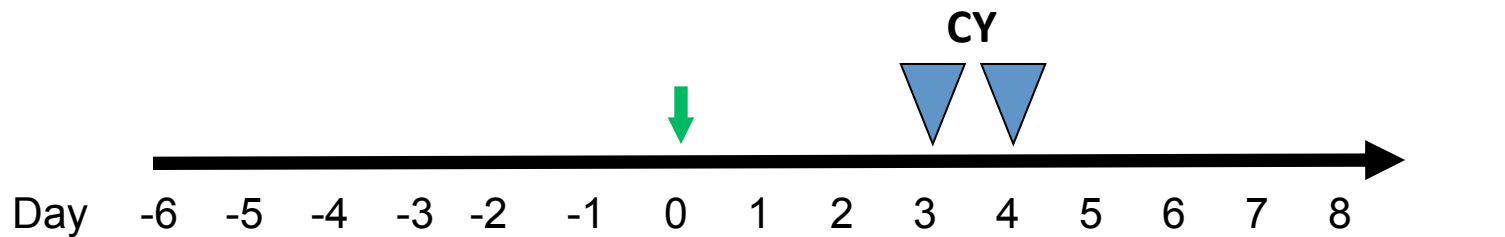


↑ ↑
↑ ↑ ↑ ↑ ↑ ↑
FLU-CY-TBI

TAC and MMF

- ↓ MMF and tacrolimus
- ▽ High dose CY
- ↓ Graft

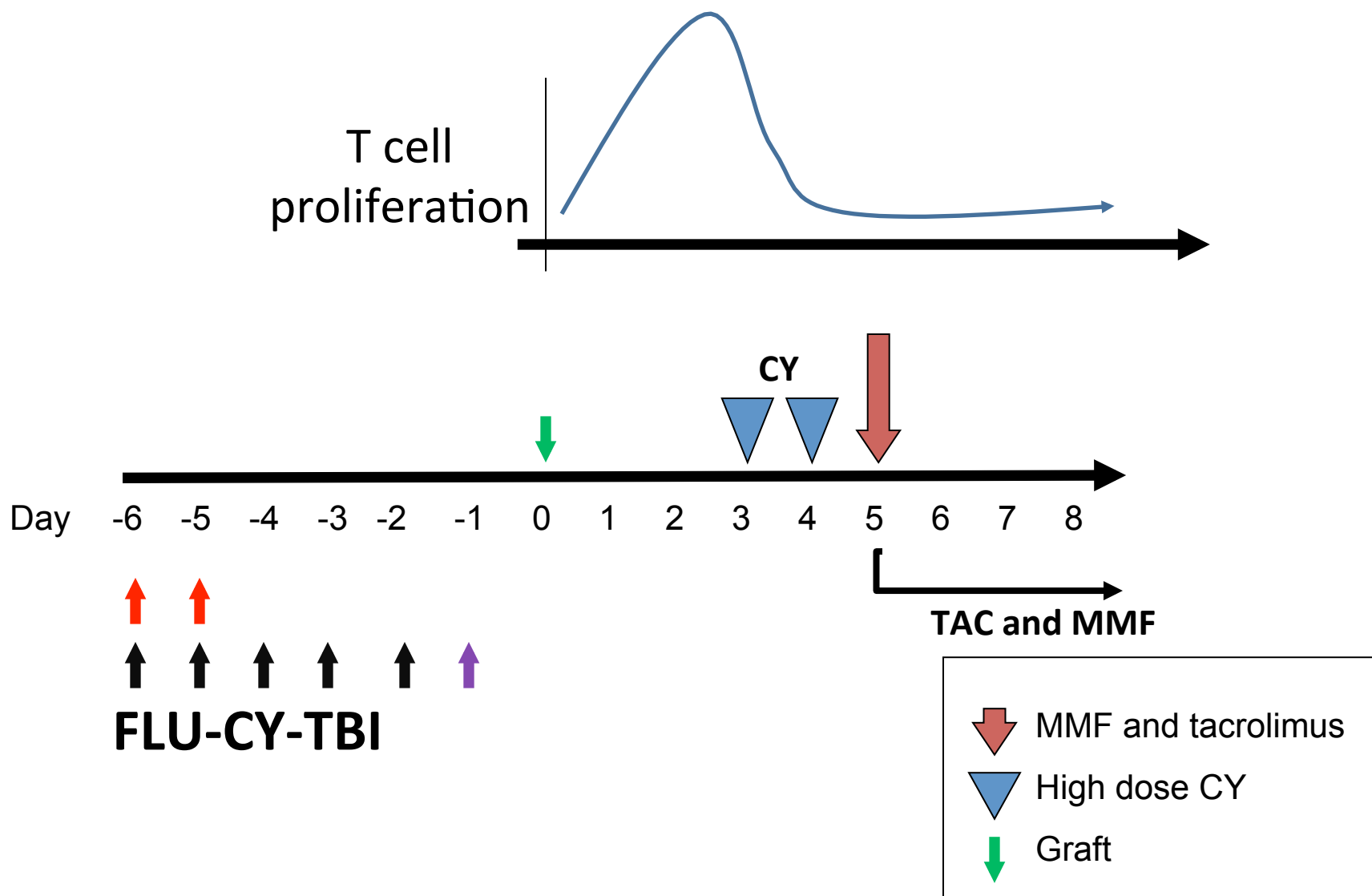
T cell
proliferation



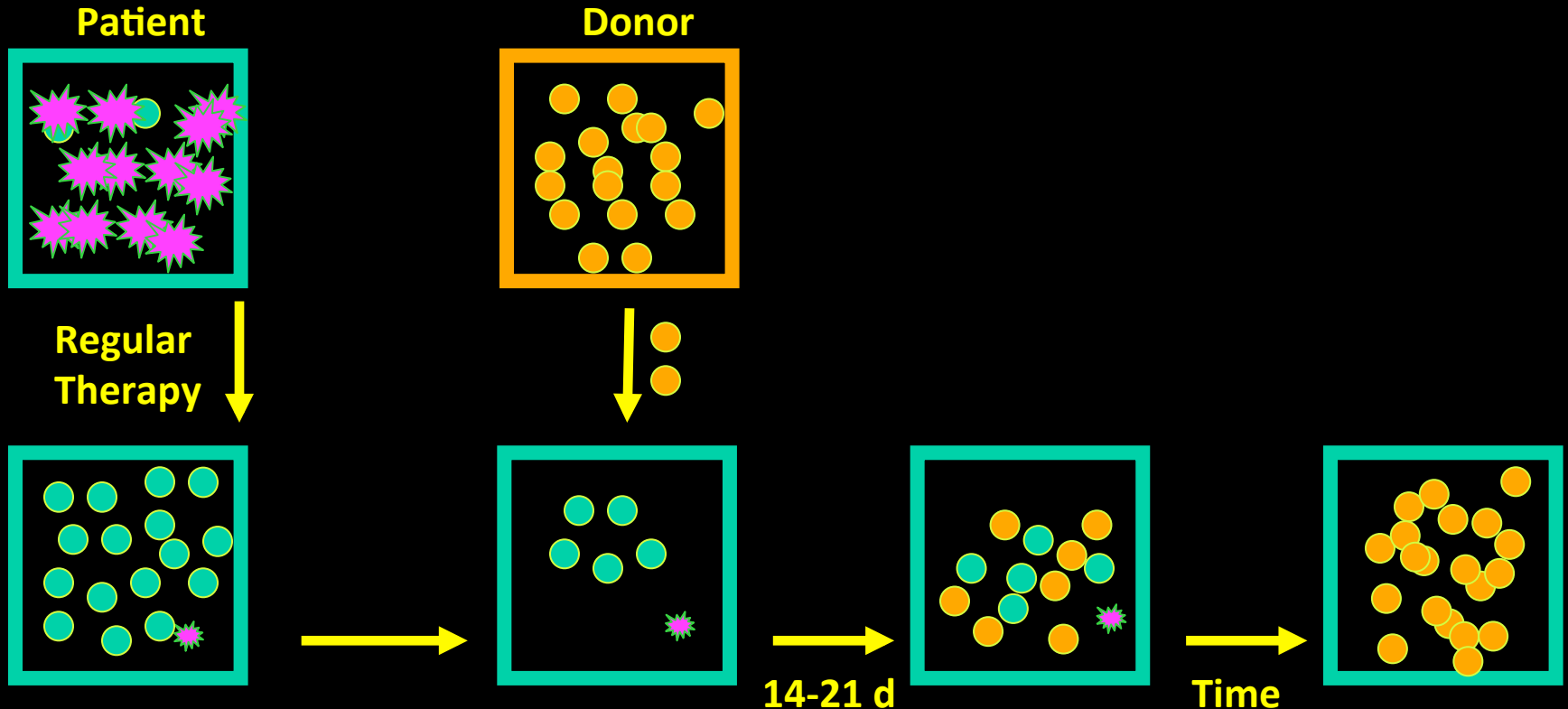
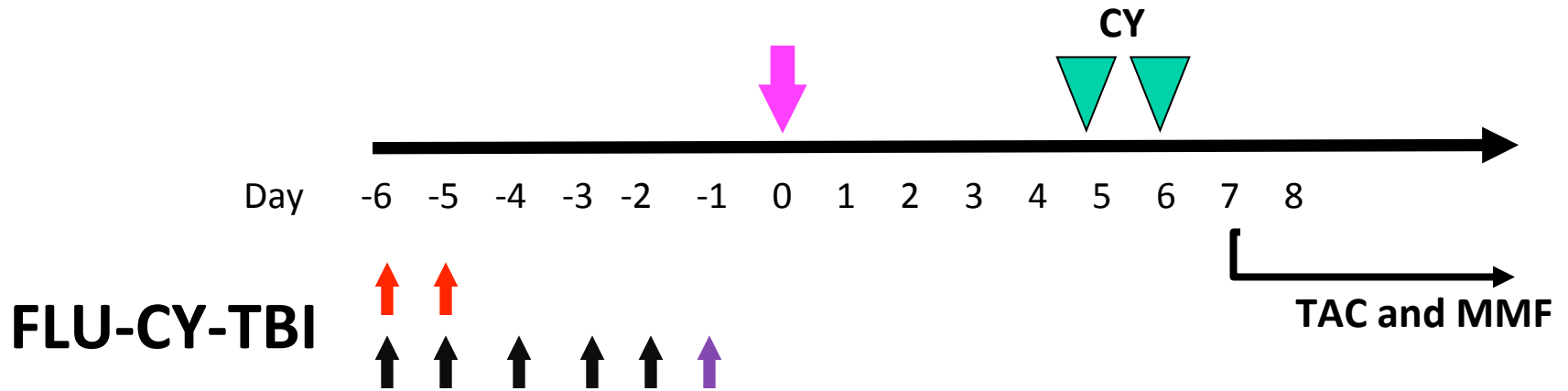
↑ ↑
↑ ↑ ↑ ↑ ↑
FLU-CY-TBI

TAC and MMF

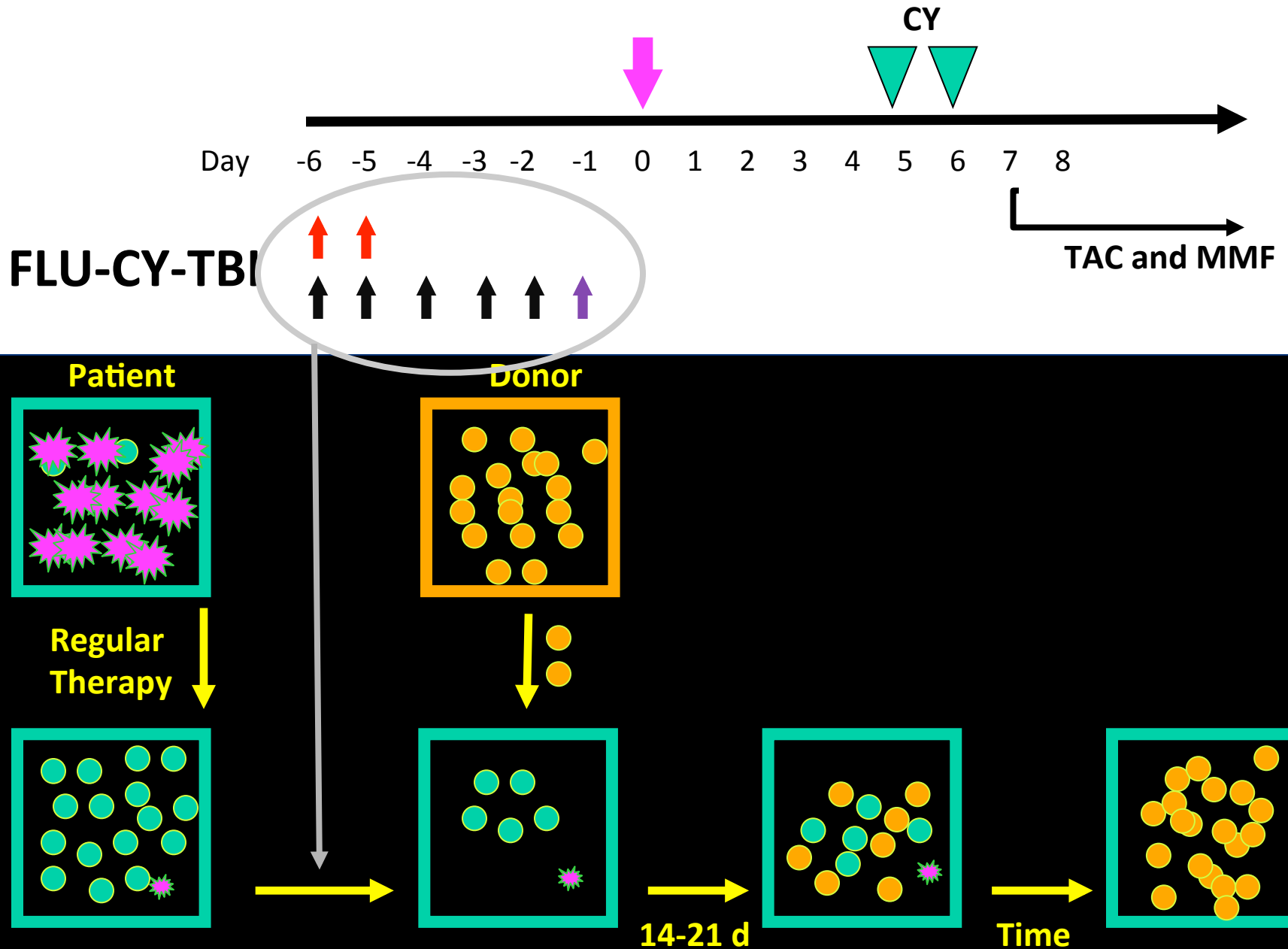
- ↓ MMF and tacrolimus
- ▽ High dose CY
- ↓ Graft



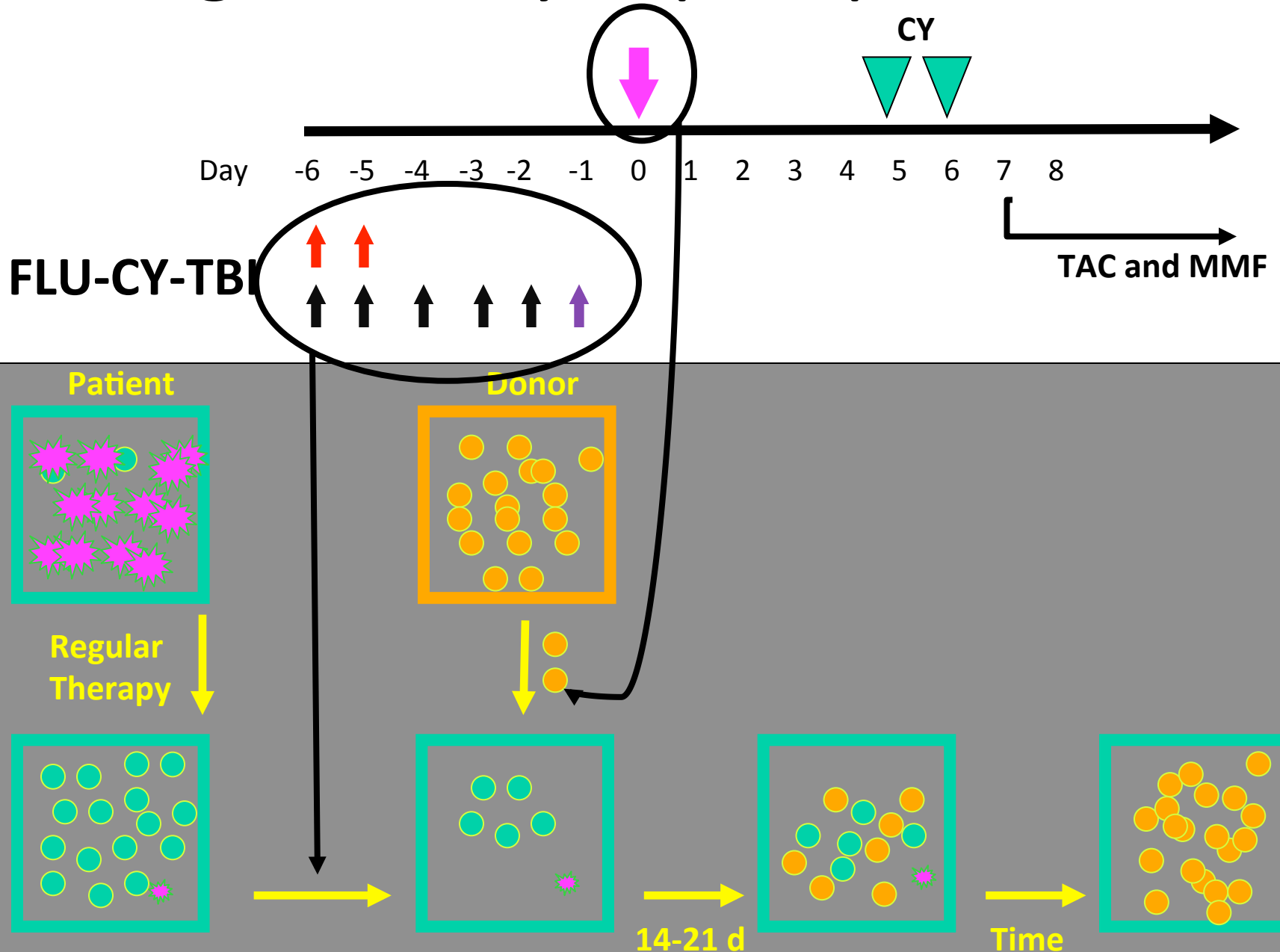
High dose cyclophosphamide



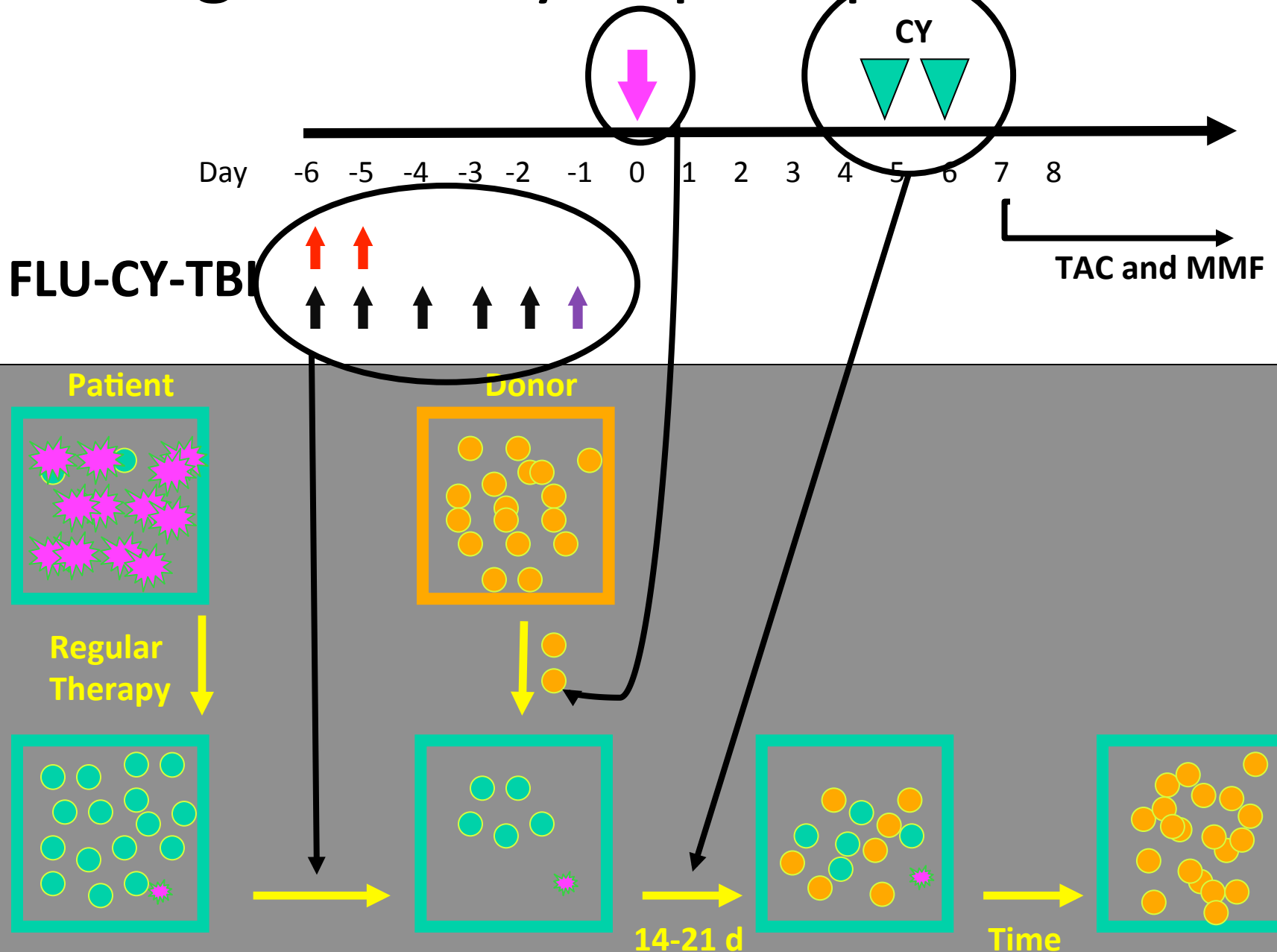
High dose cyclophosphamide



High dose cyclophosphamide

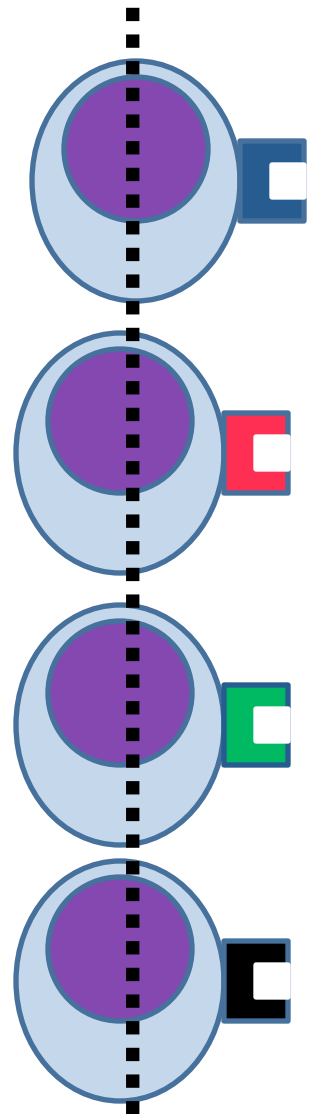


High dose cyclophosphamide

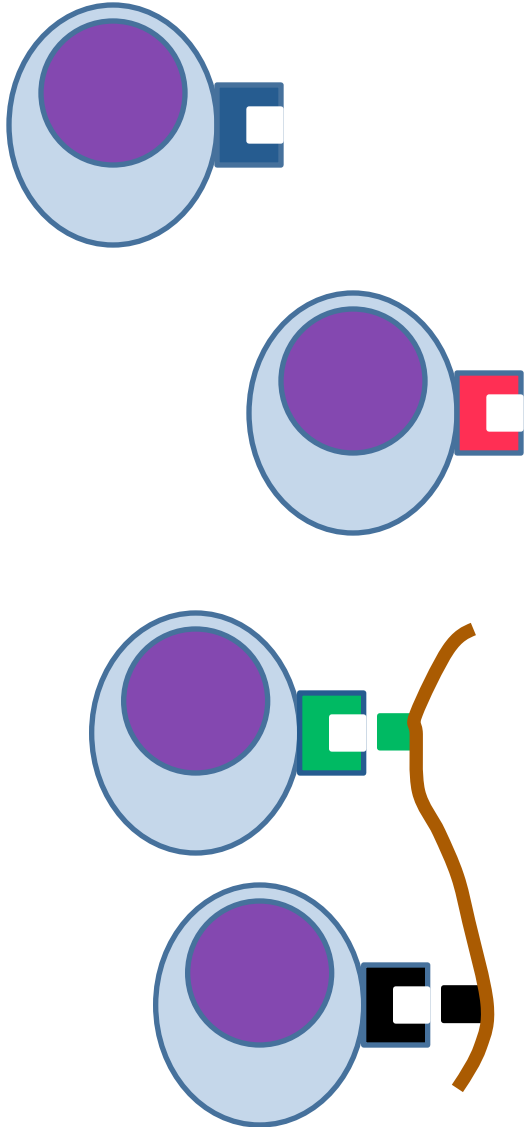


Post HCT cyclophosphamide (Cy) for GvHD

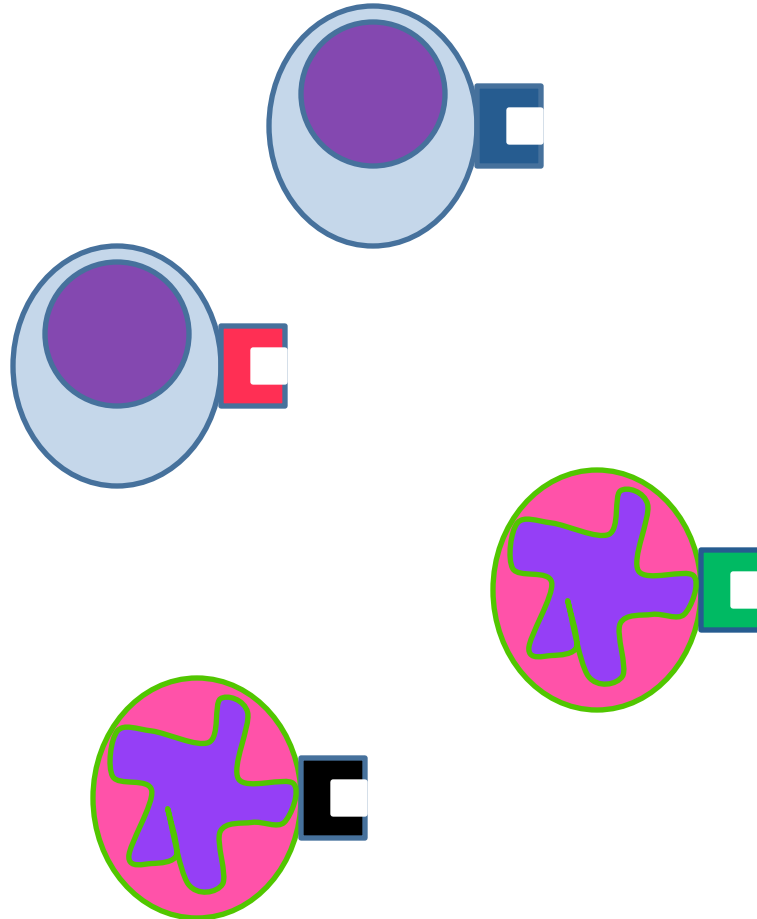
Day 0



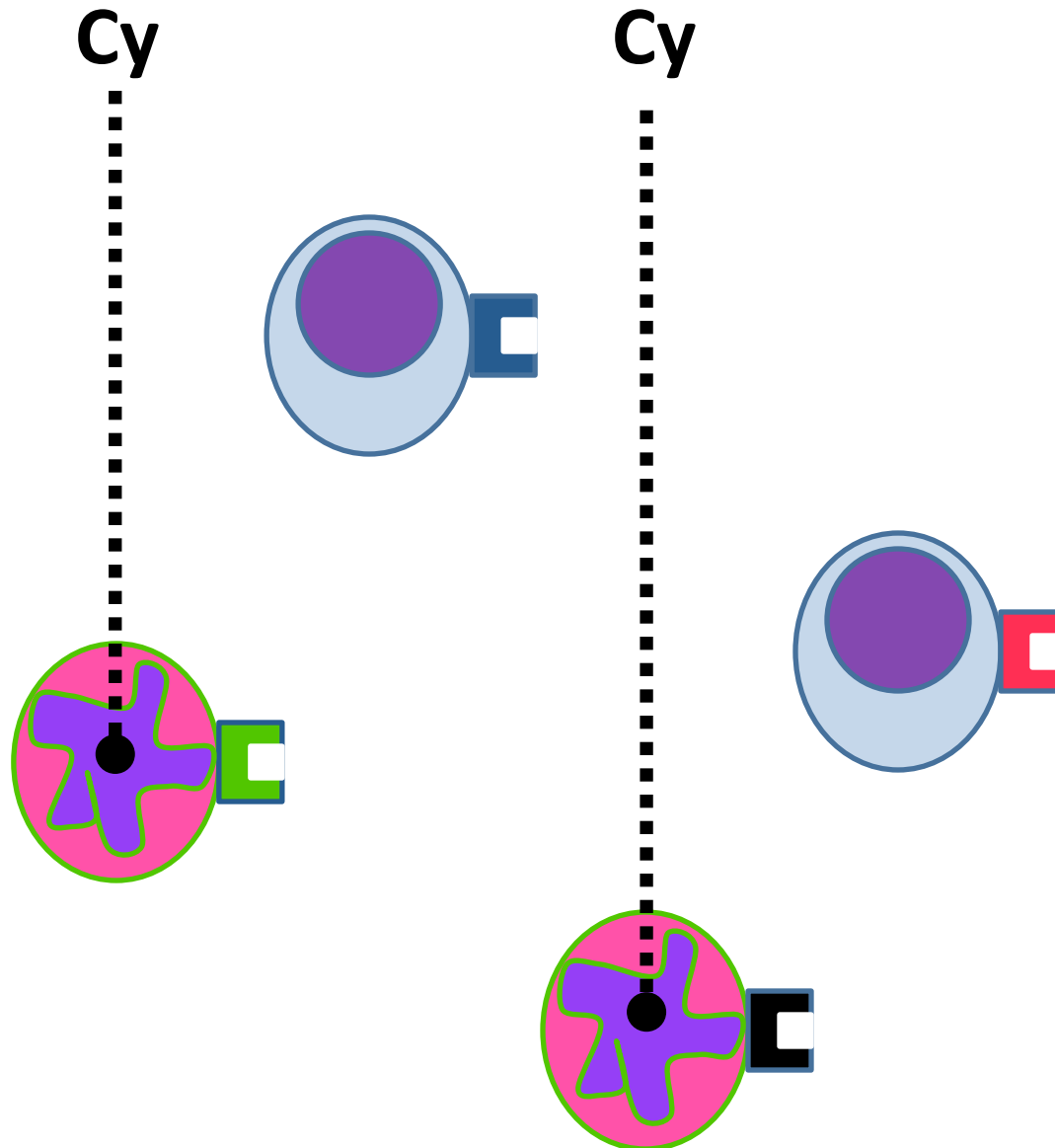
Post HCT cyclophosphamide (Cy) for GvHD



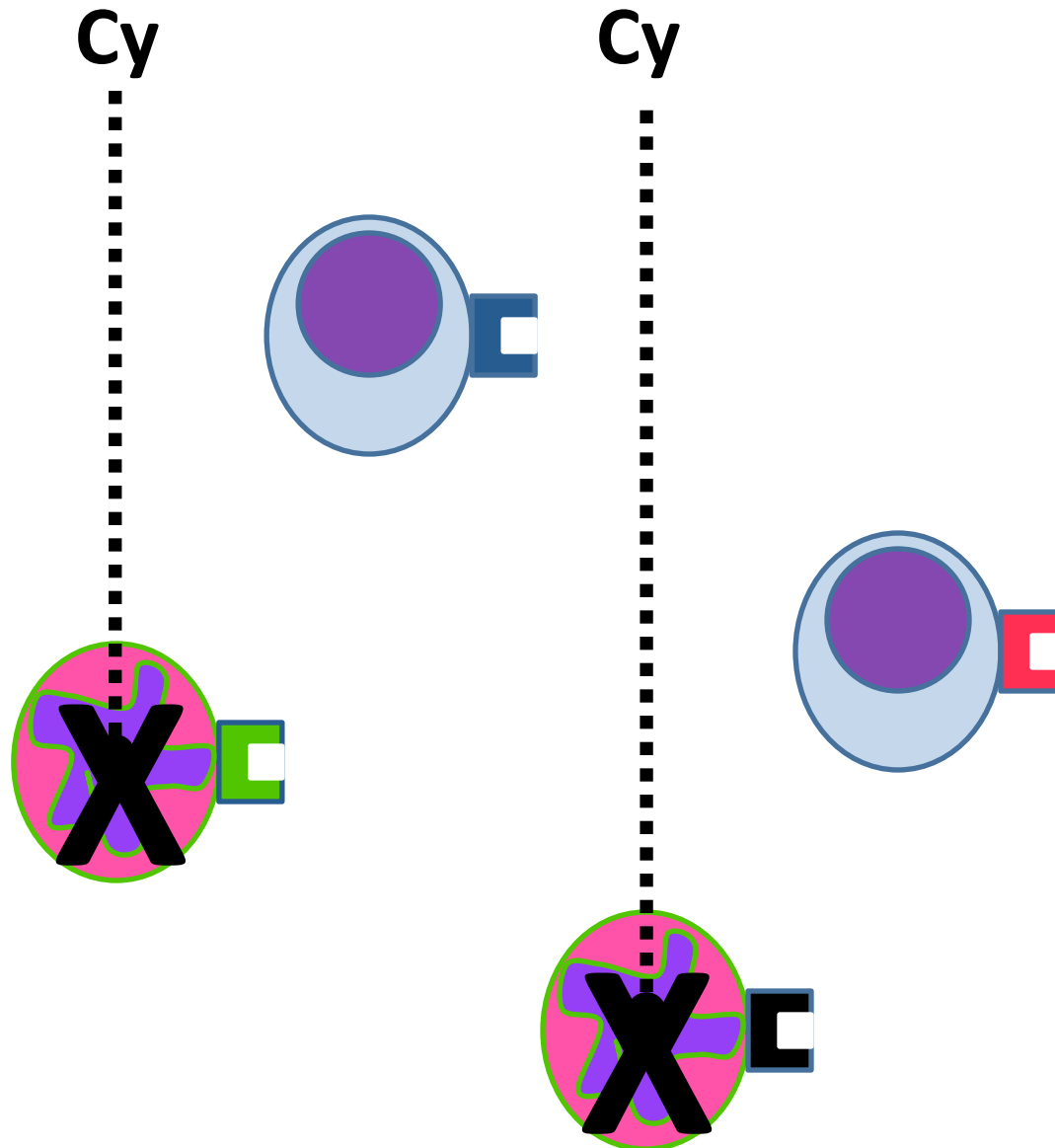
Post HCT cyclophosphamide (Cy) for GvHD



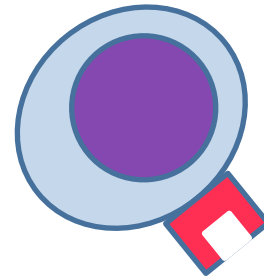
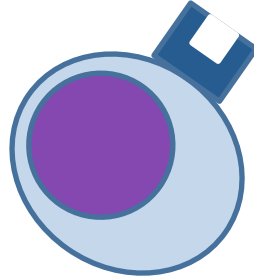
Post HCT cyclophosphamide (Cy) for GvHD



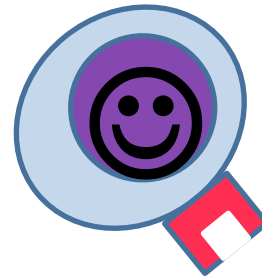
Post HCT cyclophosphamide (Cy) for GvHD



Post HCT cyclophosphamide (Cy) for GvHD



Post HCT cyclophosphamide (Cy) for GvHD



Acute GvHD Prophylaxis

- Micro methotrexate
- Post transplant cyclophosphamide
- Alpha beta T cell depletion and CD34 selection

RPCI Prophylaxis Regimens

	Pt-Cy	uMTX
Active agent	Cyclophosphamide	Methotrexate
Target	Proliferating T cells	Proliferating T cells
Place of action	In vivo	In vivo
T cell	Depletion	Depletion
Other	Tacro Cellcept	Tacro Cellcept

HCT for hematologic malignancy

	Haplo*	Standard#
Conditioning	Flu/Cy/TBI	Flu/Mel/TBI
aGvHD prophylaxis	Cy/Tac/MMF	uMTX/Tac/MMF
Graft failure	6%	0%
aGvHD Gr. III-IV	3% (day 180)	27% (day 100)
Progression free survival	37% (3 years)	44% (2 years)
Overall survival	46% (3 years)	47% (2 years)

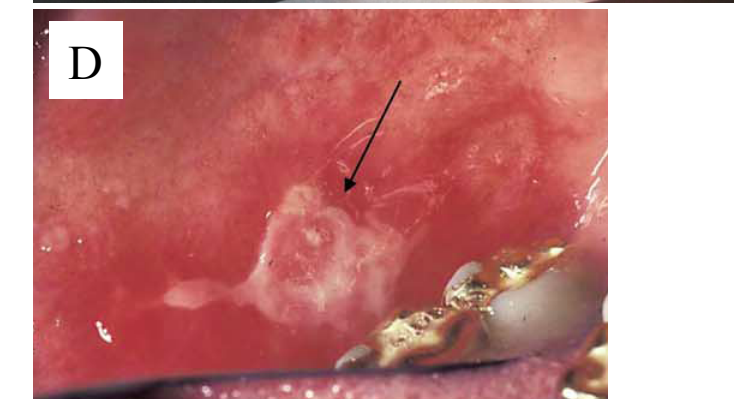
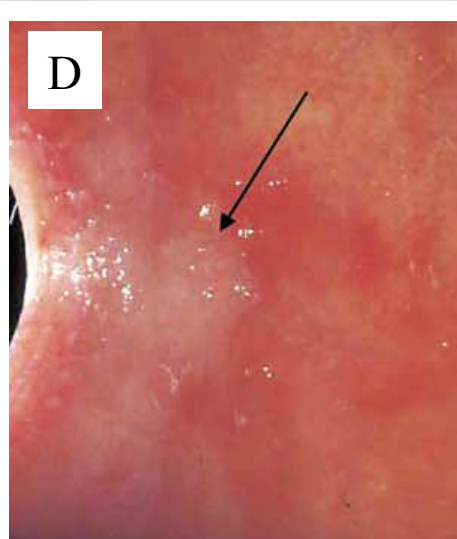
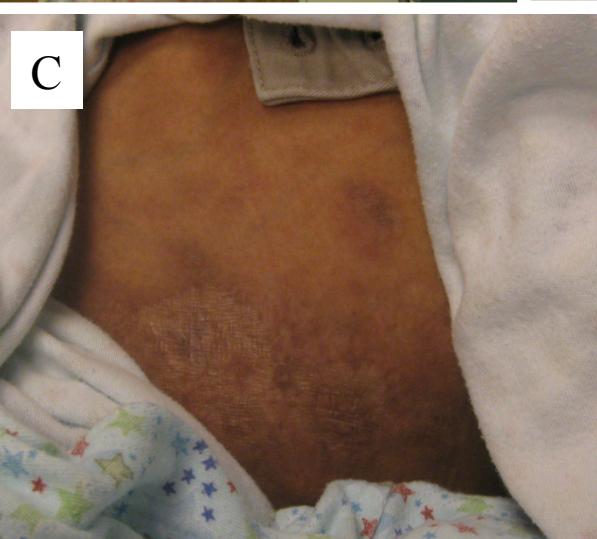
* Kasamon, et al. JCO 2015, # RPCI unpublished data

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**



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

