BMT: The Original Immunotherapy

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Conflict of Interest Disclosure

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Autologous and Allogeneic Hematopoietic Cell Transplantation

- Autologous HCT
  - High dose chemotherapy: anti-tumor activity
  - autologous HSC rescue
- Allogeneic HCT
  - Conditioning (total body irradiation, chemotherapy, antibodies): anti-tumor activity, tolerance and GVHD prophylaxis
  - Allogeneic HSC rescue

Diseases Commonly Treated with Hematopoietic Cell Transplantation

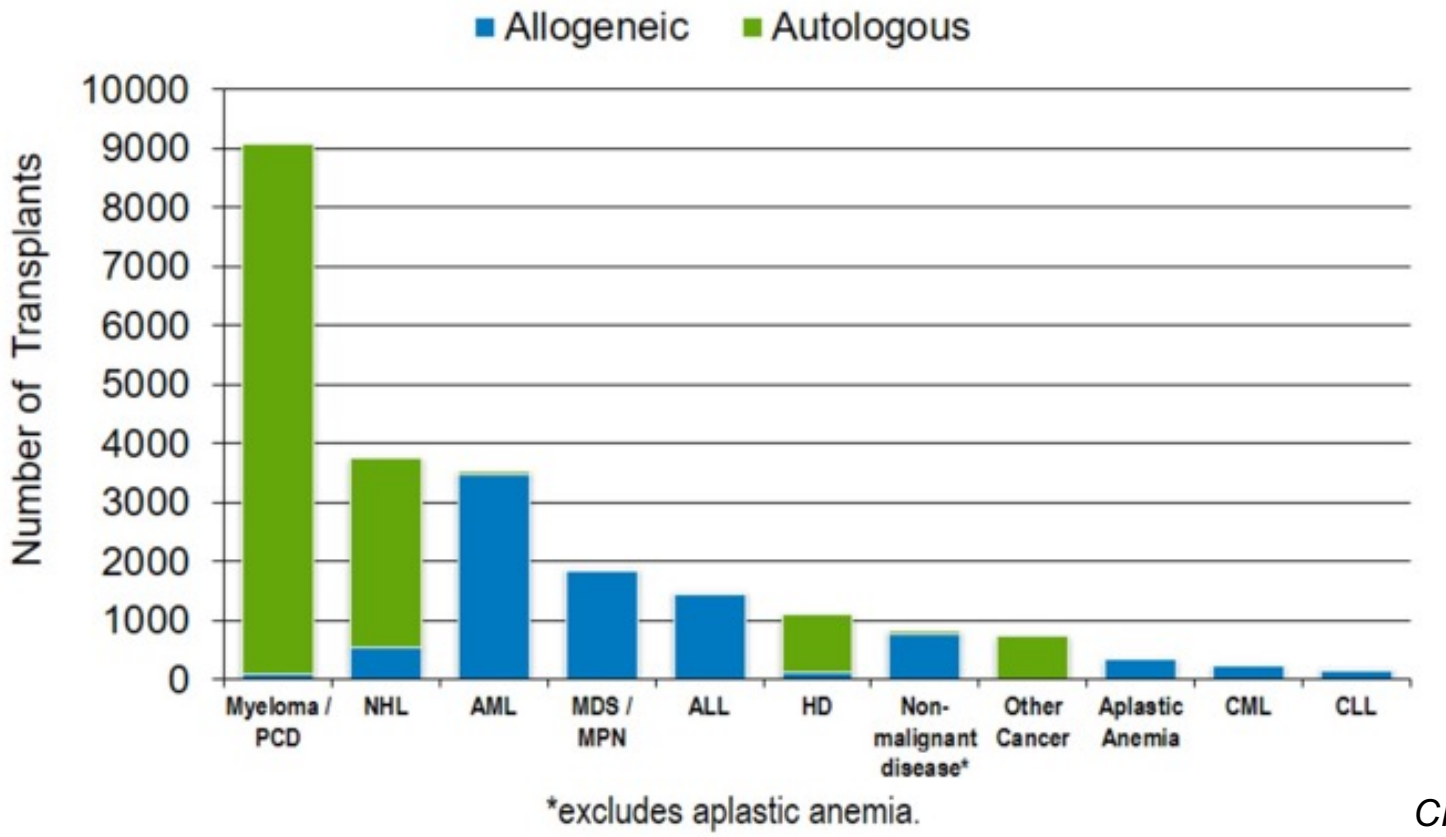
Autologous transplantation

- **Cancers**
  - Multiple myeloma
  - Non-Hodgkin's lymphoma
  - Hodgkin's disease
  - Acute myeloid leukemia
  - Neuroblastoma
  - Ovarian cancer
  - Germ-cell tumors
- **Other diseases**
  - Autoimmune disorders
  - Amyloidosis

Allogeneic transplantation

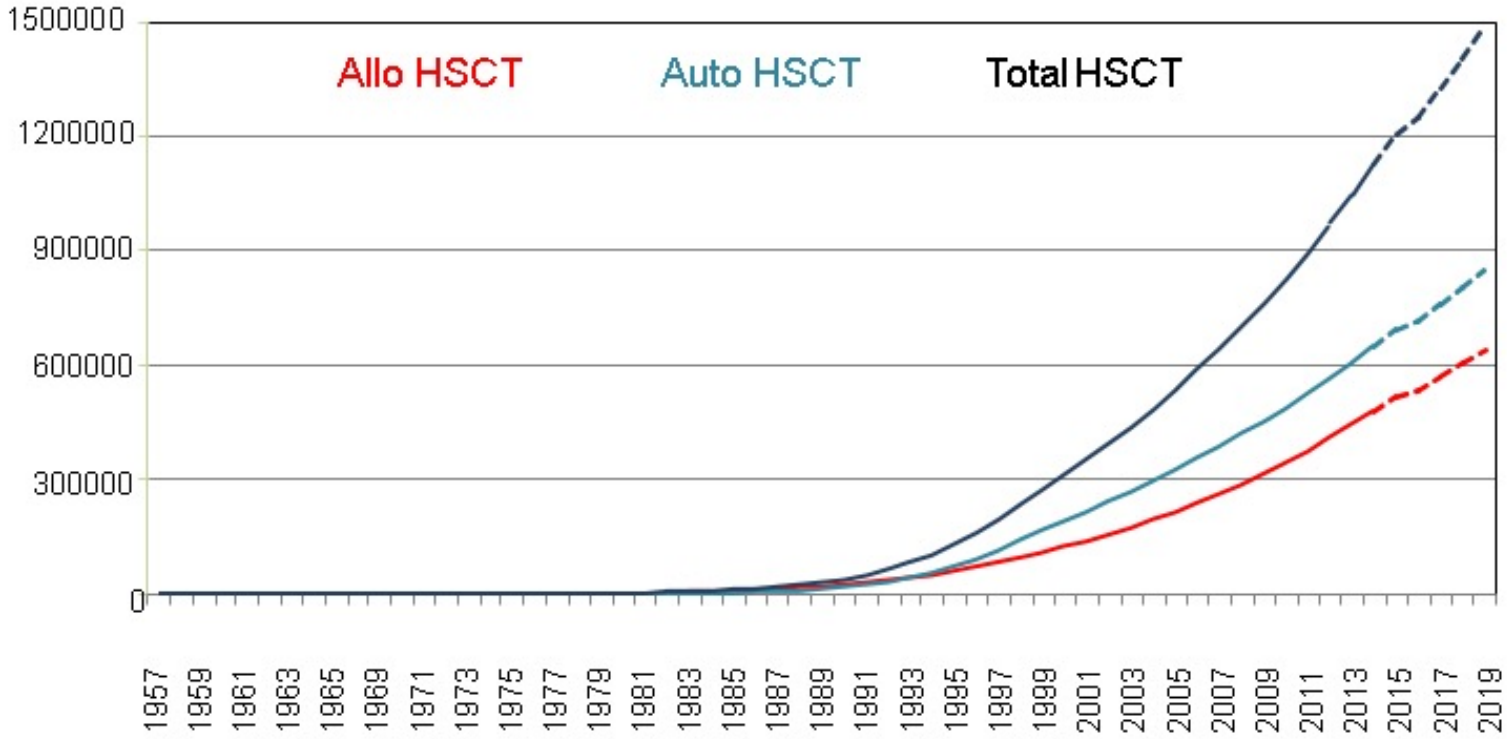
- **Cancers**
  - Acute myeloid leukemia
  - Acute lymphoblastic leukemia
  - Chronic myeloid leukemia
  - Myelodysplastic syndromes
  - Myeloproliferative disorders
  - Non-Hodgkin's lymphoma Hodgkin's disease
  - Chronic lymphocytic leukemia
  - Multiple myeloma
  - Juvenile chronic myeloid leukemia
- **Other diseases**
  - Aplastic anemia
  - Paroxysmal nocturnal hemoglobinuria Fanconi's anemia
  - Blackfan–Diamond anemia
  - Thalassemia major
  - Sickle cell anemia
  - Severe combined immunodeficiency
  - Wiskott–Aldrich syndrome
  - Inborn errors of metabolism

Indications for hematopoietic cell transplant in the US, 2018

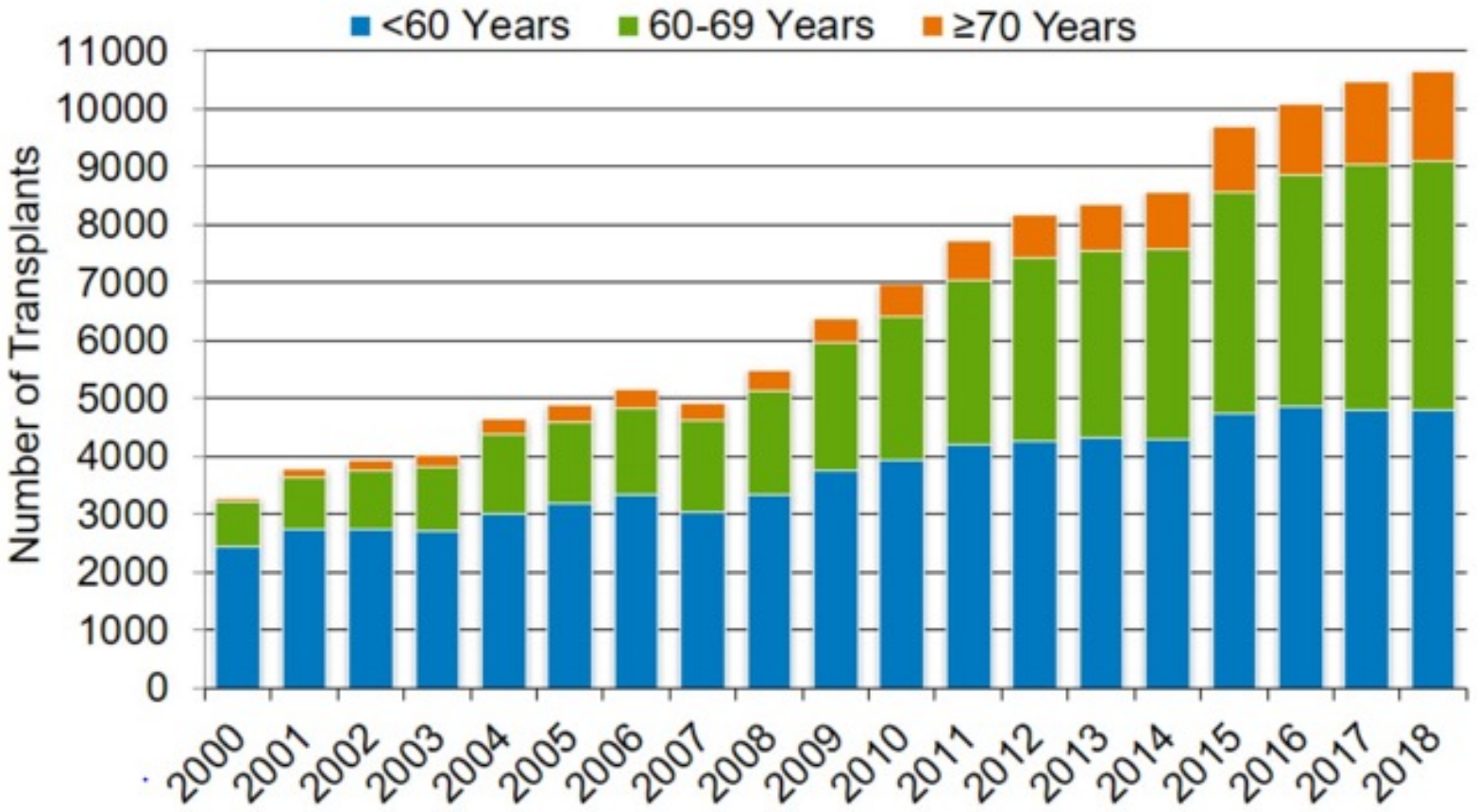


CIBMTR Summary Slides, 2019

WBMT global survey: predicted activity 2020



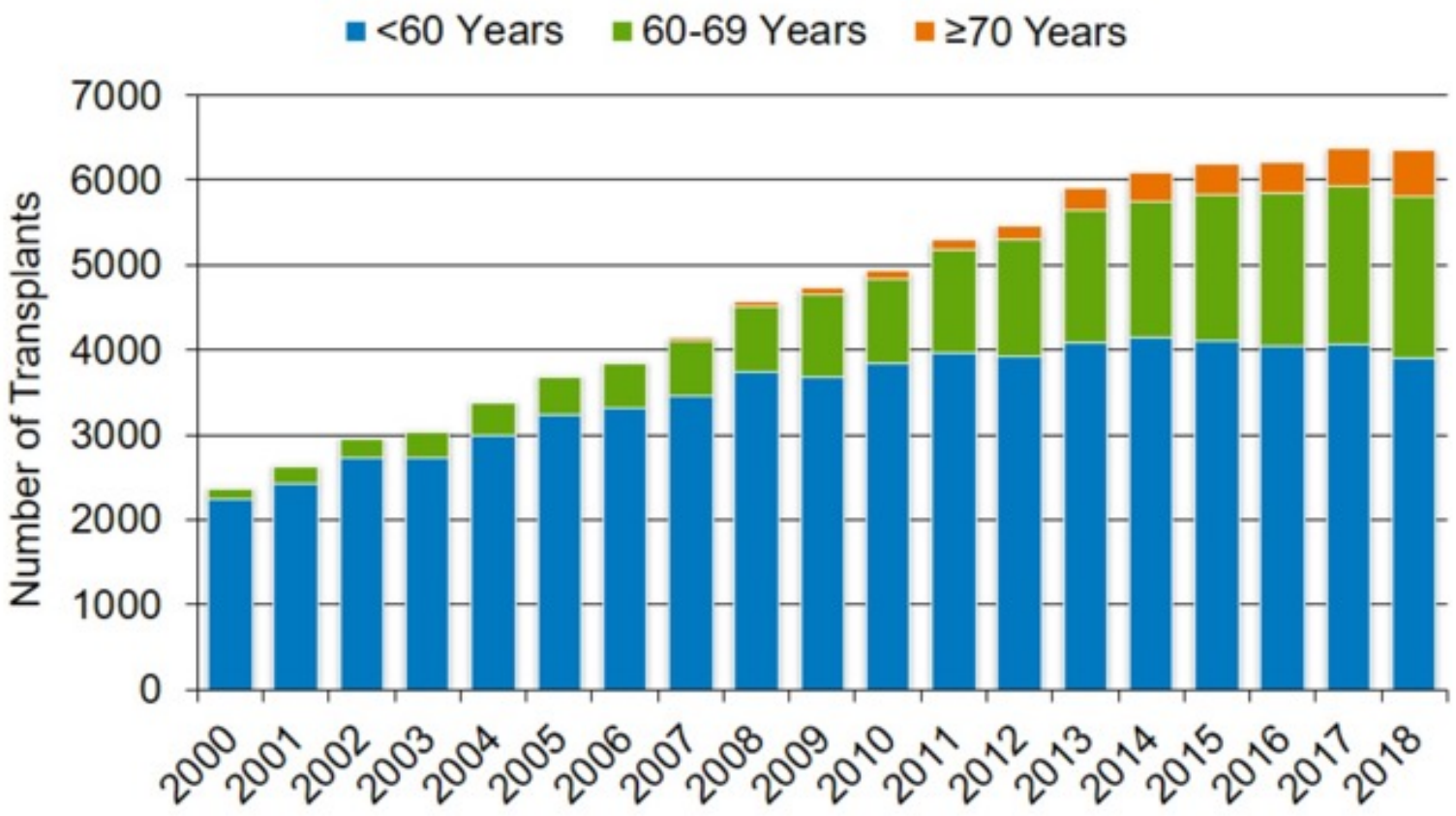
Trends in autologous HCT in the US by recipient age



^Transplants for NHL, HD, MM

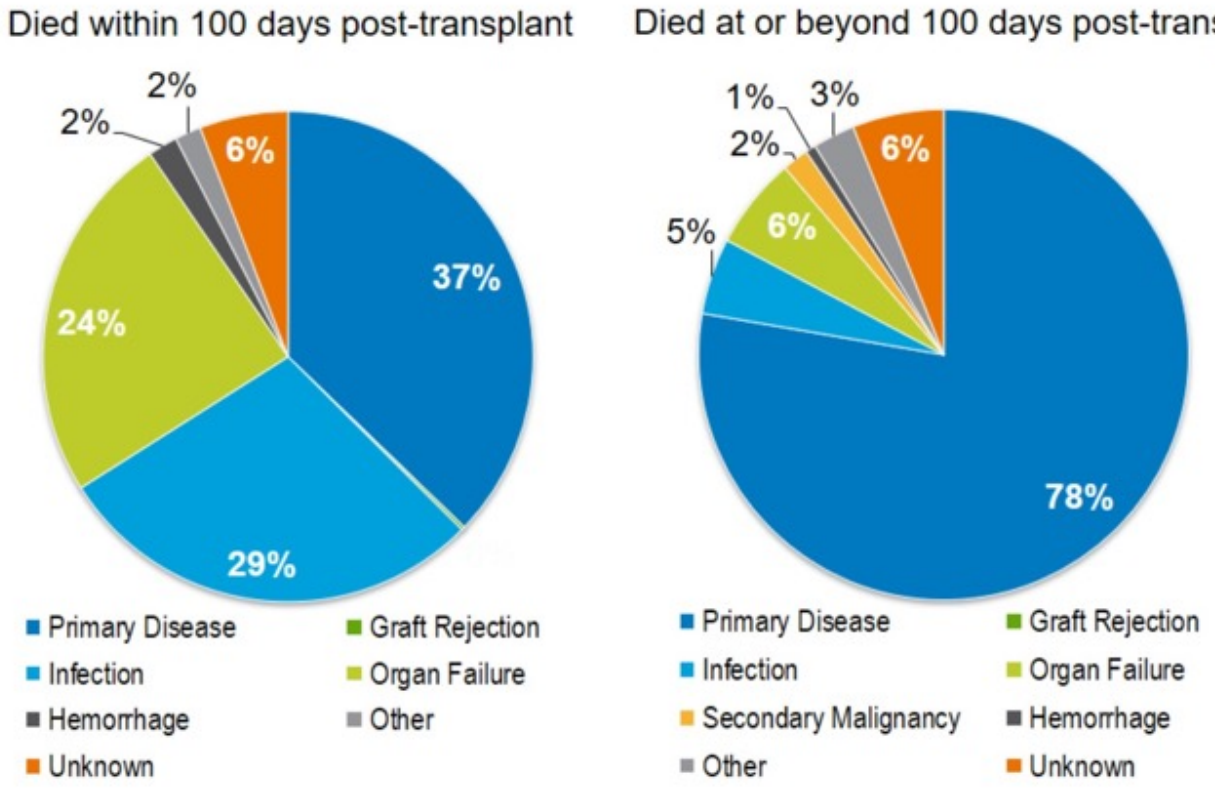
CIBMTR Summary Slides, 2019

Trends in allogeneic HCT in the US by recipient age



CIBMTR Summary Slides, 2019

Mortality after auto-HCT: relapse



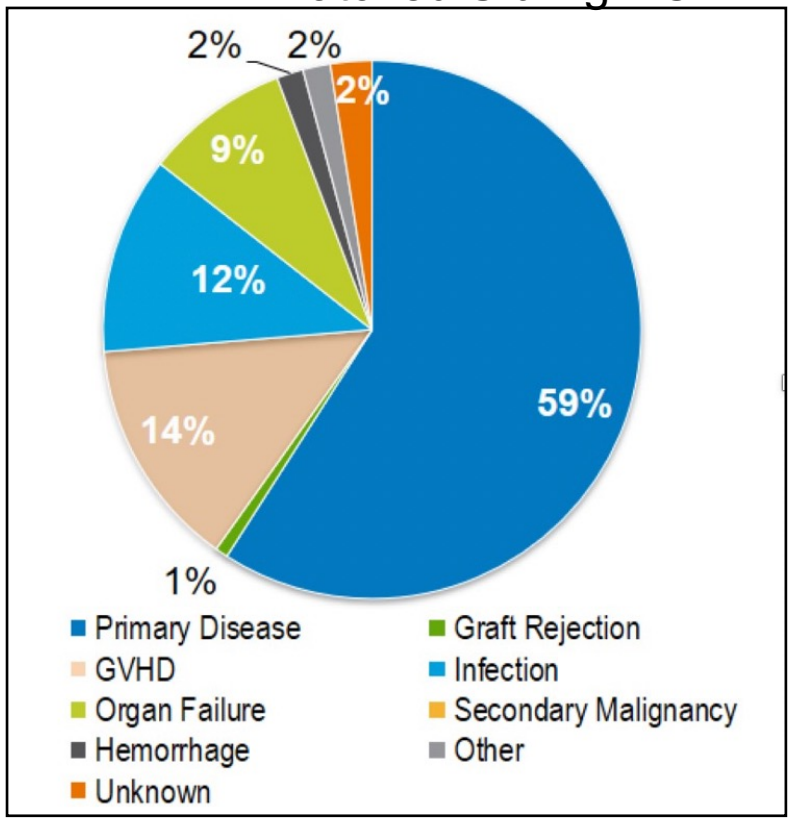
*Data reflects 3-year mortality

CIBMTR Summary Slides, 2019

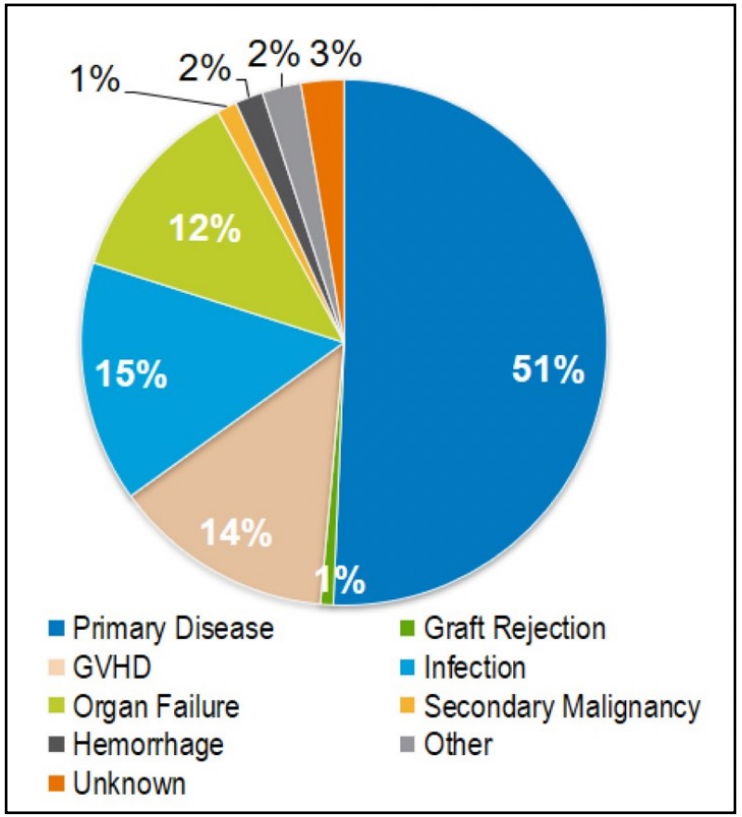
Mortality after Allo-HCT: Relapse, GVHD and Infections

Cause of death at or beyond 100 days post-HCT

HLA-Matched Sibling HCT

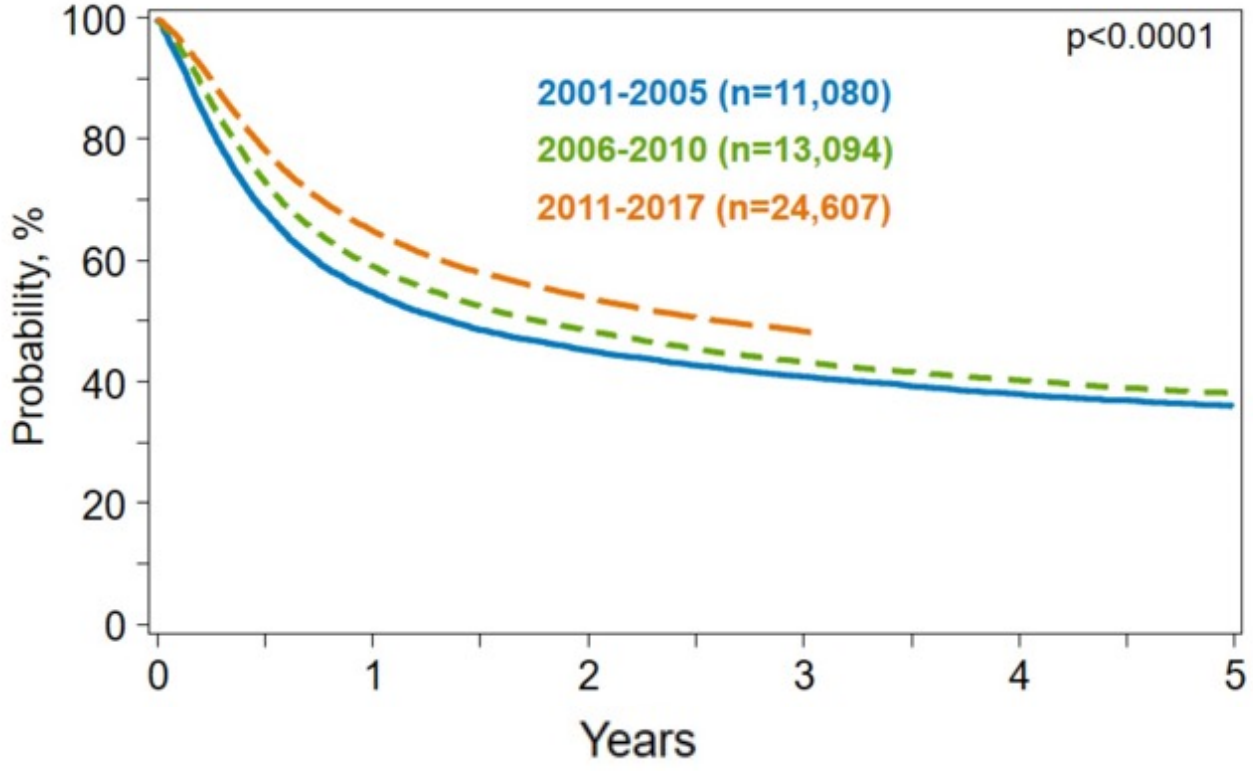


Unrelated donor HCT



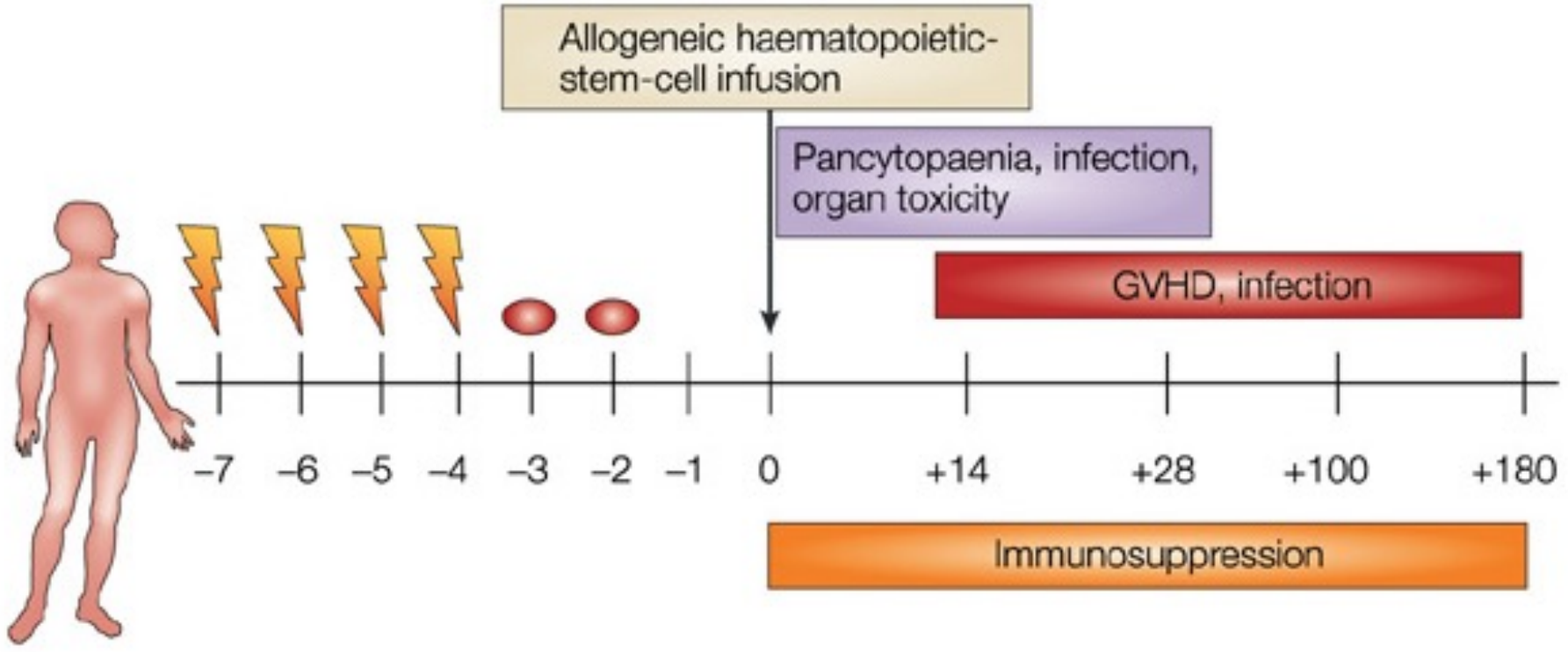
D'Souza et al., BBBMT, 2020 (CIBMTR)

Trends in survival after allogeneic HCT for AML ≥ 18, 2001-2017



CIBMTR Summary Slides, 2019

Allo-HSCT in a timeline



Bleakley & Riddell, Nat Rev Cancer 2004

Conditioning before allo-HCT

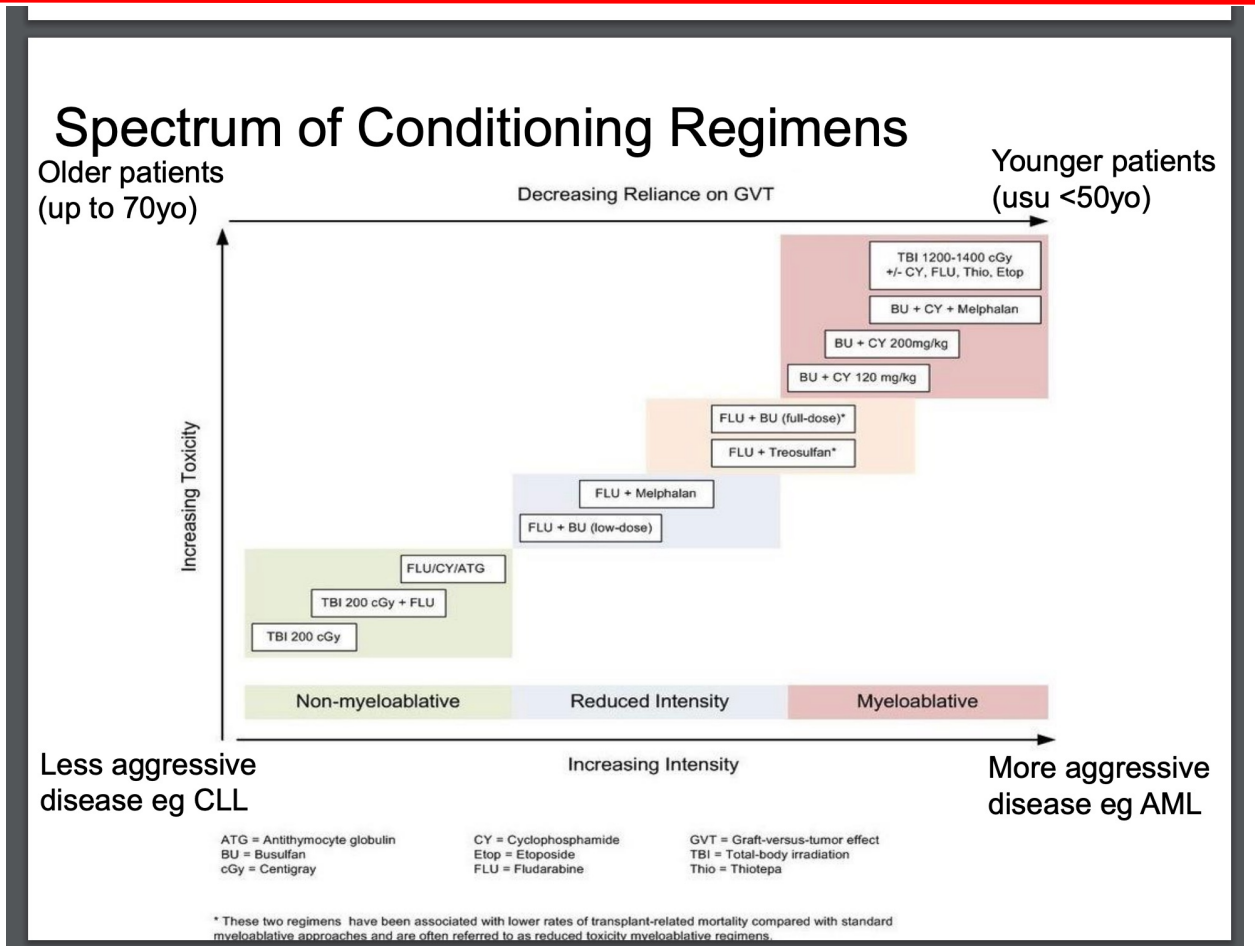
- 2 goals (in case of malignant diseases):
  - Prevent graft rejection
  - Decrease tumor burden

- Myeloablative (MA) or High-dose Regimens:
  - Ablate hematopoiesis
  - No autologous hematologic recovery, hematopoietic stem cell support necessary

- Nonmyeloablative regimens:
  - No hematopoietic stem cell support necessary
  - Tolerance for allograft

- Reduced-intensity Conditioning (RIC) Regimens:
  - Do not fit the definition for myeloablative or nonmyeloablative conditioning
  - No/very slow autologous hematologic recovery, hematopoietic stem cell support necessary
  - Dose of alkylating agent or TBI is generally reduced, by at least 30% (when compared to MA regimens)

Choice of a conditioning regimen



Adapted from aci.health.nsw.gov.au/

Determinants of Engraftment

Host:

- Intensive prior therapy causing recipient immune suppression
- Pre-existing HLA-antibodies

Donor:

- HLA-matching most important
- Cell dose also potential issue especially in CBT

Conditioning:

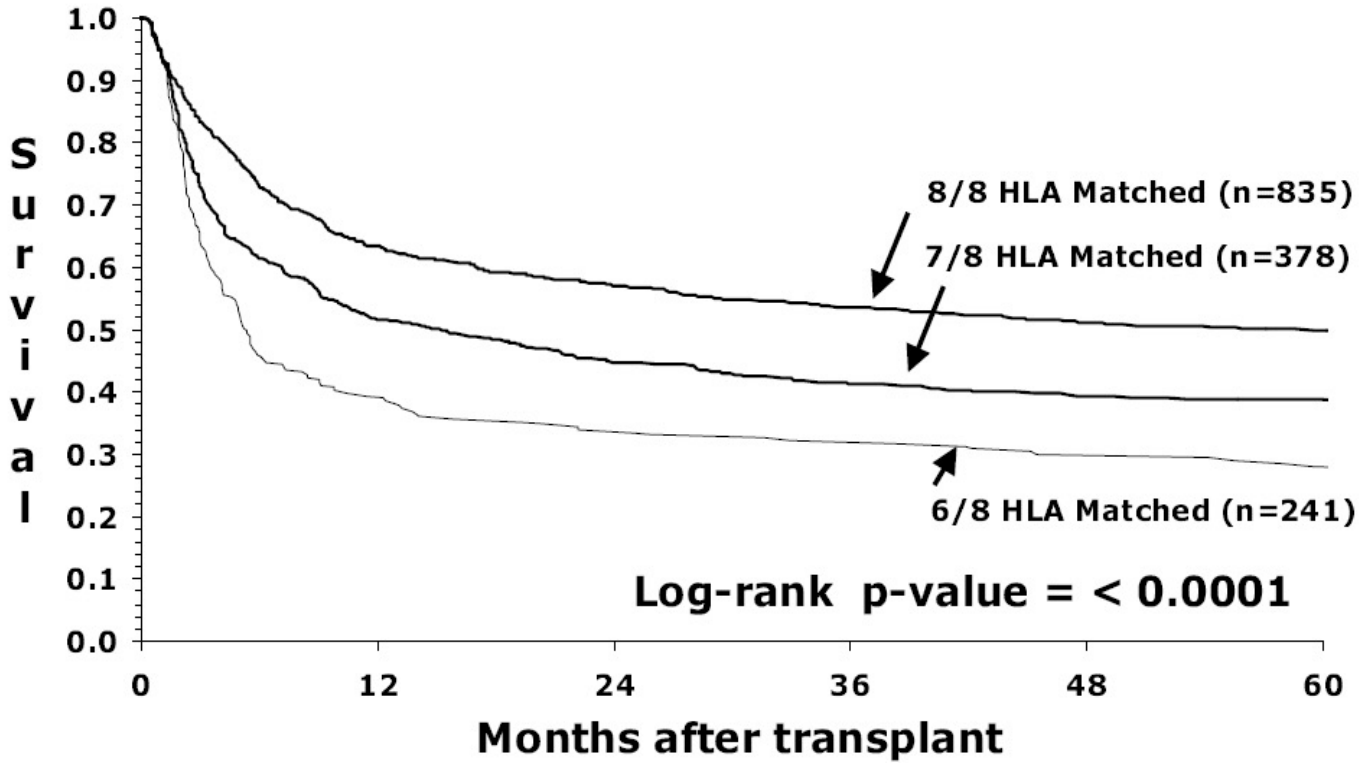
- More intensive conditioning regimens & ATG can decrease rejection.

Chimerism

Definition: the presence of donor hematopoietic cells in a transplant recipient

- **Full chimerism:** only the donor alleles are detected in the recipient.
- **Mixed chimerism:** a mixture of donor and recipient alleles are present.
- **Graft failure:** only recipient alleles are detectable.

Better HLA match correlates with superior Overall Survival

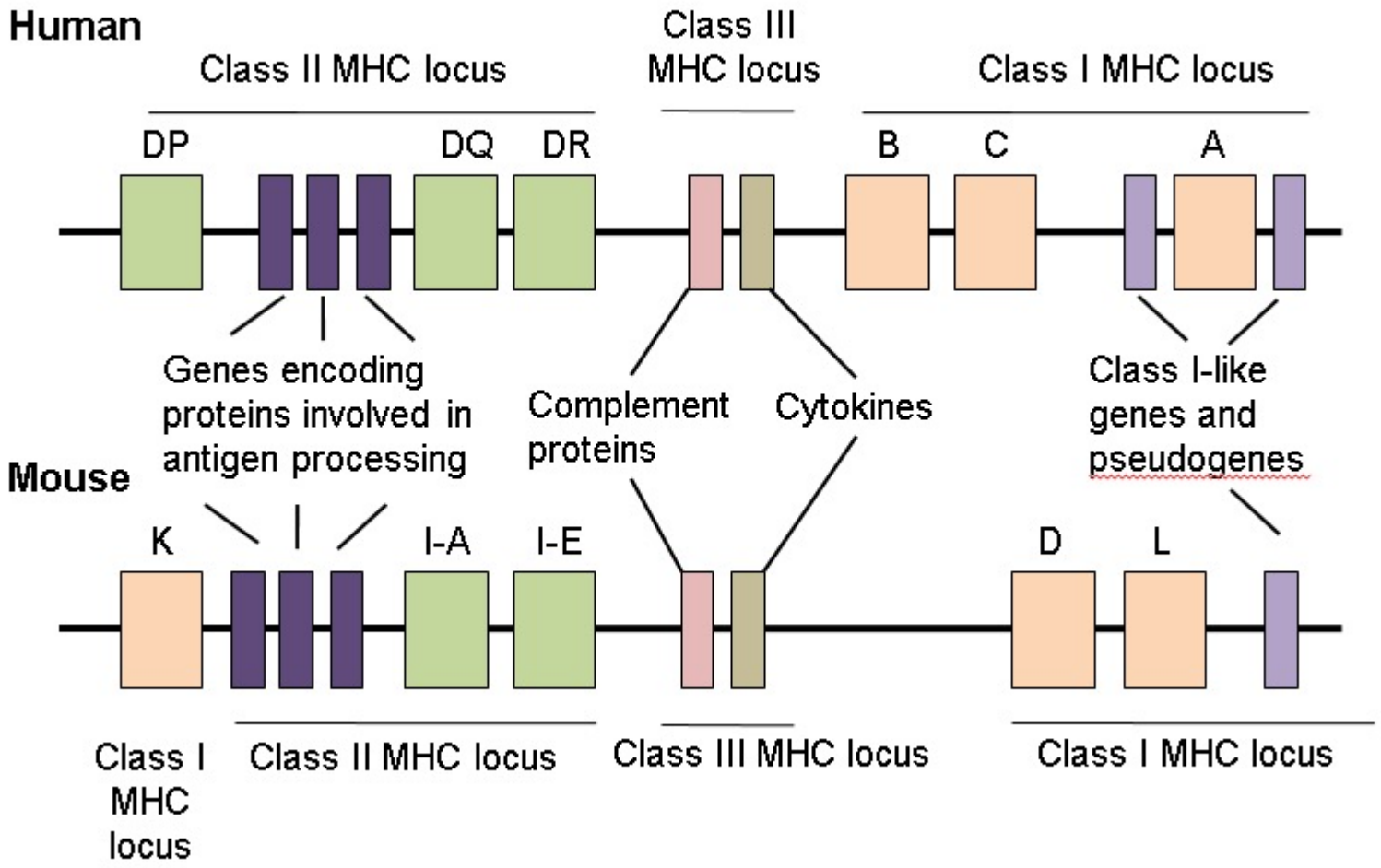


Underlying disease:

- AML
- ALL
- MDS
- CML

Lee SJ, et al. (2007) Blood.

Schematics of human and mouse MHC loci



HLA polymorphisms

HLA molecules:

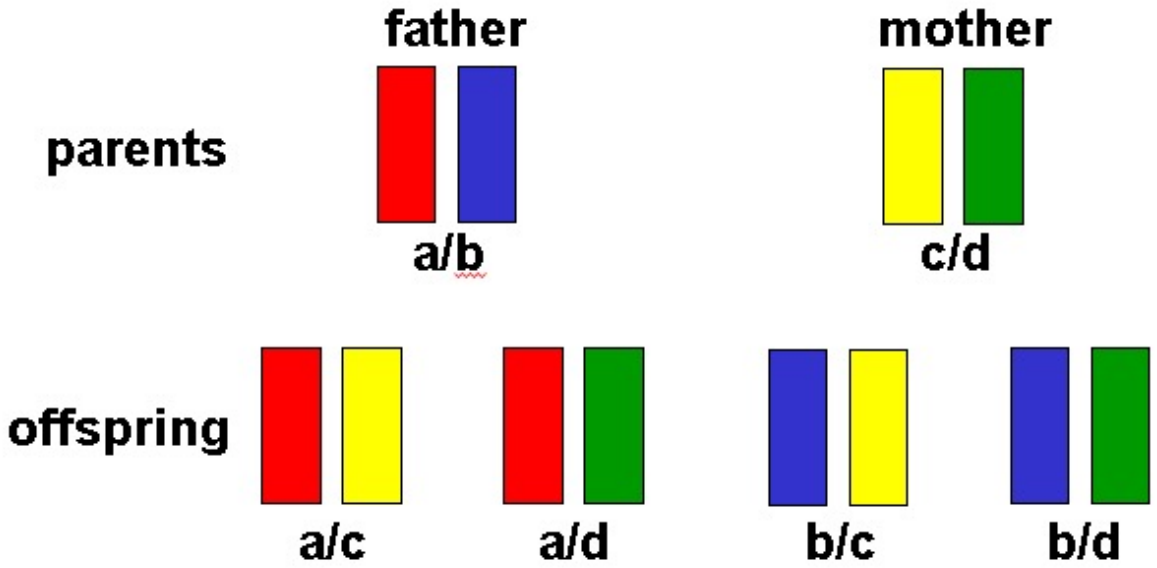
- conserved in regions that bind the TCR and co-receptors
- extensive diversity in their peptide binding regions
- diversity leads to dramatic differences in peptide binding and antigen presentation

Jin P and Wang E, J Transl Med, 2003

	Number of alleles
HLA Class I Alleles	21,040
HLA Class II Alleles	7,898
HLA Alleles	938
Other non-HLA Alleles	479

http://hla.alleles.org/nomenclature/stats.html, as of February 2021

Inheritance patterns of codominant HLA alleles



Probability of matching:

	# matched haplotypes		
	0	1	2
Parent-> child	0	100	0
Sib -> Sib	25	50	25

HLA typing

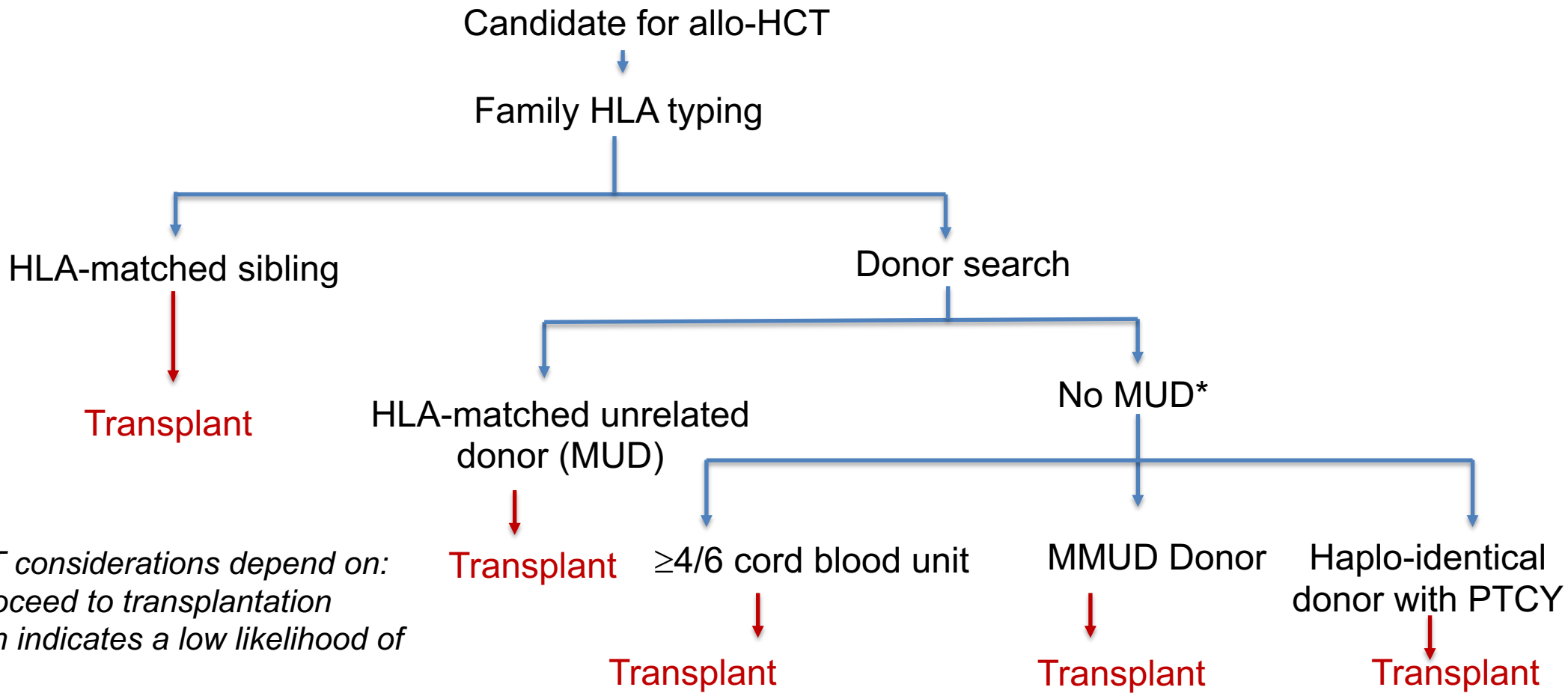
- Serologic typing: used for antigen matching
  - Detects HLA proteins using serologic antibody-based assays
  - Can be used for typing within families
  - Largely replaced by molecular typing

- Molecular typing*: used for allele matching
  - Detects HLA genes by DNA sequencing
  - Necessary for HLA matching in unrelated donor transplants
  - Preferred for HLA matching related donor transplants

  - *High resolution:* defines sets of alleles that encode the same protein sequence for the HLA molecule's antigen binding site (eg HLA-A*02:1010)
  - *Low resolution*: provides information regarding the allele group, but not the specific HLA protein (eg, HLA-A*02)

**American Red Cross – Blood services*

Match and Typing Recommendations: Source selection



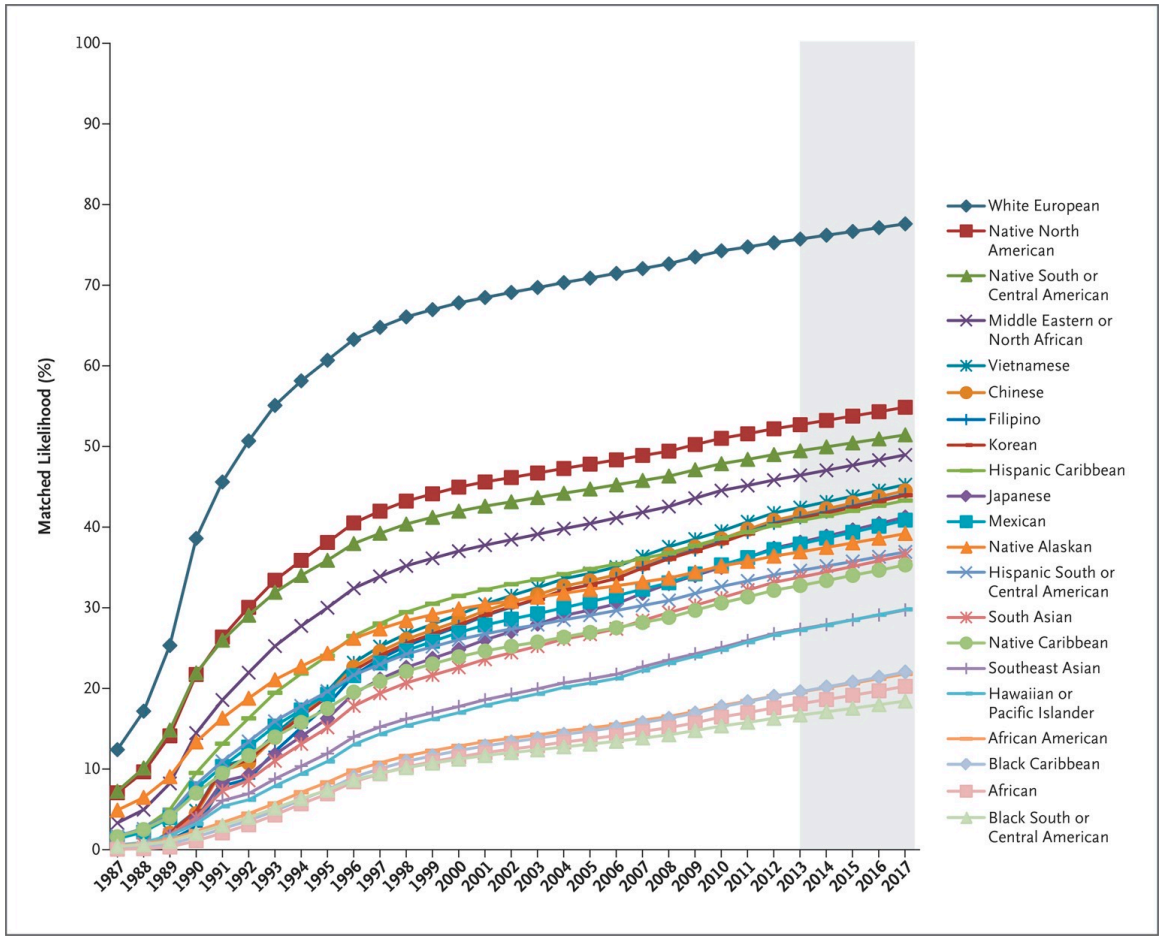
**UCT and haplo-HCT considerations depend on:*

- *urgent need to proceed to transplantation*
- *preliminary search indicates a low likelihood of finding an MUD.*

Donors for Allogeneic Bone Marrow Transplantation

- Only 30% of patients have an HLA-identical sibling
- 30-80% have a matched unrelated donor
- Mean interval from search to transplant: 4 months
- <20% of donor searches result in a transplant
- More than 27 million donors are registered in the international database (*www.bmdw.org*)

Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017

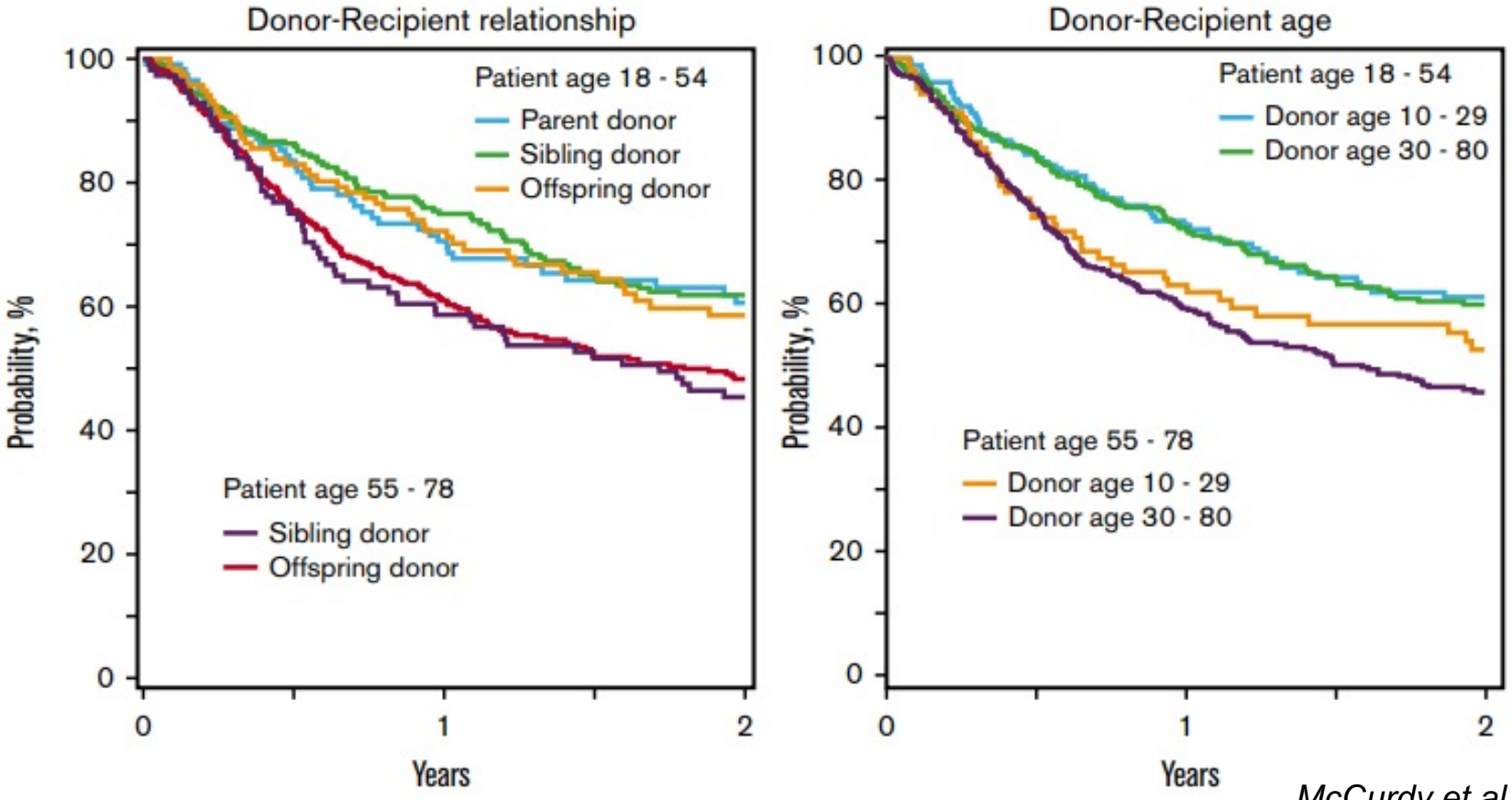


Gragert L, et al. N Engl J Med. 2014

Allograft characteristics

	Cord blood	Matched sibling	Unrelated	Haplo/PT-Cy
Acquisition	Fastest (<2 weeks)	Intermediate (2-4 weeks)	Slowest (4-8 weeks)	Intermediate (2-4 weeks)
Availability	Almost universal	30%	30-80%	>80%
Cost	Highest	Low	High	Low
GVHD	Int-high (low cGVHD)	Low-Int	Intermediate	Int (low cGVHD)
Immune reconstitution*	Poor	Best	Good	Intermediate

Haploidentical donor age is the only factor predictive for survival



McCurdy et al. Blood Advances 2018

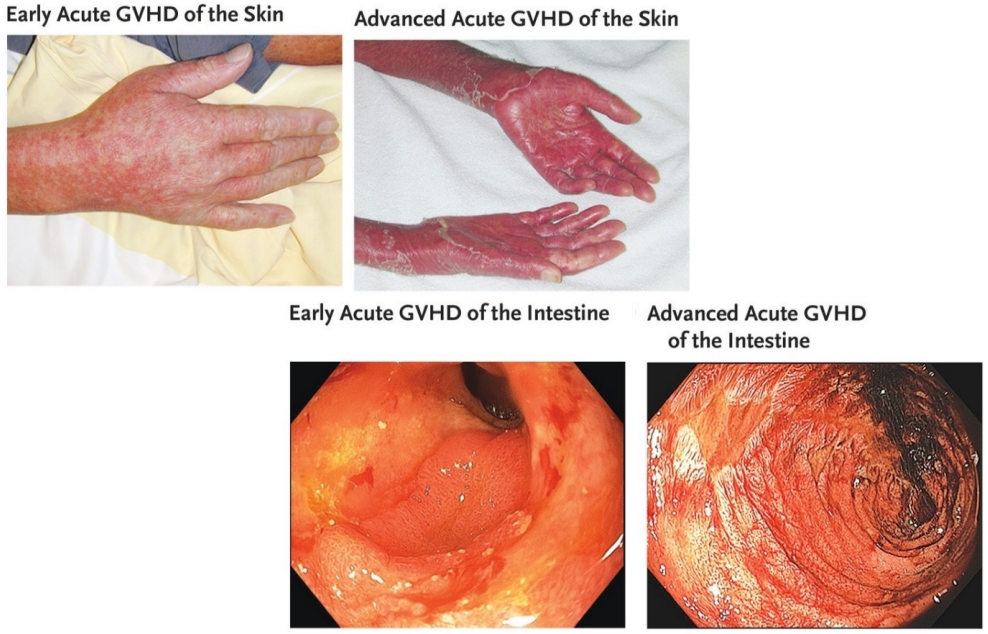
Graft-versus-Host Disease is the most common life-threatening complication after allo-HCT

- **~50%** of patients after allo-HCT despite prophylaxis

- **Donor T cell-mediated** attack on host tissues against
  - MHC
  - minor histocompatibility antigens
  - tumor antigens

- **Acute GVHD**
  - <100 days after allo-HCT (mostly 3-12 weeks)
  - mainly skin, liver and intestinal tract

- **Chronic GVHD**
  - >100 days after allo-HCT (mostly ≥ 6 months)
  - every organ (“autoimmune like“ syndrome)



Risk factors

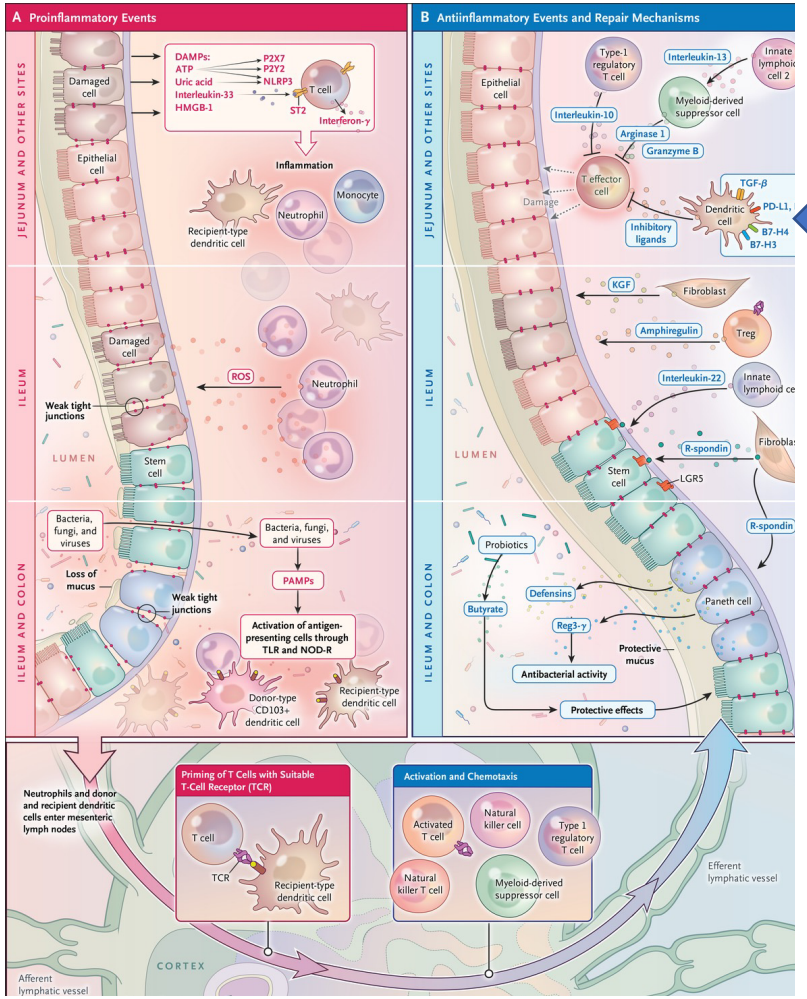
- HLA mismatch
- Unrelated donor
- Sex
- PBSC
- Conditioning regimen intensity

Zeiser and Blazar, NEJM, 2017

Key Event in acute GVHD Pathophysiology is the Interaction of alloreactive Donor T cells with Recipient APCs

Phase I: **Initiation**
- Tissue damage by conditioning regimen
- Neutrophils (ROS production) and monocytes infiltration
- PAMP translocation and DAMP release
- Host APC activation

Phase II: **Immune priming**
- Donor T cell activation and expansion



Phase III: **Effector responses**
- Donor T cell differentiation (Th1, Th17)
- Cytokine production (INFg, IL-17)
- Tissue destruction

Infection
Microbiome
Altered mechanisms of tissue repair and protection

Zeiser and Blazar, NEJM, 2017

Immunosuppressive Strategies for the Prevention or Treatment of Acute GVHD

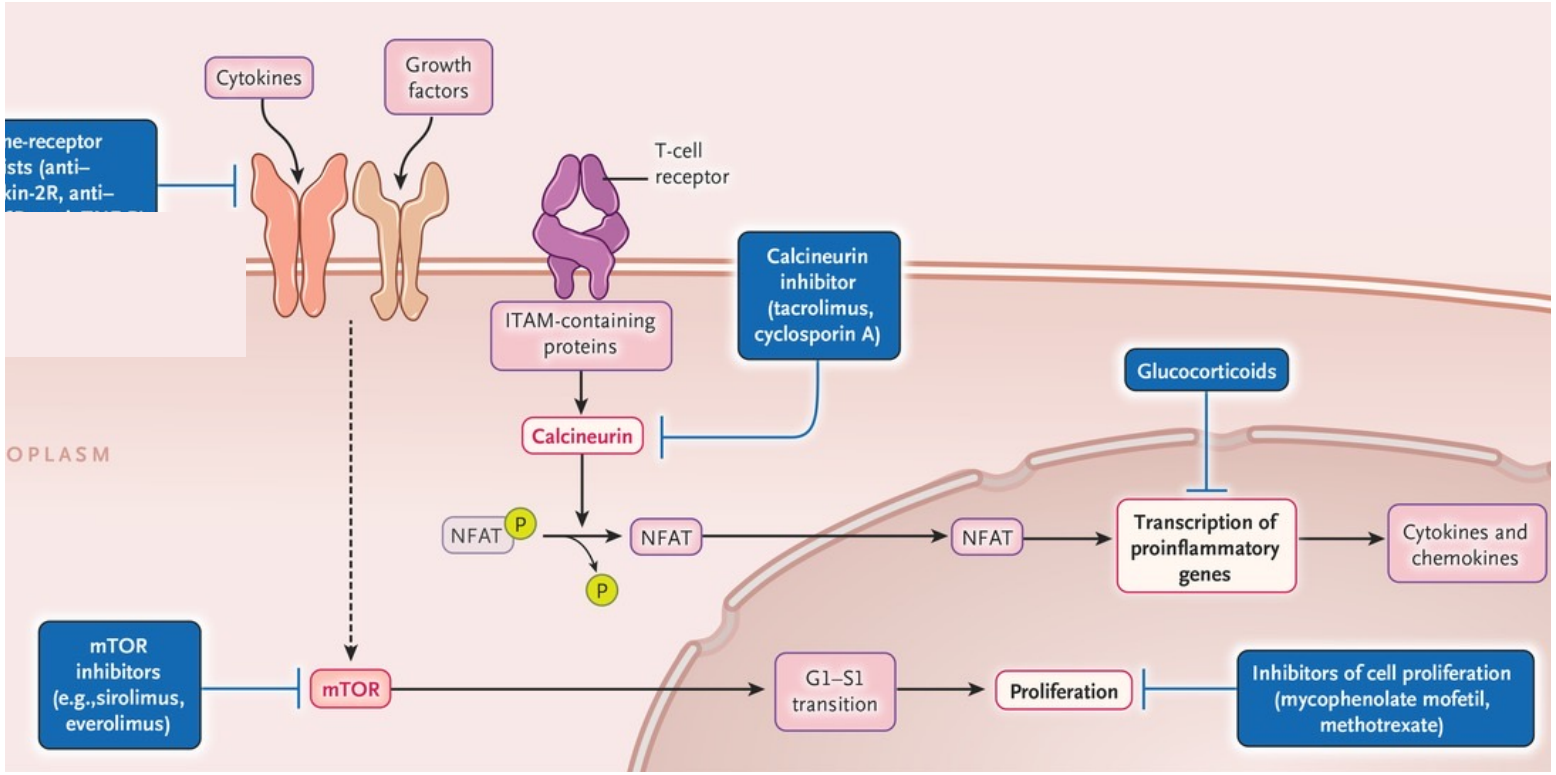
GVHD prophylaxis

- Pharmaceutical
  - Calcineurin inhibitor (CSA, tacrolimus)
  - Antimetabolite (MTX, MMF)
  - mTOR inhibitor (sirolimus)

- Graft manipulation
  - *ex vivo* T cell depletion (CD34+ selection)
  - *in vivo* T cell depletion (ATG, Alemtuzumab, PT-CY)

GVHD treatment

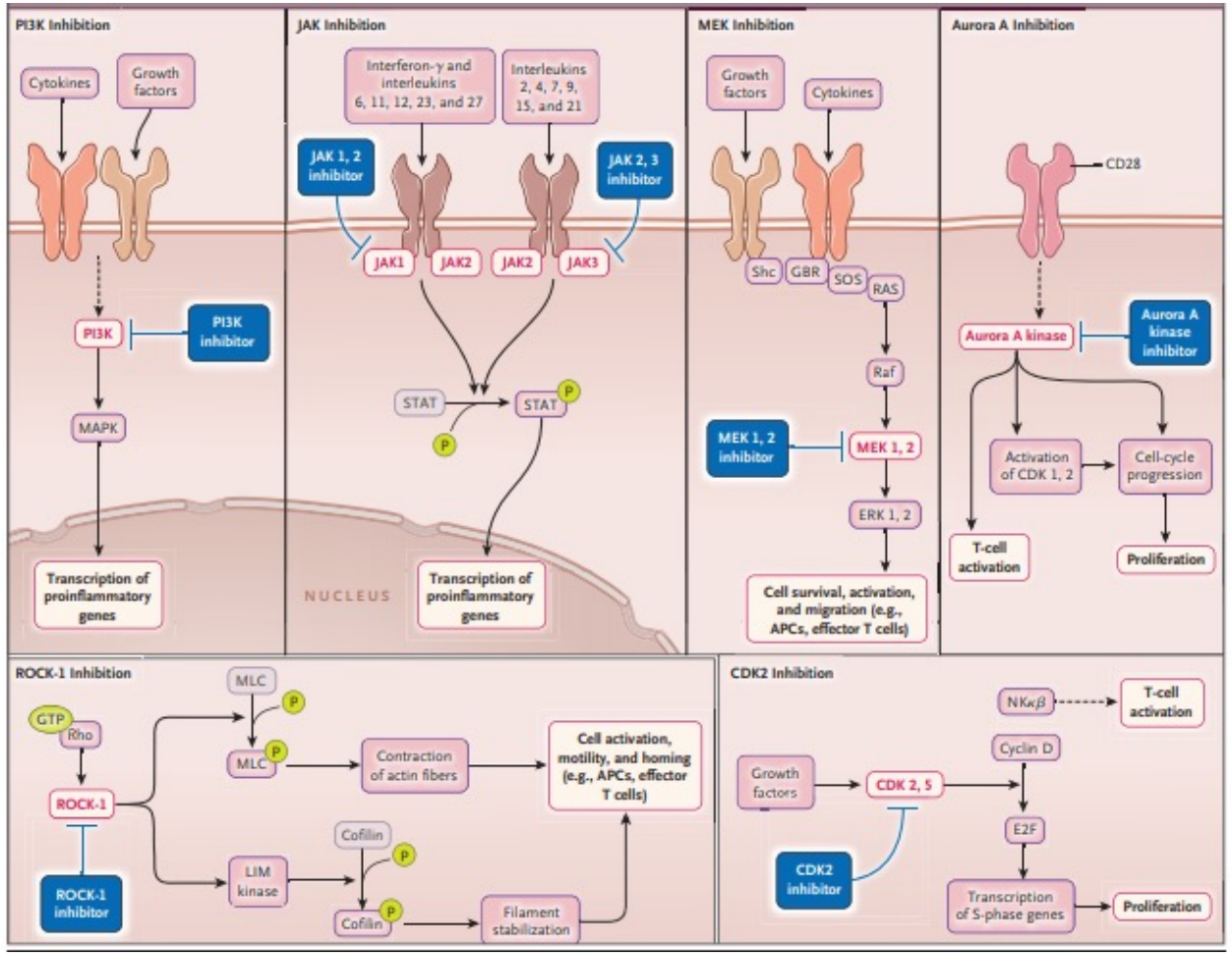
- 1st line: Steroids



Randomized, phase III, multicenter trial comparing different GVHD prophylaxis strategies are ongoing (BMT CTN #1301, BMT CTN #1703)

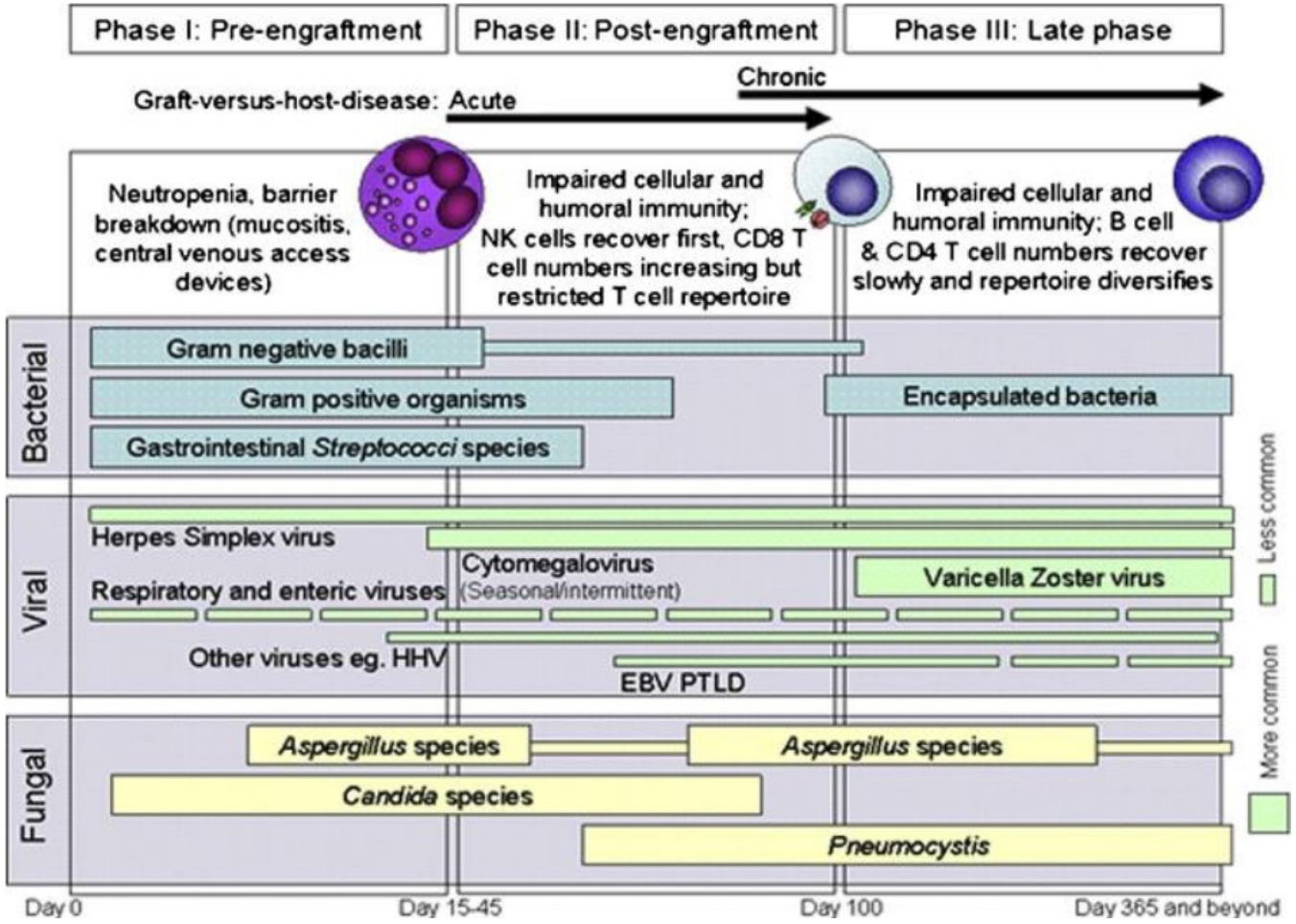
Zeiser and Blazar, NEJM, 2017

Immunosuppressive Strategies for the Prevention or Treatment of Acute GVHD

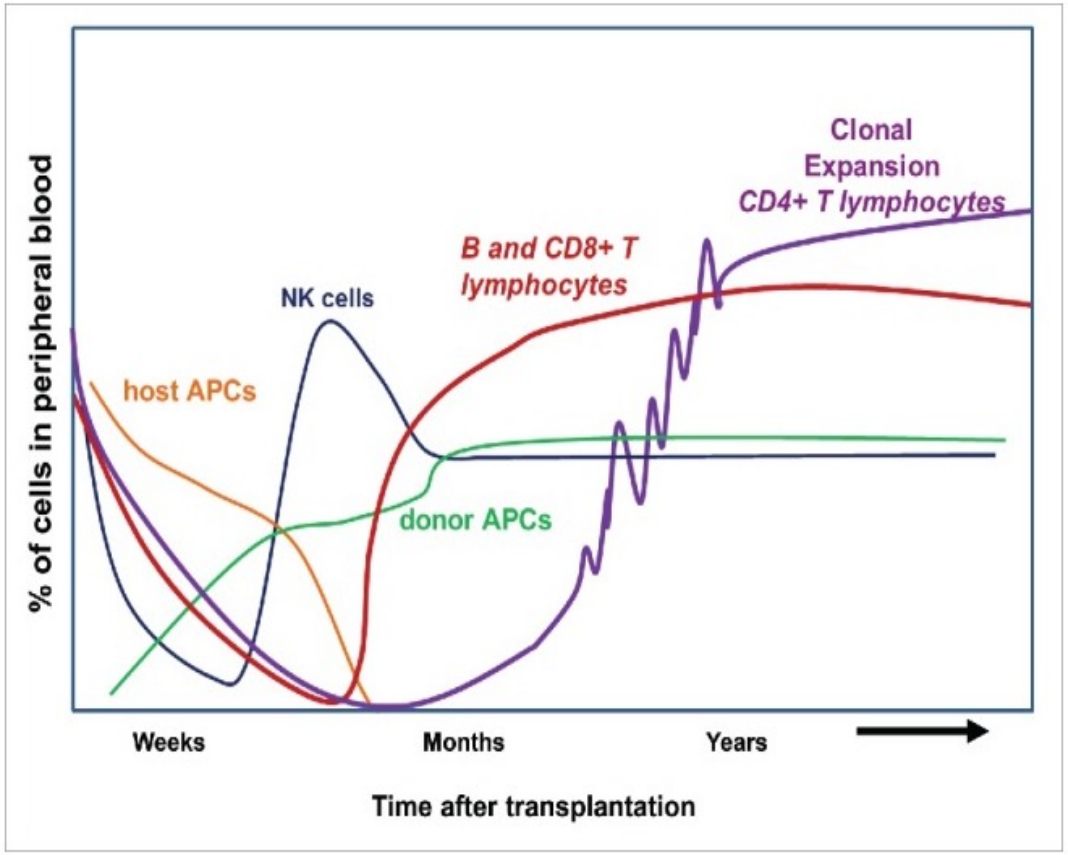


Zeiser, New England Journal of Medicine, 2017

Timeline of infections after HSCT



Tomblyn et al., Biol Blood Marrow Transplant, 2009



Mehta and Rezvani, Virulence, 2016

Relapse After Allo-HCT: Limited Treatment Options

Principles of Post-Allo Relapse

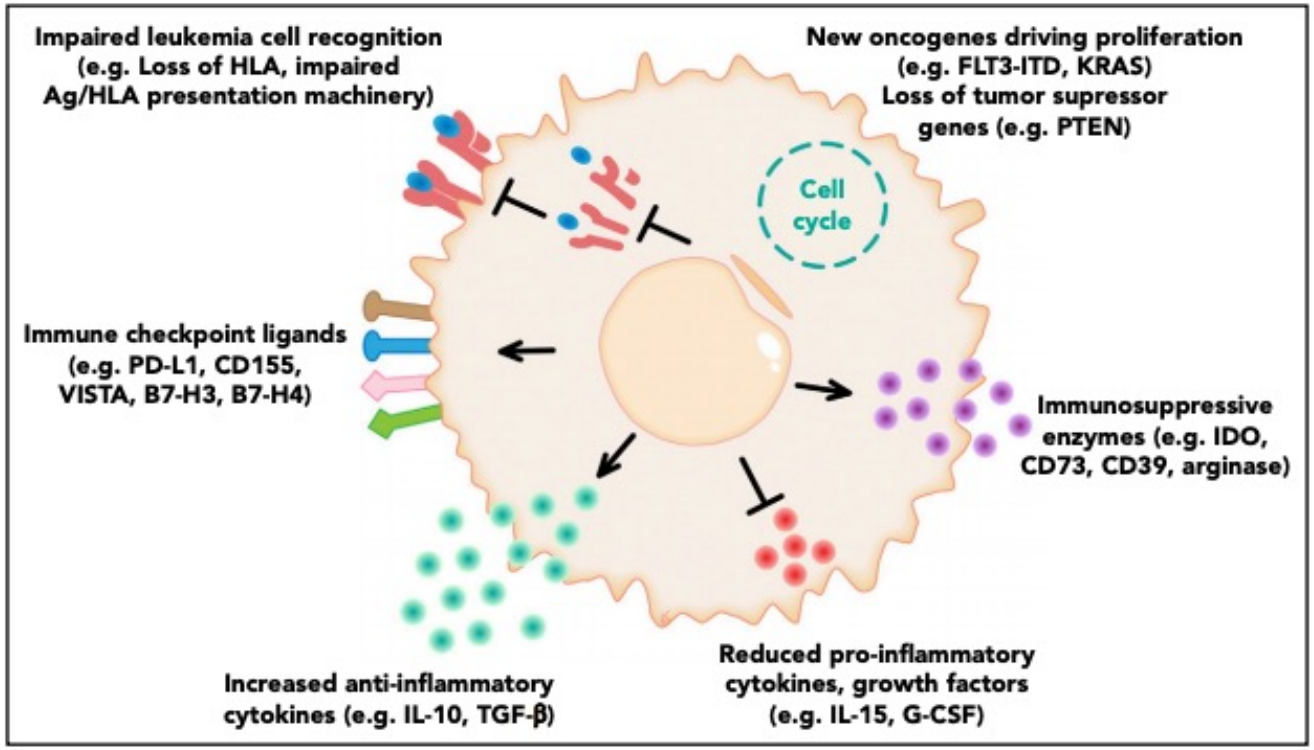
- May occur in the blood, bone marrow, CNS, or extramedullary sites (~10% relapses extramedullary)
- Detection of MRD by flow cytometry post-transplant often portends relapse

Treatment options

- Clinical trial
- Donor lymphocyte infusion
- Salvage chemo or targeted therapy (guided by mutation profile)
- 2nd Allo-HCT (typically only if patient achieves remission)
- Checkpoint blockade (limited data)

Vago L, Hematology Am Soc Hematol Edu Program, 2019
DeWolf & Tallman. Blood, 2020.
Davids et al. NEJM, 2016.

Immunologic Mechanisms of Relapse



- Genomic loss of HLA haplotype (HLA-loss)
  - 30% of haploidentical transplants *(Vago et al. NEJM 2009)*
  - 5-15% of unrelated transplants (*Taffalori et al. Blood 2012)*
- HLA Class II down-regulation *(Chrisopher et al. NEJM 2018)*
- Increased expression of inhibitory ligands on leukemic blasts *(Toffalori et al. Nature Medicine 2019)*
- T cell exhaustion in the bone marrow *(Novielllo et al. Nature Communications 2019)*

Vago & Zeiser, Blood, 2019

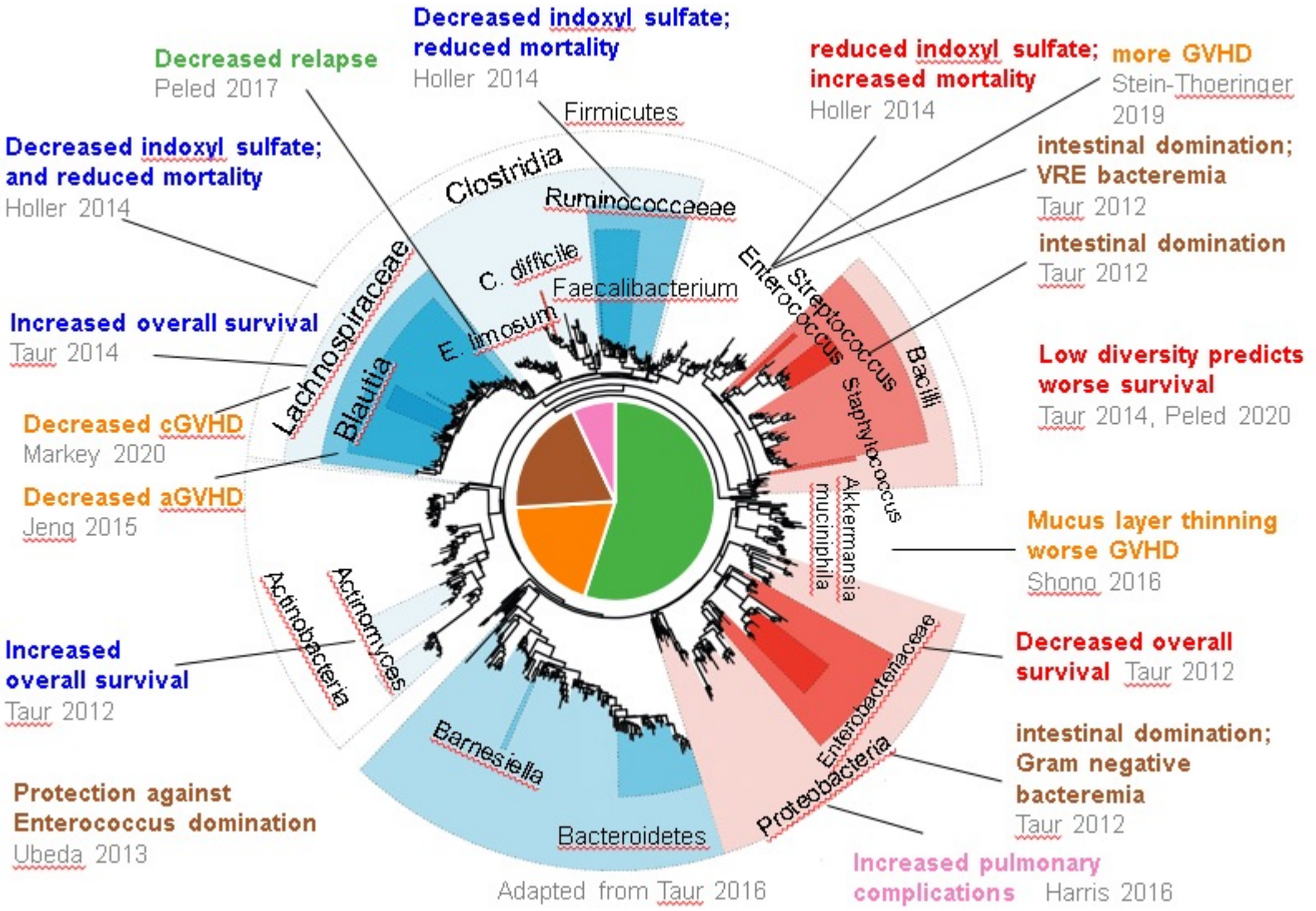
Donor Lymphocyte Infusion (DLI)

- Post-transplant infusion of donor-derived polyclonal T product from the donor aiming to augment GVL effects
  - *Given for confirmed low-level relapse (or relapse prevention).*
  - *Usually no prior GVHD >> supporting the idea that fresh T cells should be safe from a GVHD induction point of view.*
  - *Less immune suppression on board than at d0*
  - *OR (in the case of CD34 selected graft or other TCD method) this is the first introduction of mature donor T.*
  - *Up to 63% response; But max reported OS >> 31% at 2 years*

Donor CD19 Chimeric Antigen Receptor cells after Allo-HCT

- CD19 CAR T cells induce disease remission in patients with relapsed or refractory B cell malignancies
- Primarily used in the autologous setting
- Investigational studies have assessed their use in the donor context following allo-HCT

Gut bacteria associated with allo-HCT outcomes: Overall Survival, Infection, GVHD, Organ Toxicity, Relapse



Summary

- Auto and Allo HCT are increasingly being used for non-malignant and malignant indications
- Major complications of Auto HCT
  - Conditioning toxicity
  - Infections
  - Relapse
- Major complications of Allo HCT
  - Conditioning toxicity
  - Infections
  - GVHD
  - Relapse

Funding

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  R01 HL125571-05
  R01 HL147584-02
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  P30 CA008748-54
  R01 CA228308-03
  R01 CA228358-03
- **NIAID:** U01 AI124275-05

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