Introduction to Cellular Therapy: Stem Cell Transplantation

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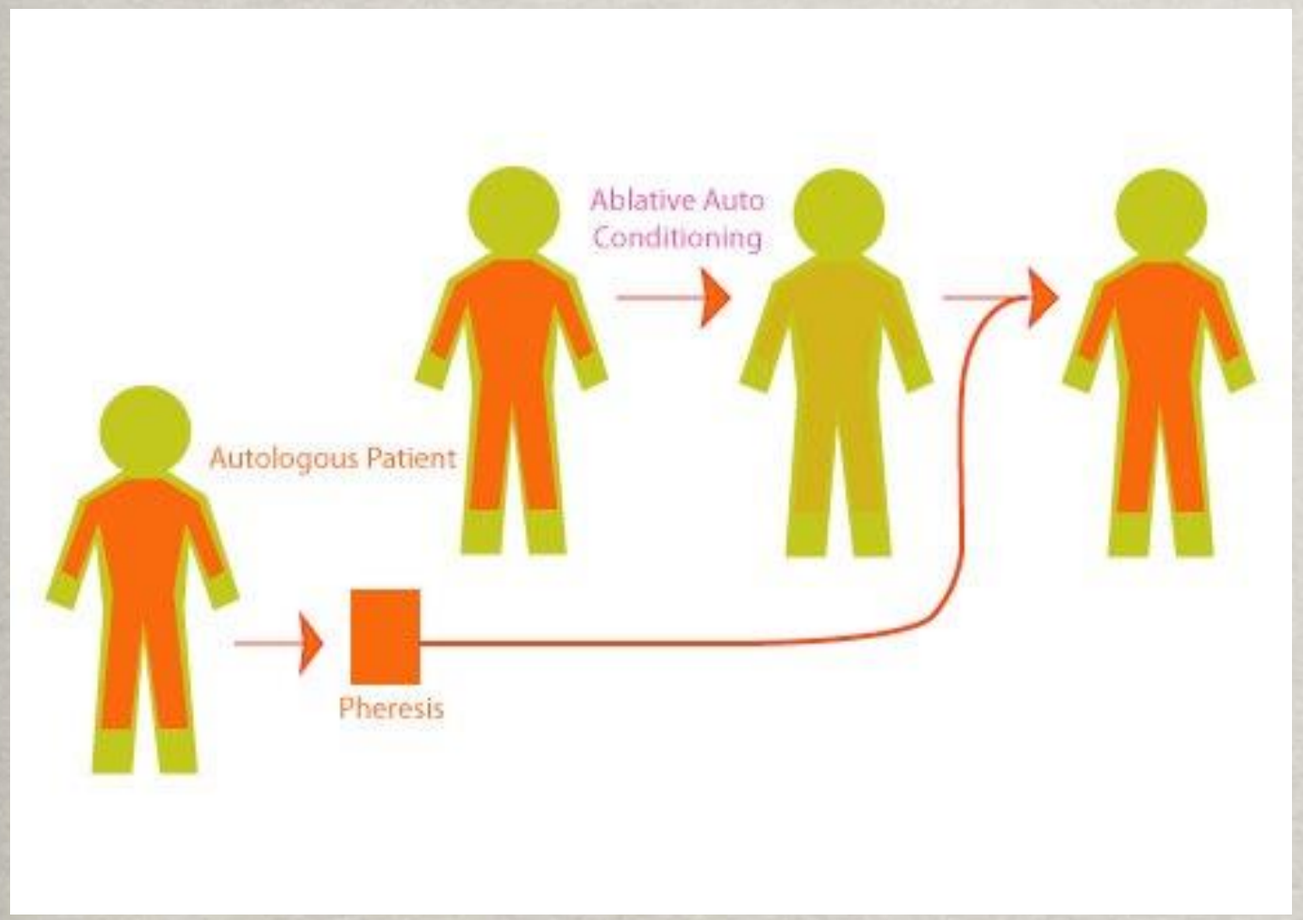
“Autologous” Transplant

- Certain cancers can respond to chemotherapy with a decrease in the number of cancerous cells with every cycle of chemotherapy.
- However, there is sometimes a point reached where a small number of residual cancer cells remain that do not respond as well to the standard repeated doses of chemotherapy.

Autologous Transplant

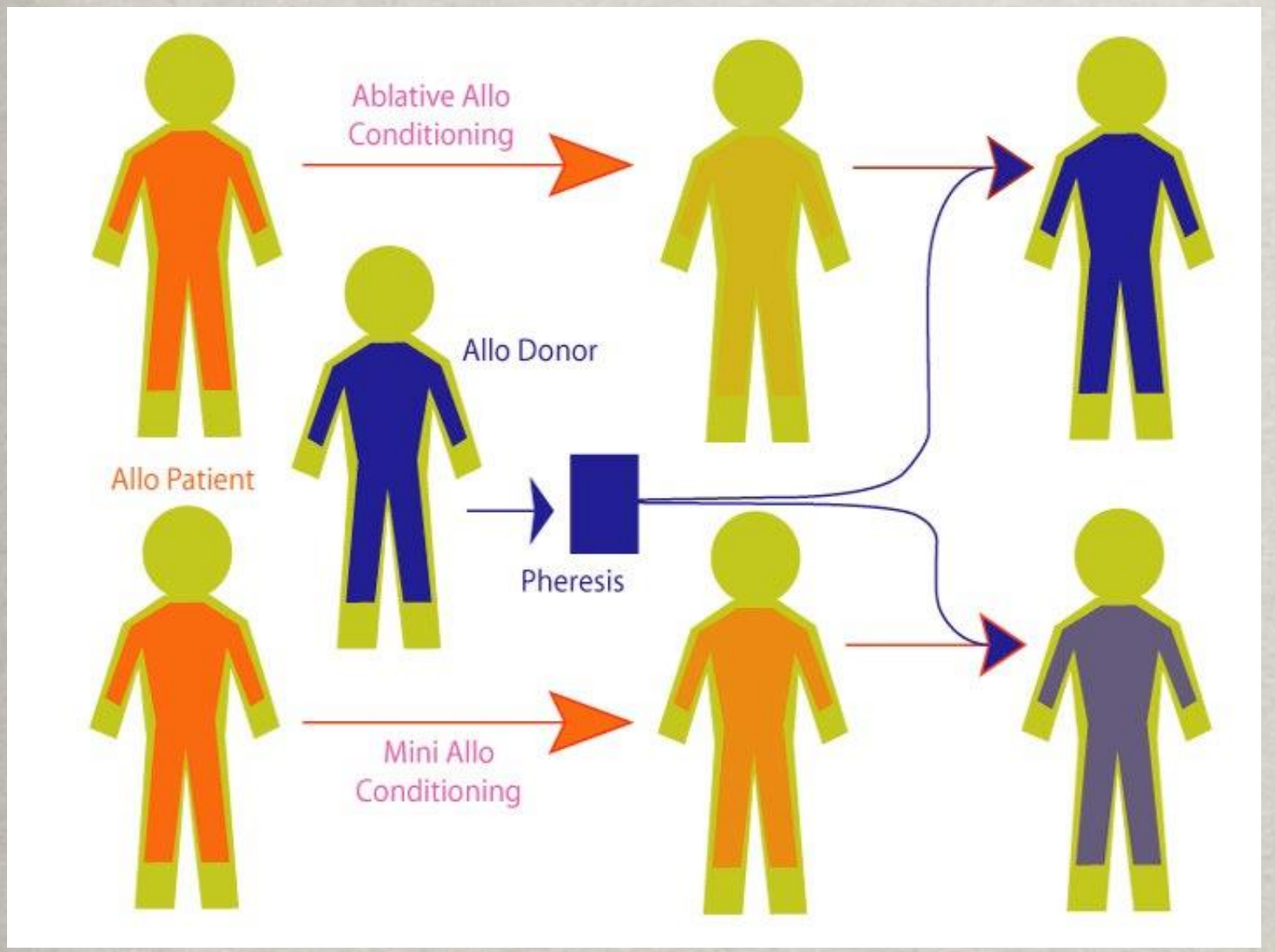


- Residual cancer cells may be cleared by higher doses of chemotherapy to cure at the price of killing other healthy marrow cells.
- Collecting stem cells ahead of time and returning them to the patient after high dose therapy saves them from other side effects of such therapy.

“Allogeneic” Transplant

- Some cancers cannot be eliminated even with the highest doses of chemotherapy
- In such cases it is sometimes possible to harness the power of a new immune system to recognize and destroy the cancer cells
- The process of identifying an appropriate donor and transplanting their cells into the recipient is called an allogeneic stem cell transplant

“Allogeneic” Transplant

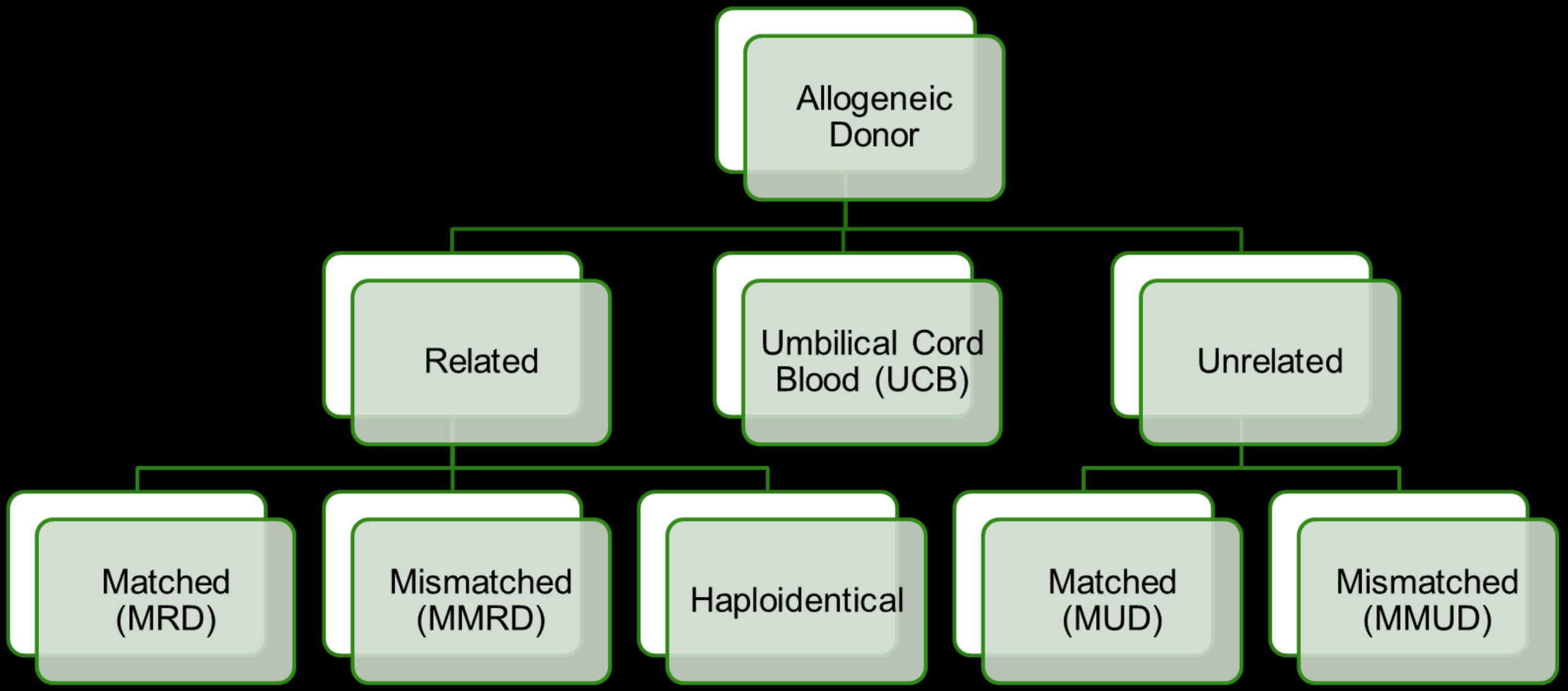


- In this procedure a donor's HLA matched stem cells are collected and transplanted into the patient.
- HLA matching is the process of determining if the donor and the patient share certain critical genes that educate the immune system.

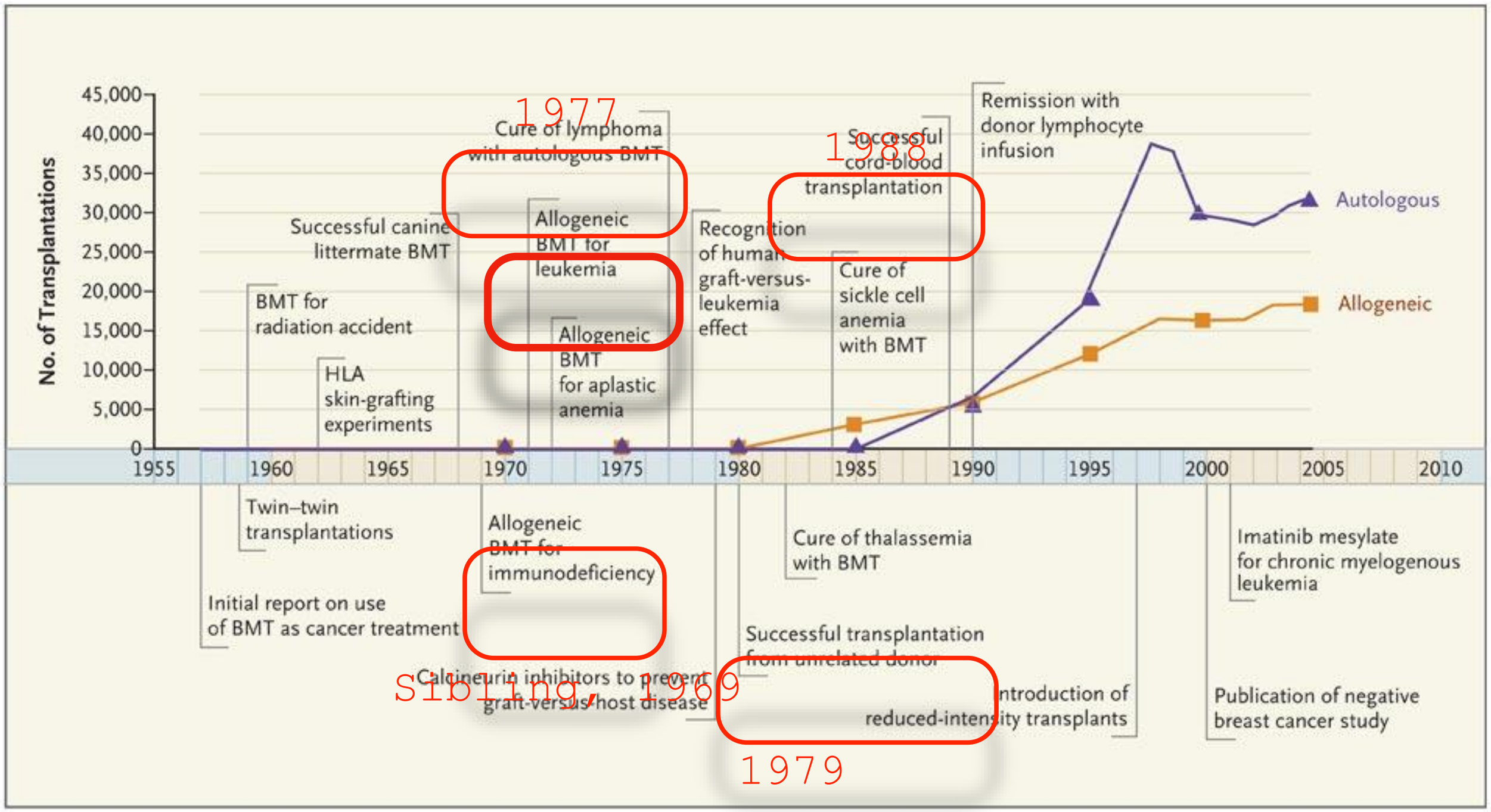
Allogeneic Transplant

- The safest allogeneic transplants occur when donors and patients share the same HLA genes.
- The goal of allogeneic transplants is provide the patient with a NEW IMMUNE SYSTEM that can potentially ATTACK ANY REMAINING TUMOR CELLS.
- All cancers differ in their sensitivity to the allogeneic attack or "Graft vs Tumor Effect".
- However, sometimes the new cells can attack the normal cells of the host "Graft vs Host Disease".

Immunologic Stem Cell Sources



History of Transplant



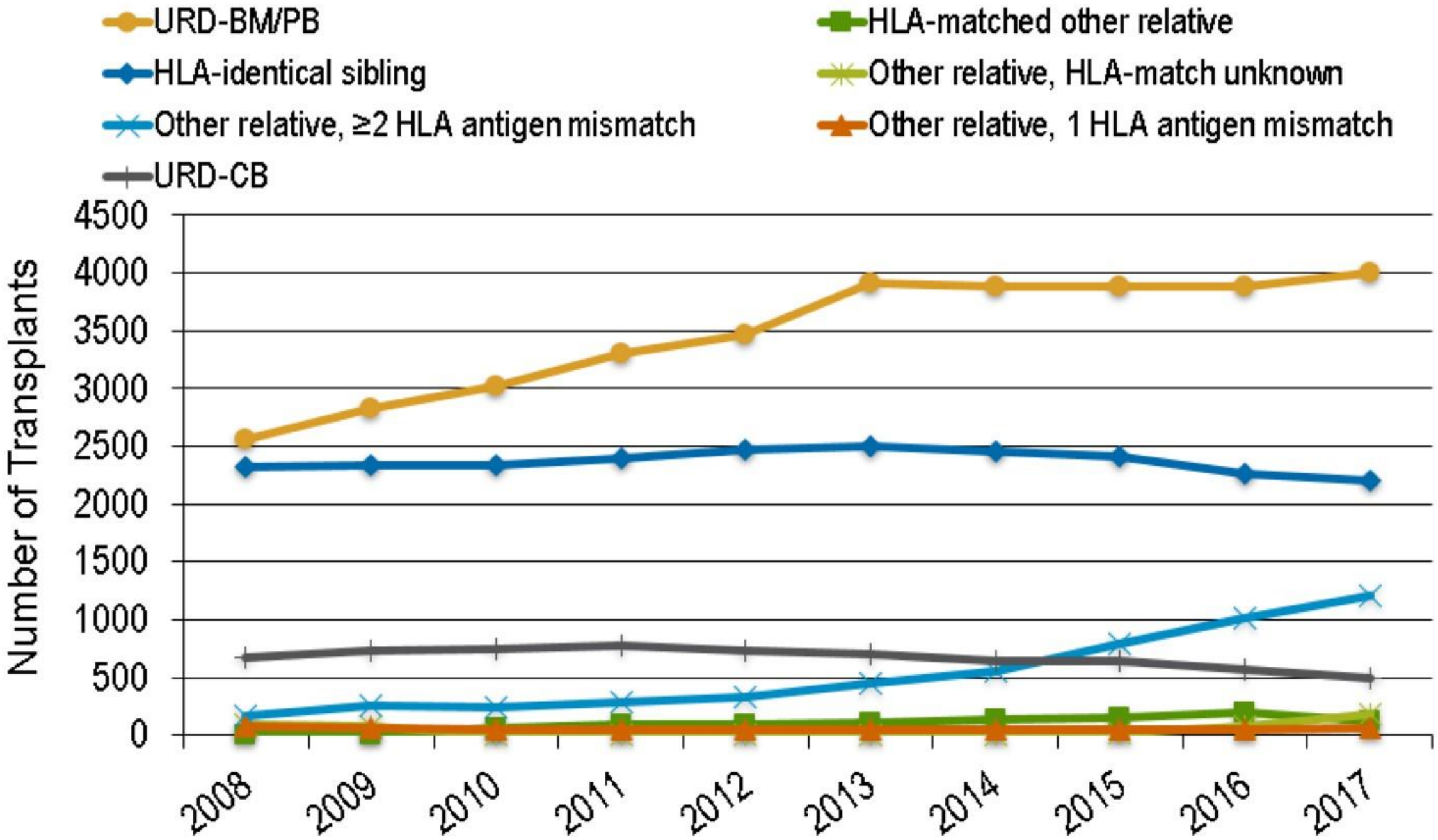
1977

1988

Sibling, 1969

1979

Allogeneic HCT Recipients in the US, by Donor Type



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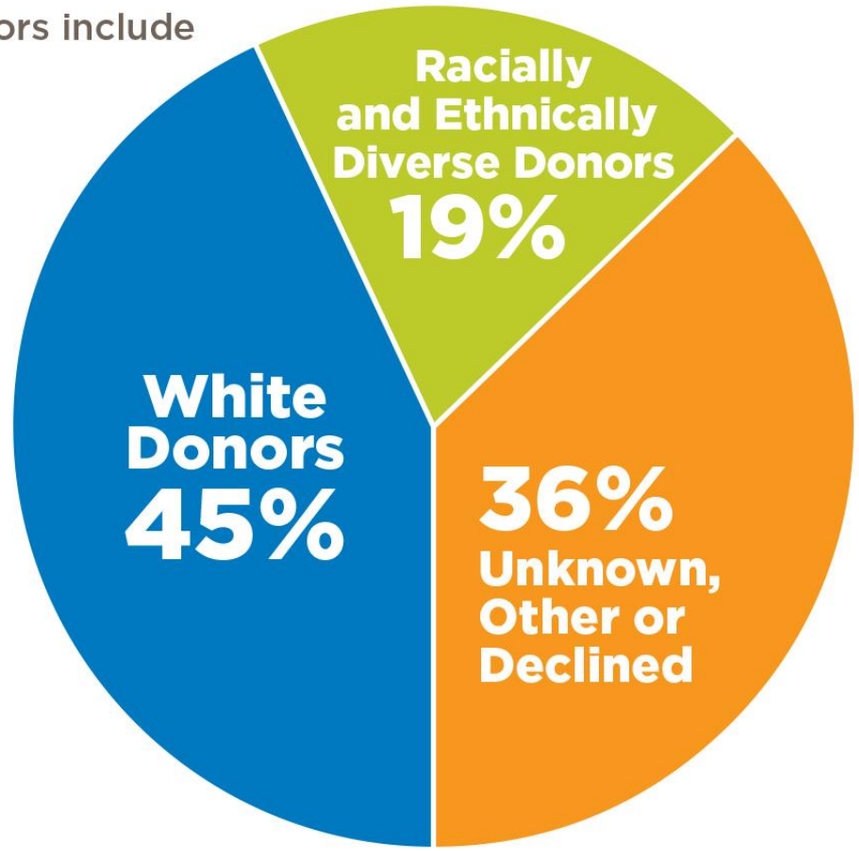
Diversity of Adult Donors on the Be The Match Registry® 2017

Racially and ethnically diverse donors include those who identify as:

- American Indian or Alaska Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander



NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

Source: National Marrow Donor Program/Be The Match FY 2017

Location of Centers Participating in the CIBMTR 2017*

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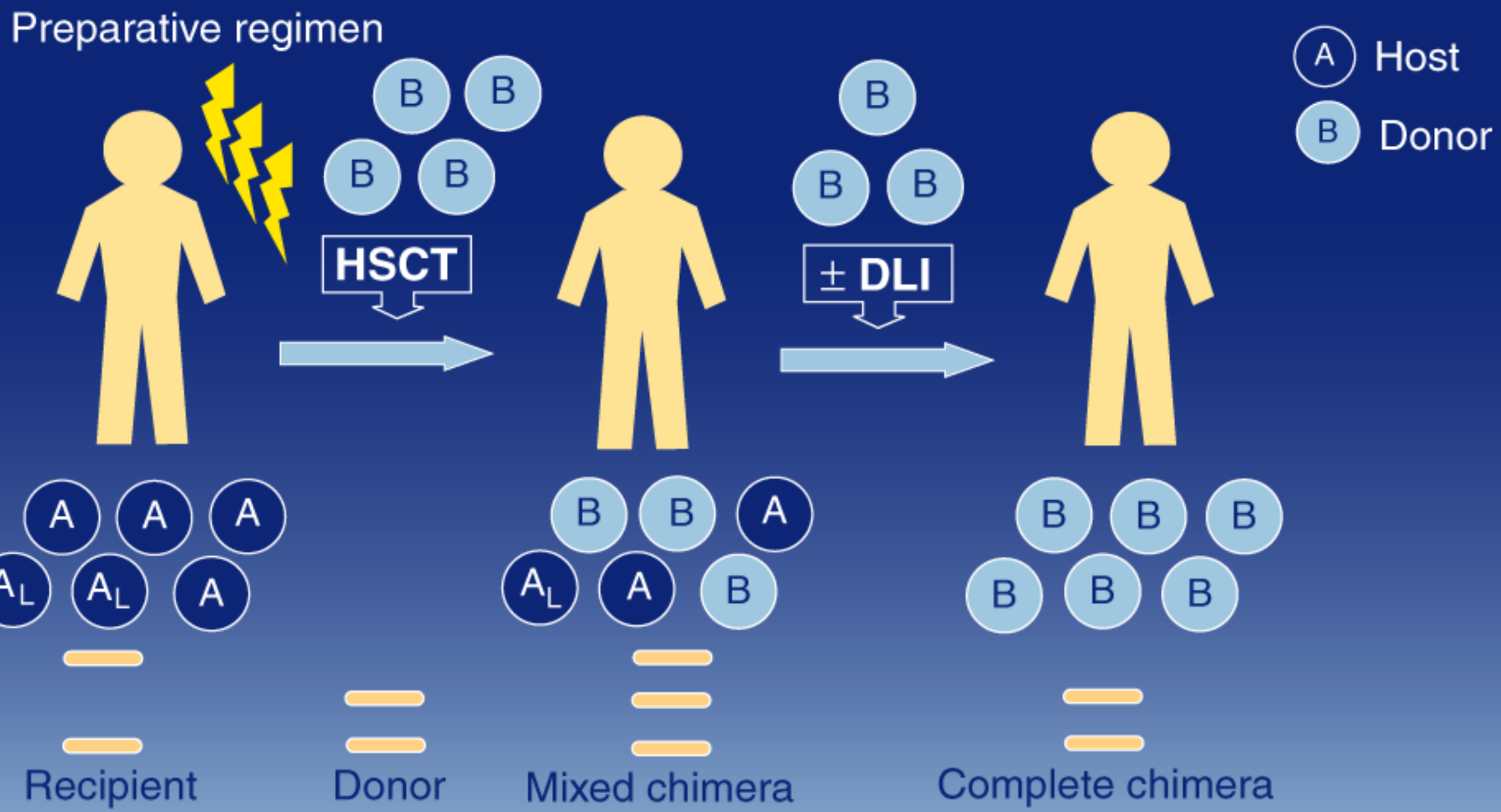
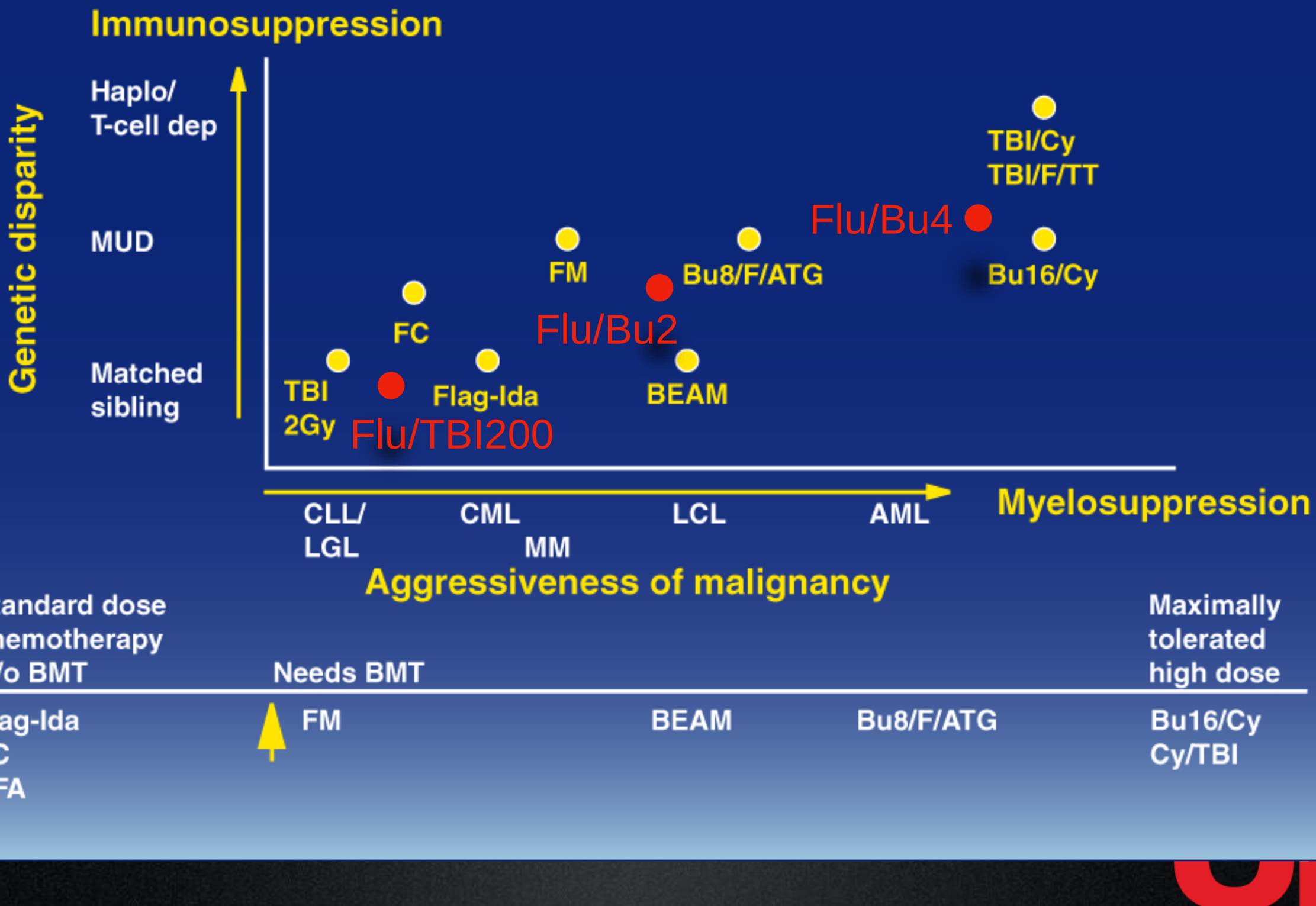
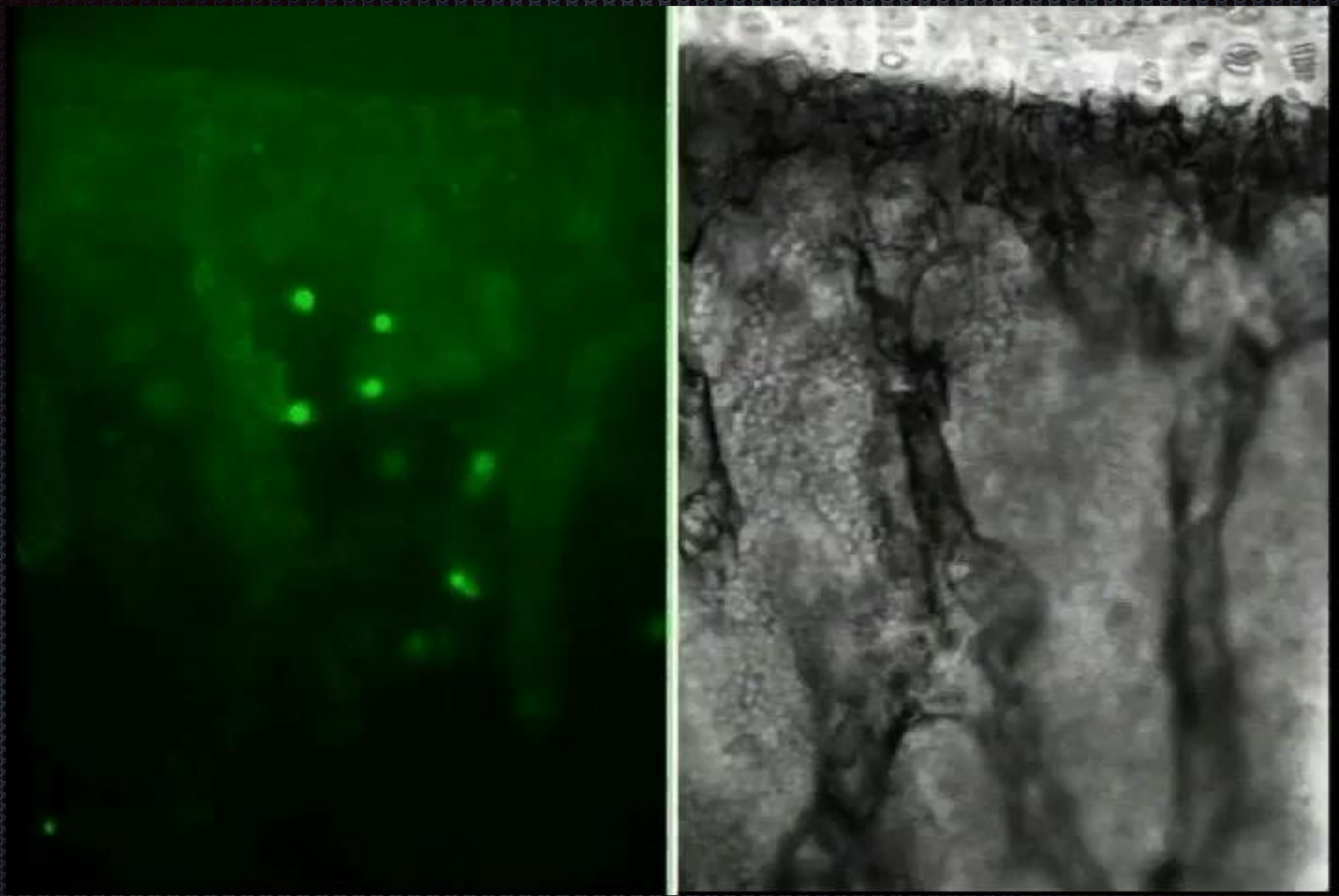
*Data through July 2017

Non-myeloablative hematopoietic cell transplant



Intensity of preparative regimens



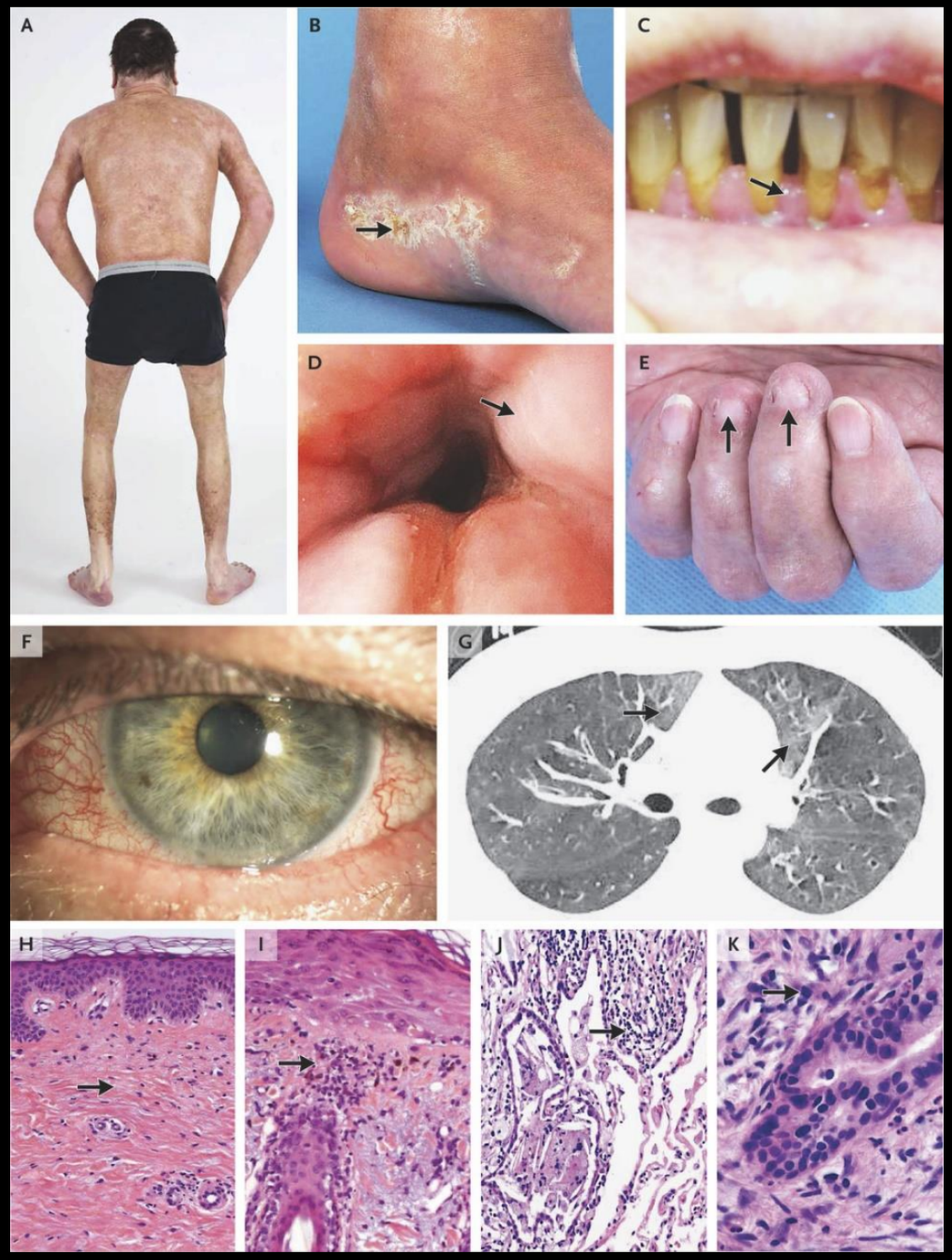


PNAS 1/06

Major problems with stem cell transplant: Infections

And for allogeneic transplant: Graft vs Host Disease

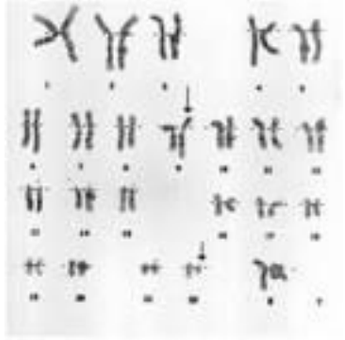
Clinical and Histopathological Findings in Chronic Graft-versus-Host Disease (GVHD).



Zeiser R, Blazar BR. N Engl J Med 2017;377:2565-2579.

The NEW ENGLAND JOURNAL of MEDICINE

Genomics: Cancer Etiology (Therapy)



The abnormality seen by Nowell & Hungerford on chromosome 22. Now known as the Philadelphia Chromosome.

Philadelphia Chromosome Discovered (bcr-abl): Mutation: Cancer (CML)

First Cancer Causing DNA Change: HRAS in Bladder Cancer

DNA Structure Discovered

Sanger Method for DNA Sequencing

Abl inhibitor Discovered (Imatinib)

1953 **1960** **1977** **1982** **1998**

50 YEARS

Genomics: Cancer Etiology (Therapy)

HAP MAP
Database of all
Inherited variations

Detailed understanding
Of tumor genetic
Evolution

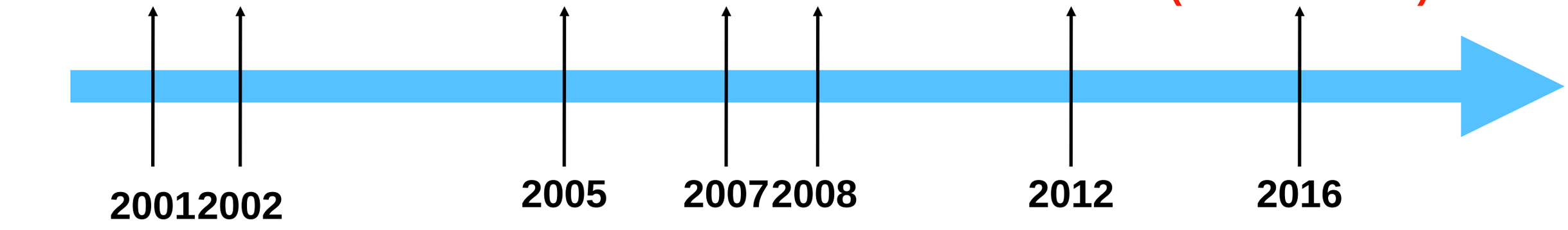
BRAF mutations
Discovered in subset
Of Melanoma

International Cancer
Genome Consortium started,
First cancer Genome (AML)

First Draft
Human Genome

First GWAS studies
In cancer

BRAF inhibitor
Discovered for Melanoma
(Vemurafenib)



20012002 **2005** **20072008** **2012** **2016**

15 YEARS

Cancer Immunity Poorly Understood for a LONG time

- 100 years of evolution
- T cells in cancer patients detect tumor-associated epitopes (Thierry Boon, Brussels)
- Peptide vaccines to boost T cell responses: few clinical responses
- Cytokines to boost T cell responses (IL-2, interferon): few clinical responses and toxicity

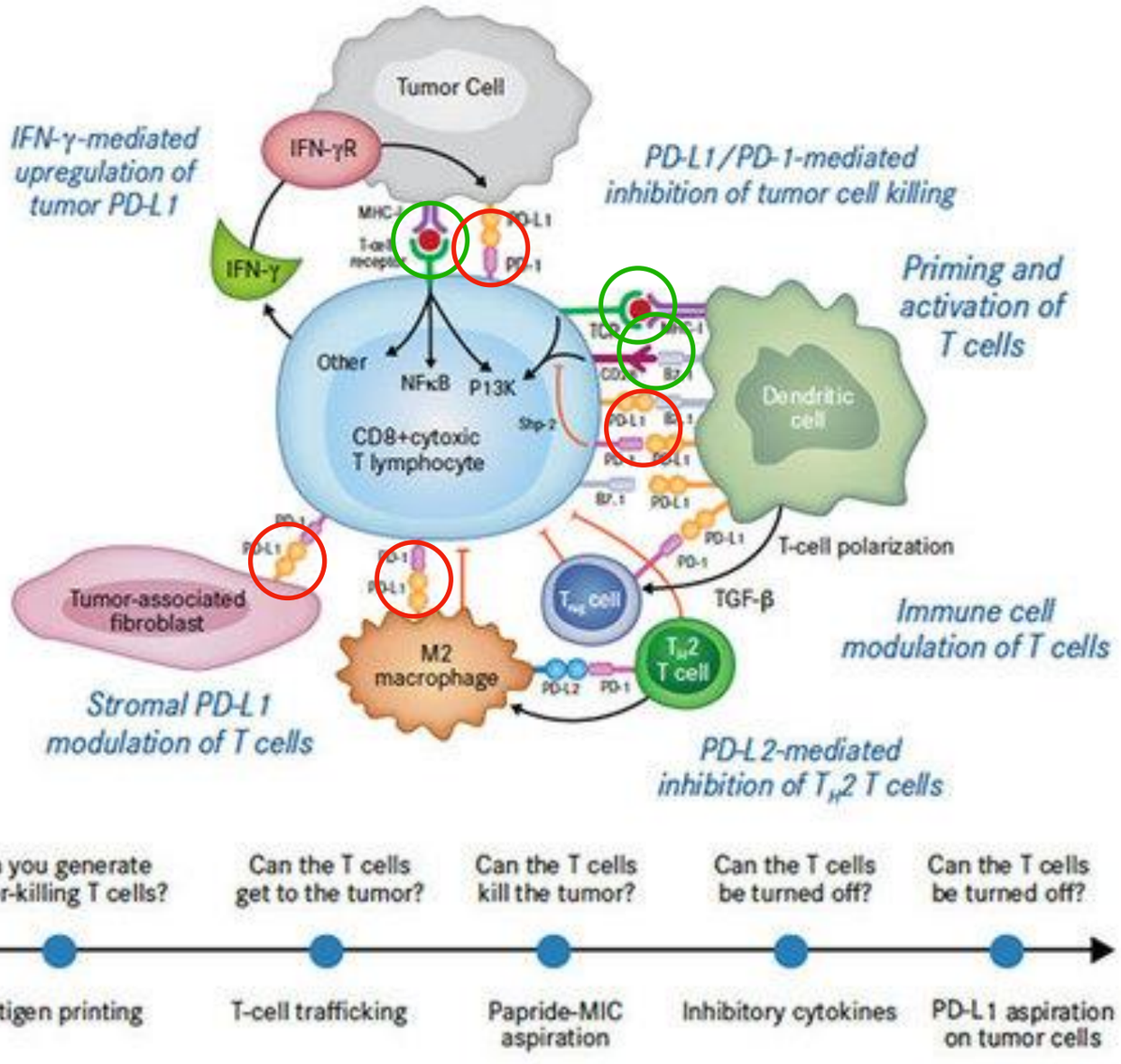
Views of immunity

- Discoveries in mice led to understanding of the immune system and associations with cancer

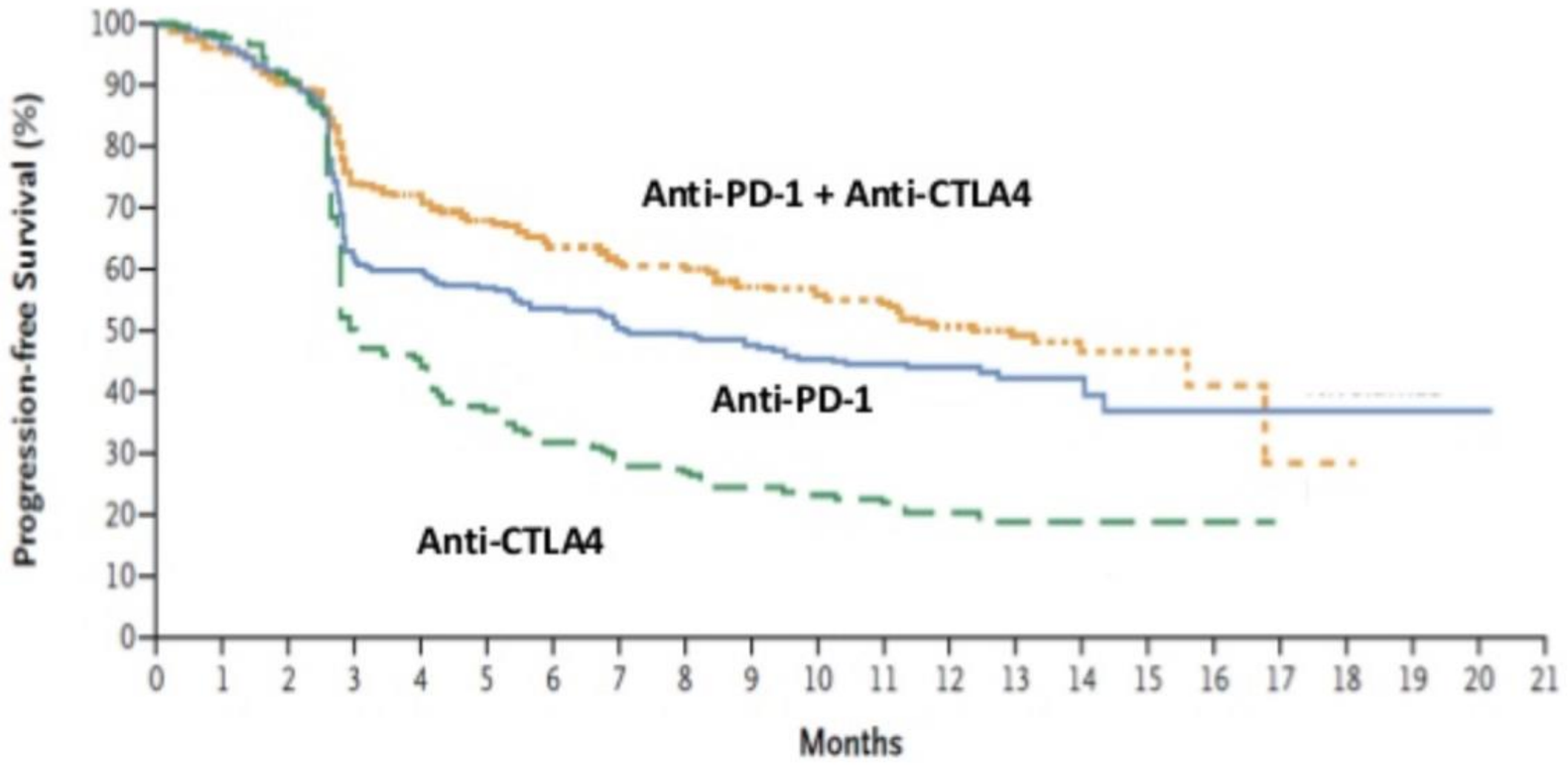
- Self vs Non-self dominated thought in immunology arguing against an important role for the immune system in cancer surveillance (a “self” tissue)

- This changed with the realization that the immune system evolved to recognize “danger” and with mouse system defective in various aspects of immunity with increased susceptibility to cancer

Cytotoxic T cell



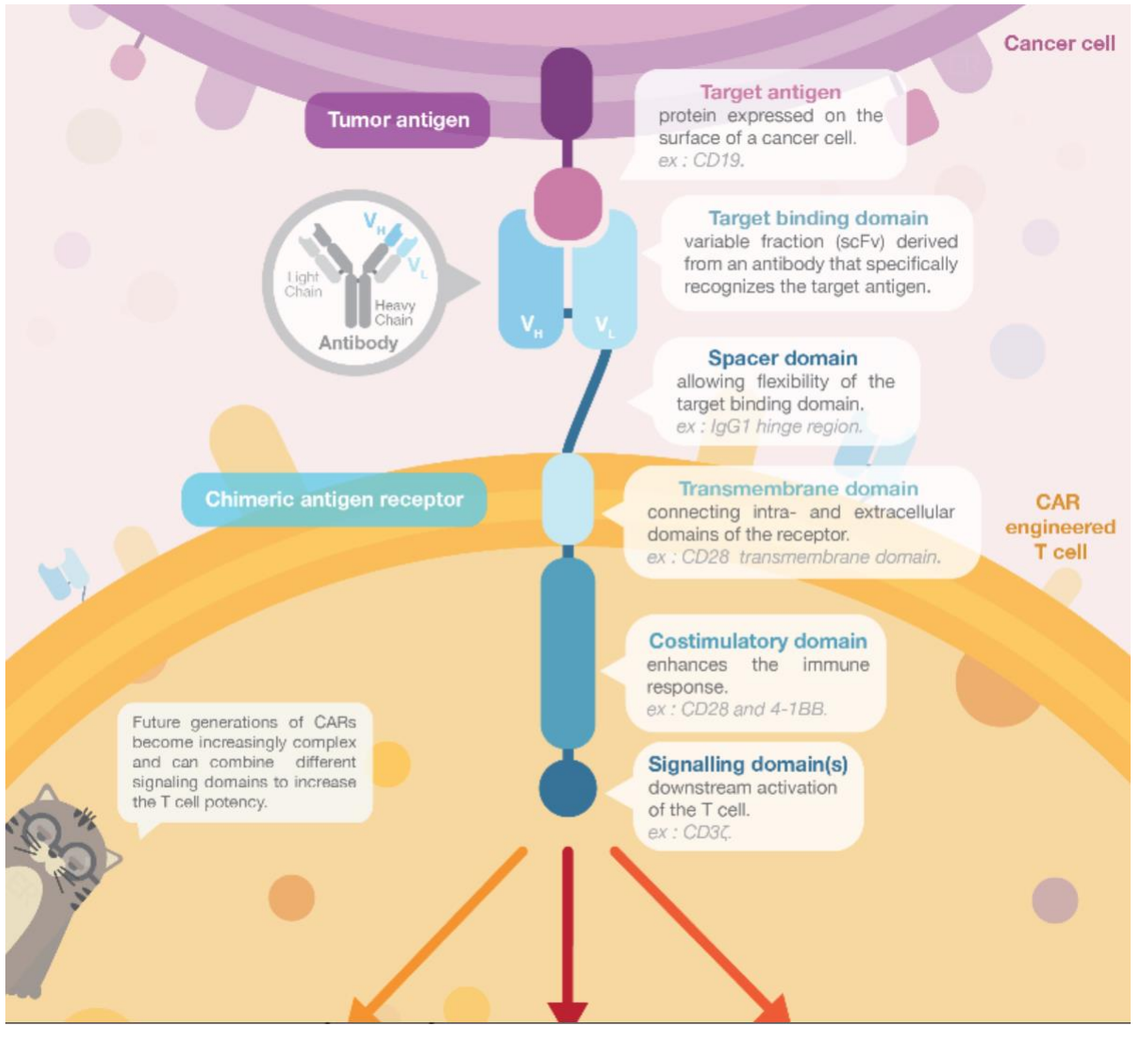
Anti-CTLA4 and Anti-PD1 in Melanoma



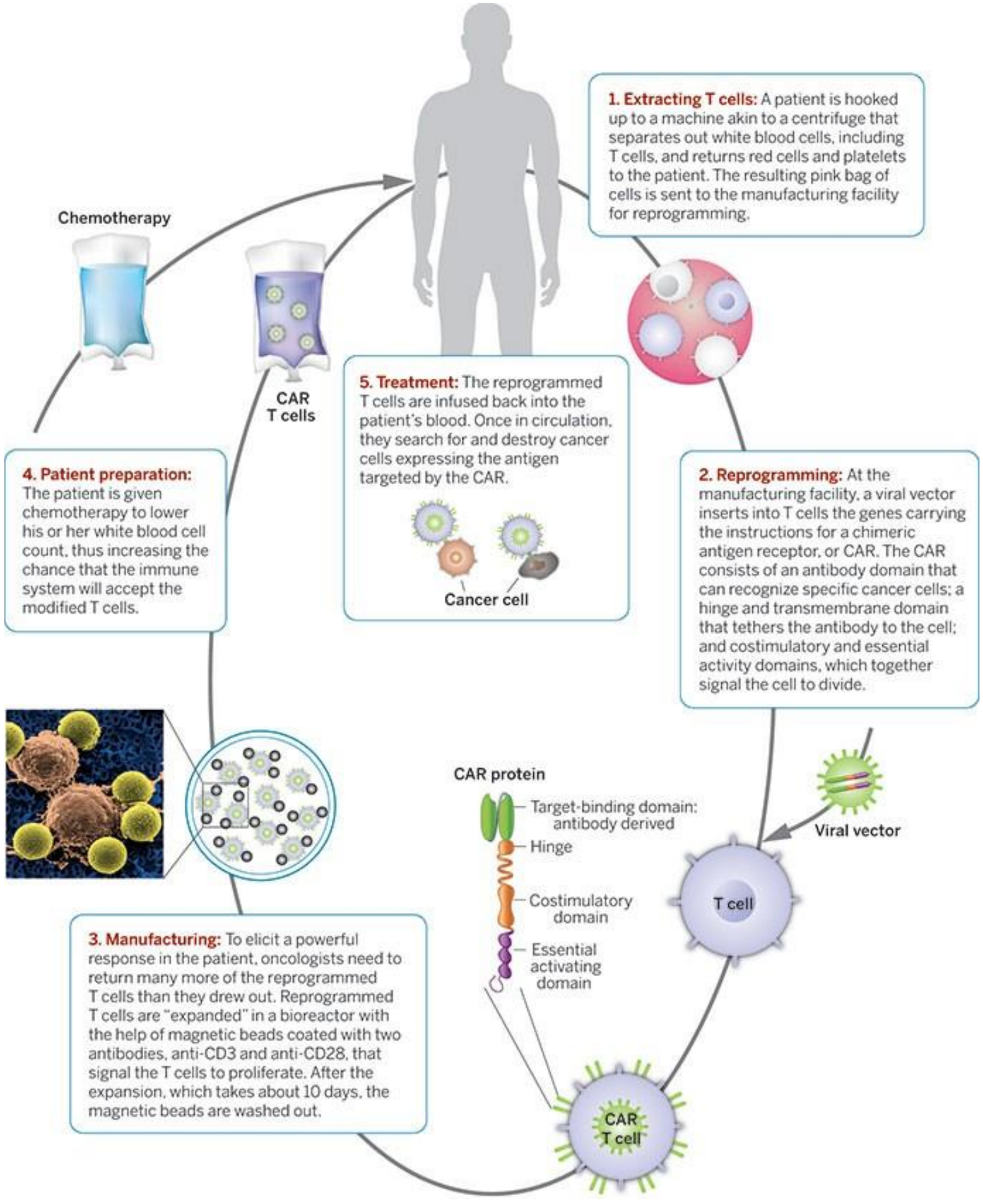
NEJM 363:8, 2010
NEJM 372:2521, 2015
NEJM 373:23, 2015

What about:
Cancers not sensitive to the allo effect?
Cancers growing too fast for allo effect to work?
Cancers not responsive to NK attack or TIL therapy?

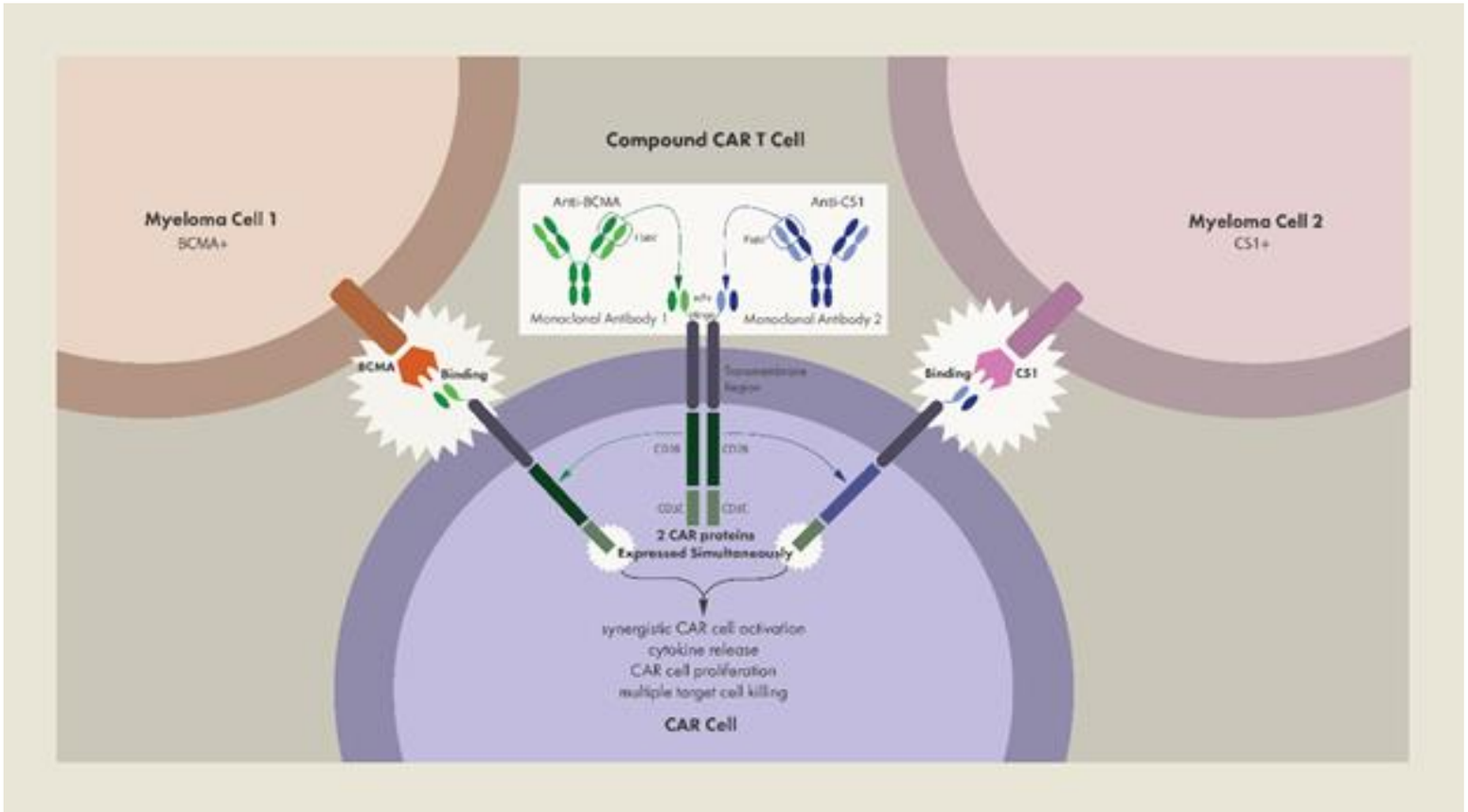
Chimeric Antigen Receptor (CAR) T cells



Car-T Therapy: Clinical Protocol



Myeloma Compound Car-T
PI: Robert Emmons



iCell Gene Therapeutics

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Questions?