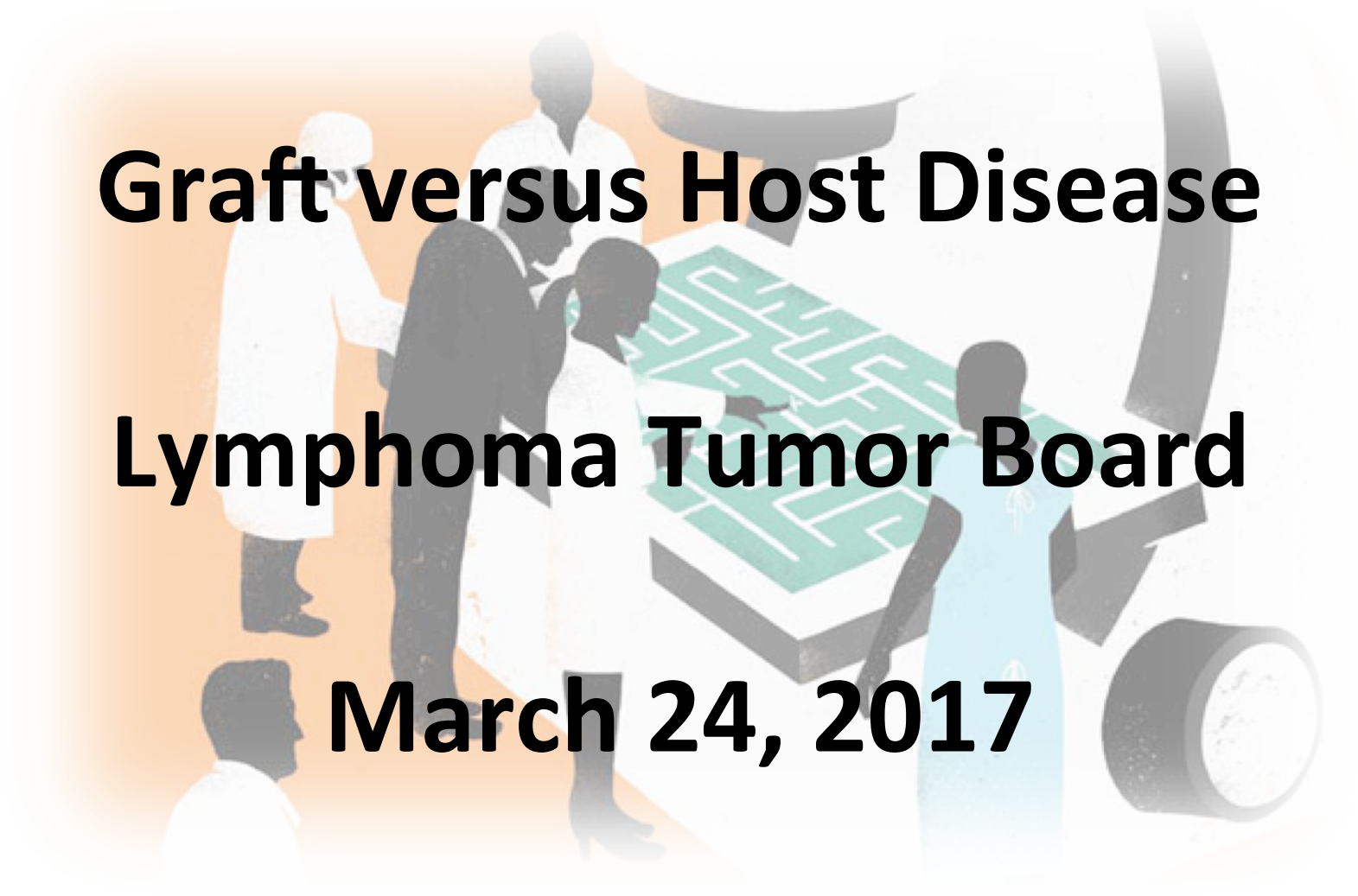
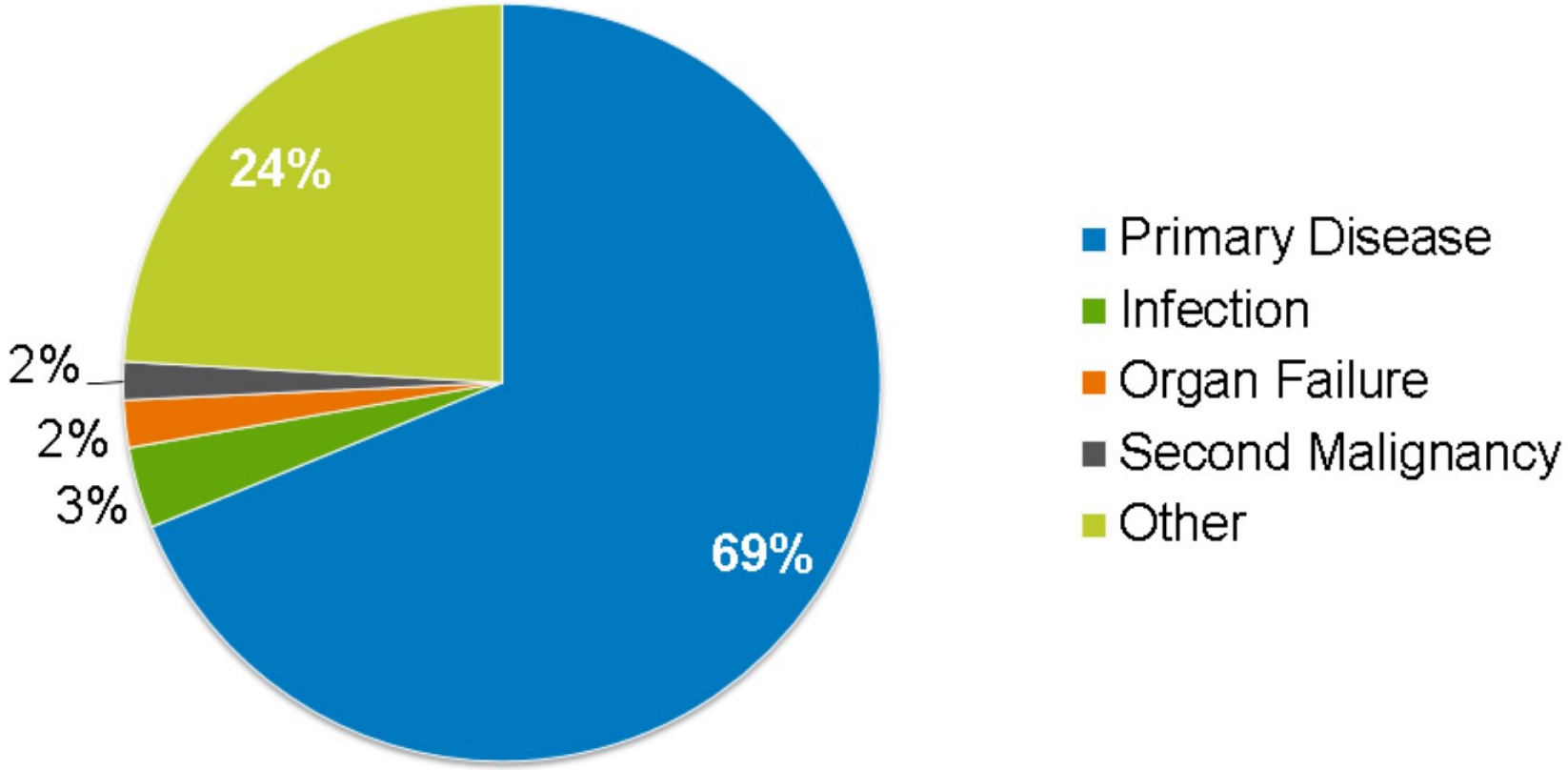


# Graft versus Host Disease

# Lymphoma Tumor Board

# March 24, 2017

# Causes of Death after Autologous HCT done in 2013-2014

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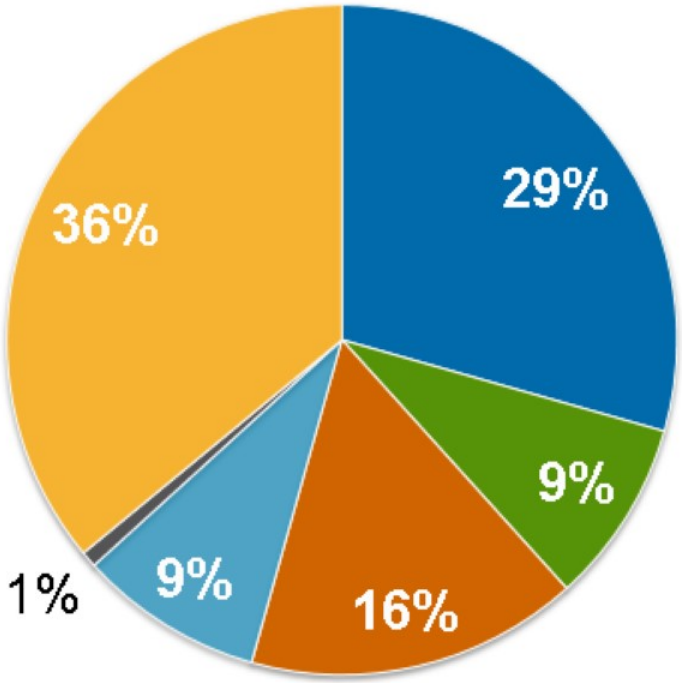
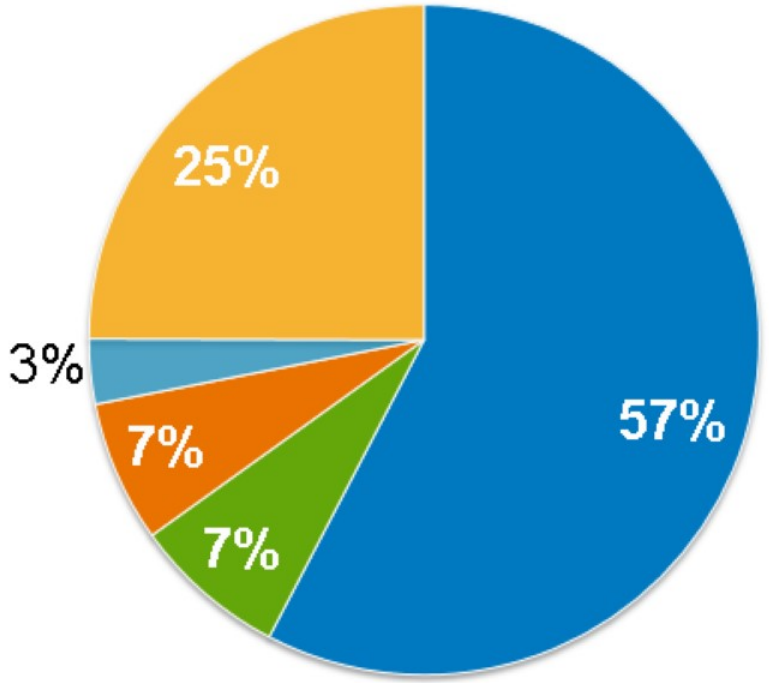
# Causes of Death after HLA Matched Sibling HCT done in 2013-2014

Died within 100 days post-transplant




Died at or beyond 100 days post-transplant

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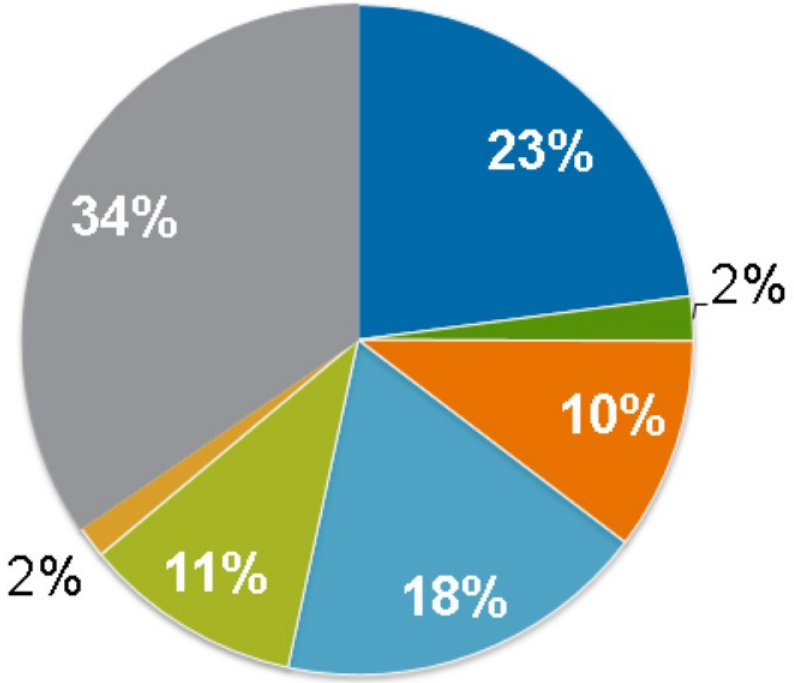
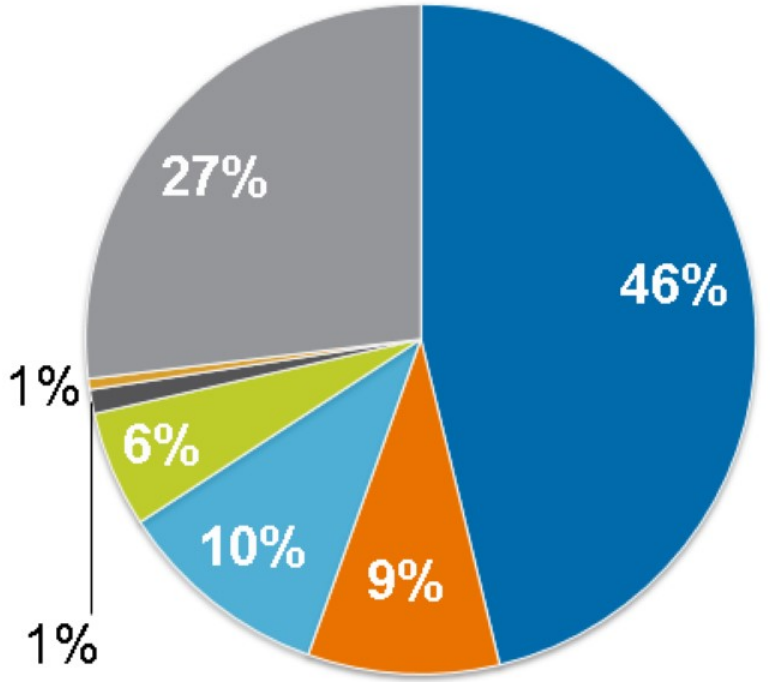
# Causes of Death after Unrelated Donor HCT done in 2013-2014

Died within 100 days post-transplant




Died at or beyond 100 days post-transplant

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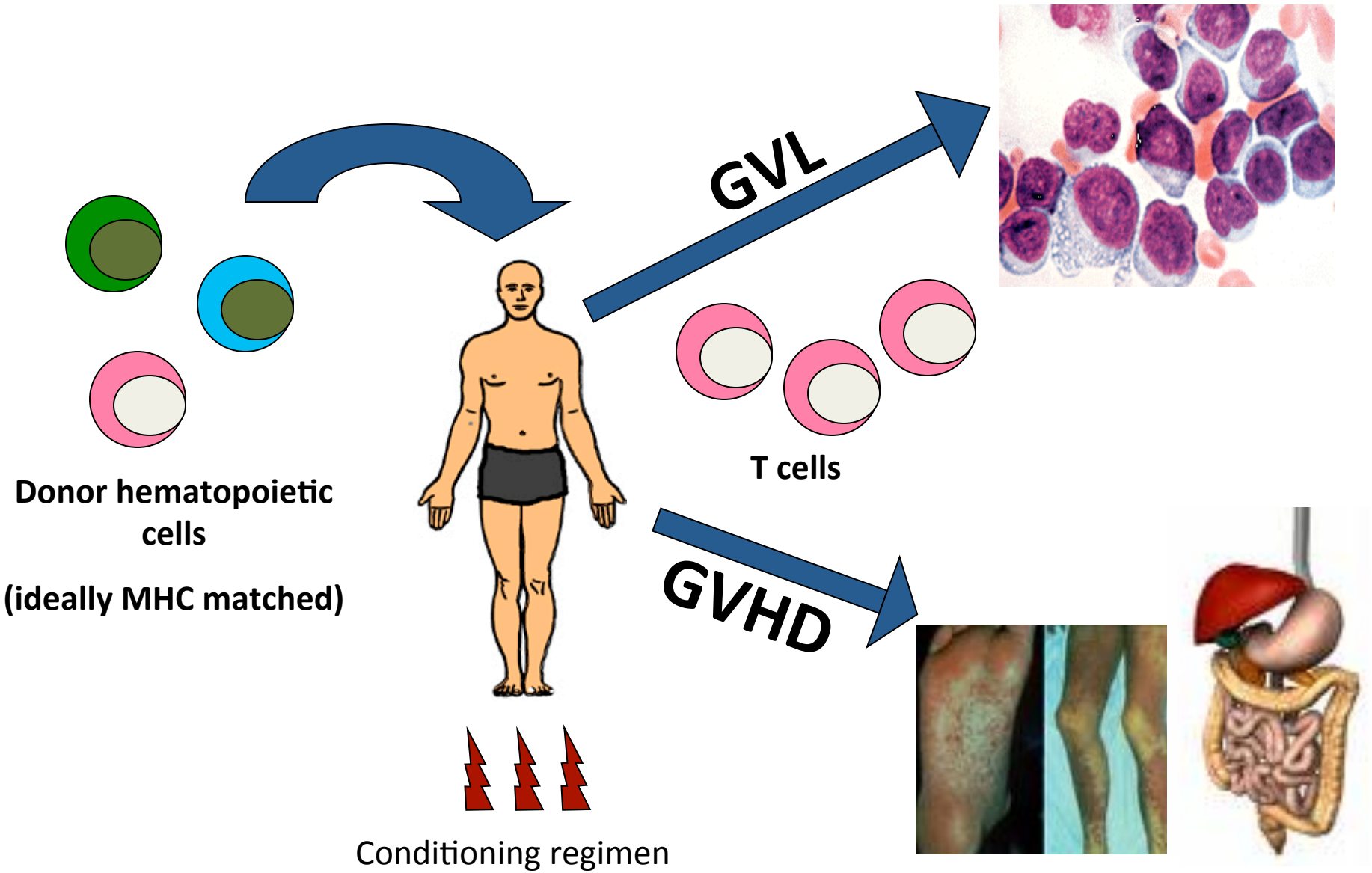
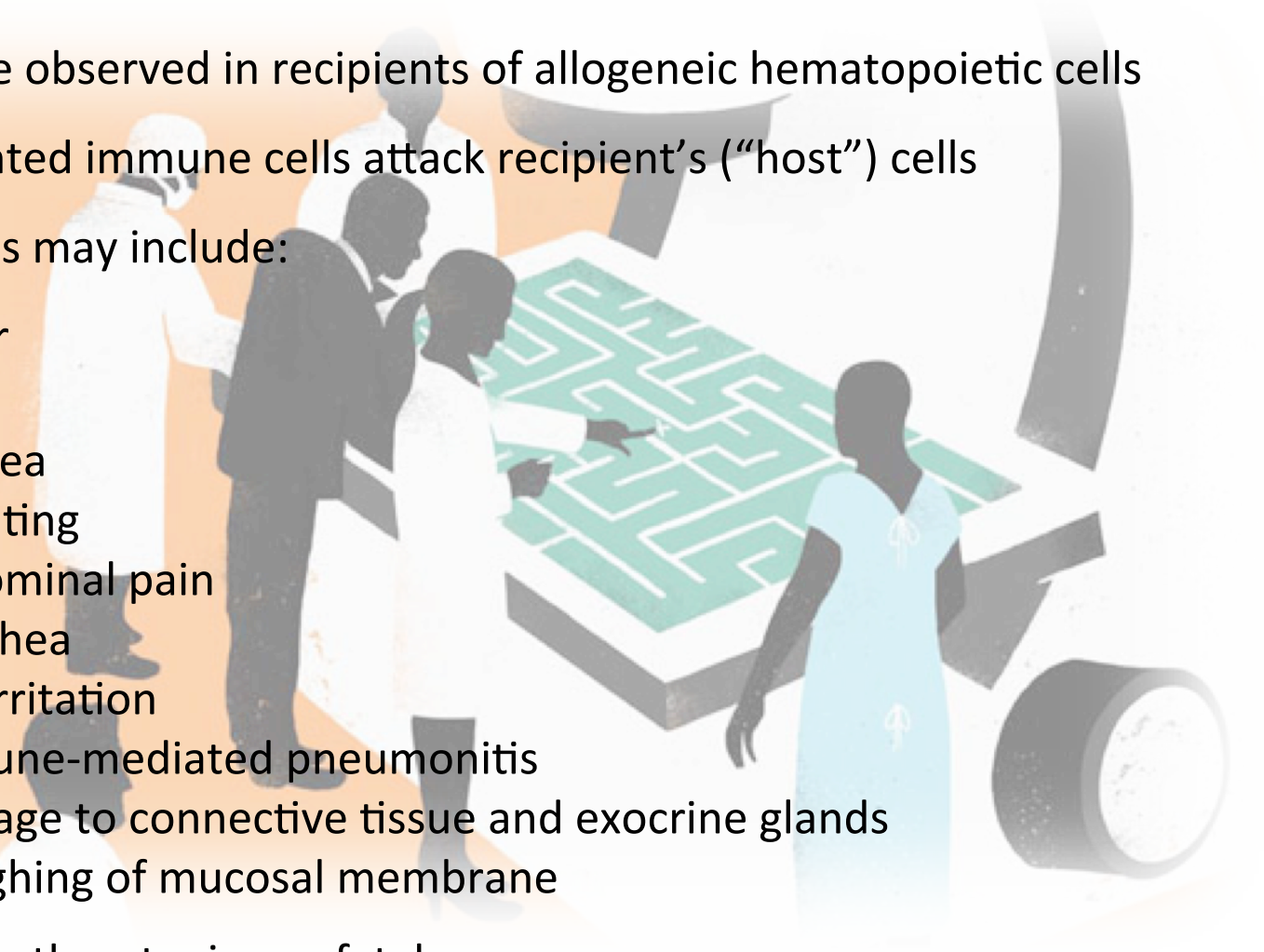
# Hematopoietic Cell Transplantation

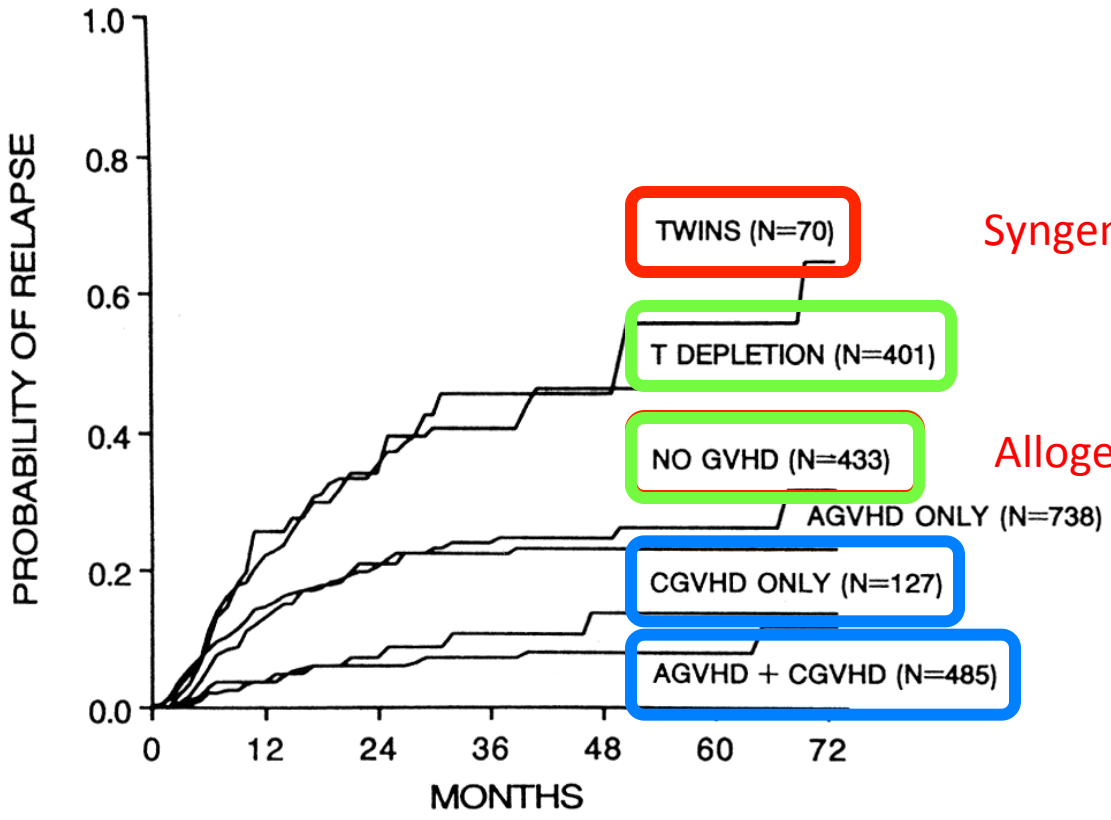


# What is Graft versus Host Disease ("GVHD")?



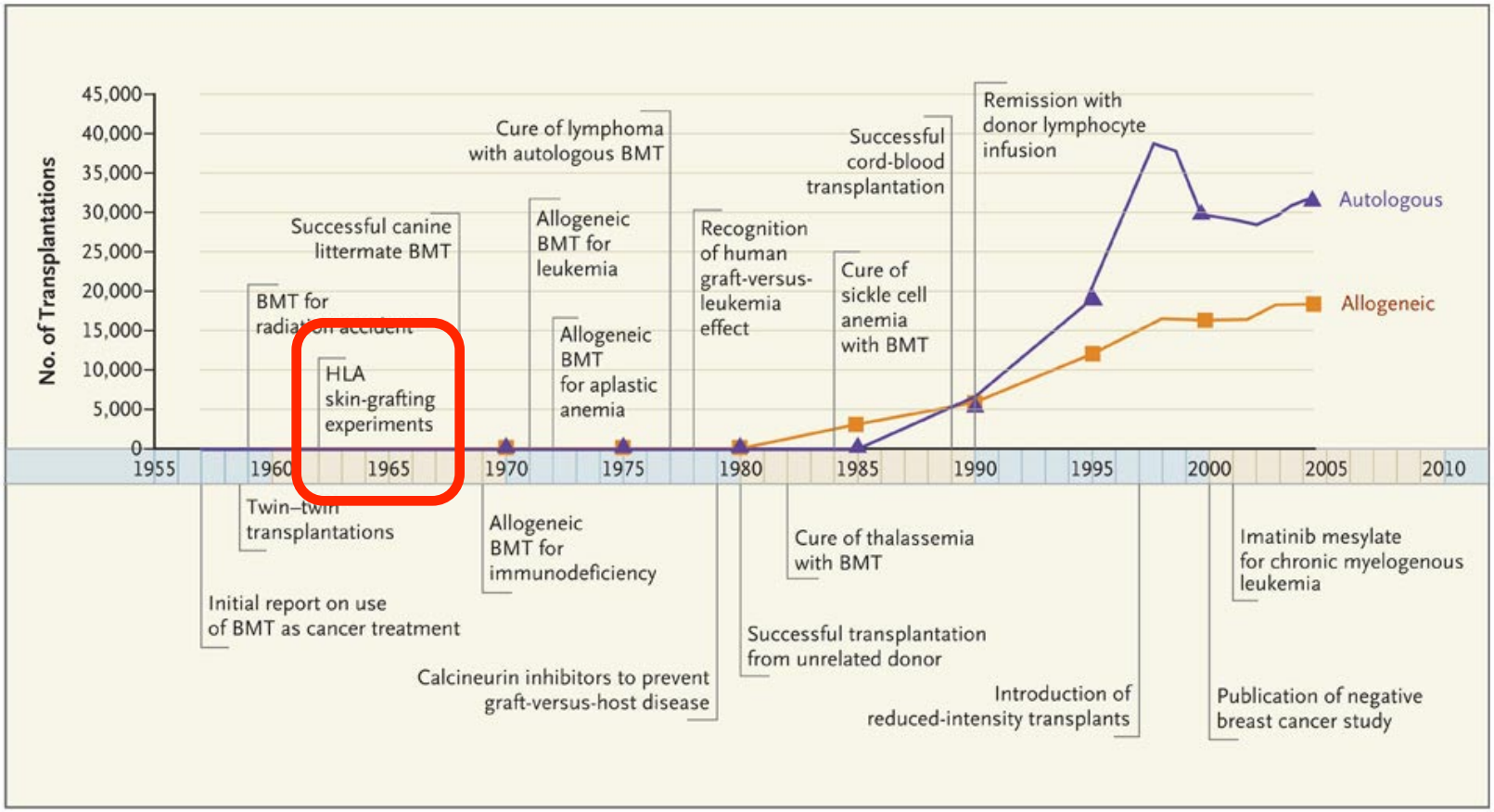
- Syndrome observed in recipients of allogeneic hematopoietic cells
- Transplanted immune cells attack recipient's ("host") cells
- Symptoms may include:
  - Fever
  - Rash
  - Nausea
  - Vomiting
  - Abdominal pain
  - Diarrhea
  - Eye irritation
  - Immune-mediated pneumonitis
  - Damage to connective tissue and exocrine glands
  - Sloughing of mucosal membrane
- Can be life threatening or fatal
- Treatment based on glucocorticoids such as prednisone, and other agents

# Defining the GVL effect: GVHD and relapse after HLA-matched allogeneic BMT




Horowitz, M *et al.,* Blood 75: 555-562 (1990)

# Timeline showing numbers of bone marrow transplants and advances in the field, 1957-2006



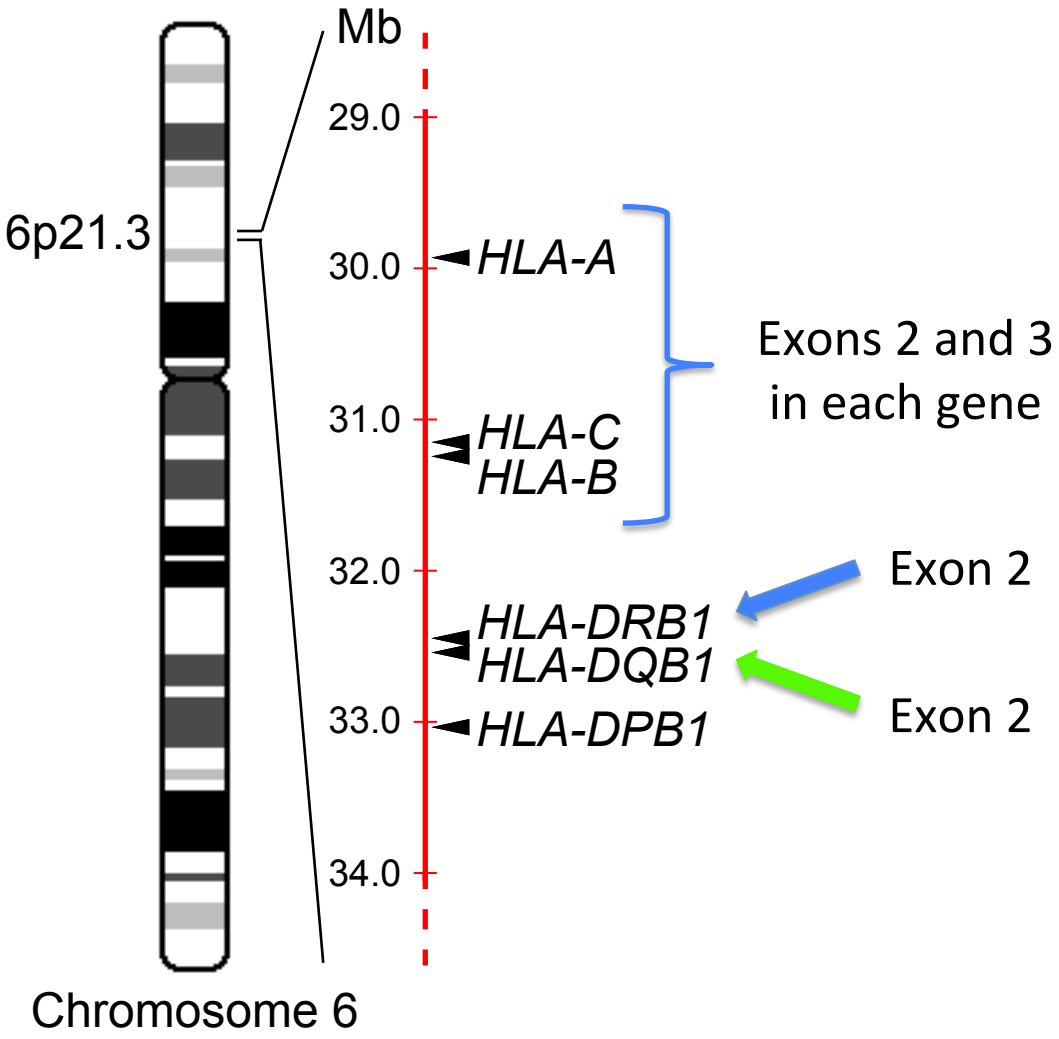

Appelbaum F. N Engl J Med 2007; 357:1472-1475

# The laws of histocompatibility in allogeneic HCT

1. Donor/recipient genetic non-identity for the HLA antigens encoded in the MHC is the single most important risk factor for the development of severe GVHD.
2. Clinically significant GVHD – that can sometimes be life-threatening or even fatal – still occurs in recipient of hematopoietic cell grafts from HLA-identical donors.

**WHY?**

# What is involved in HLA typing, anyway?




7 exons total
~275 nt each
TOTAL: 1,925 bp

Haploid genome: 3.3 x $10^9$ bp

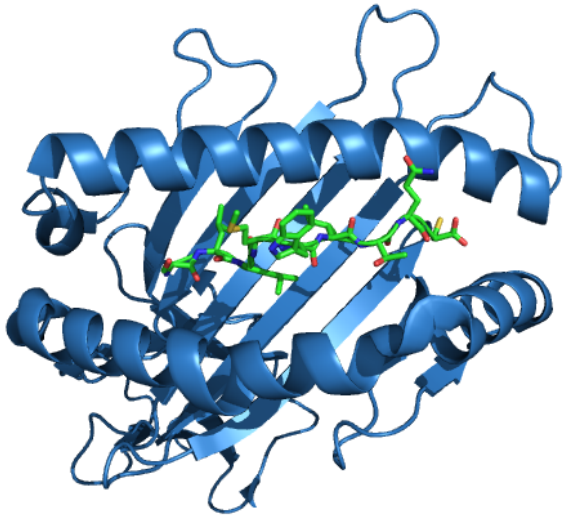
< 1 x $10^{-3}$ of the MHC

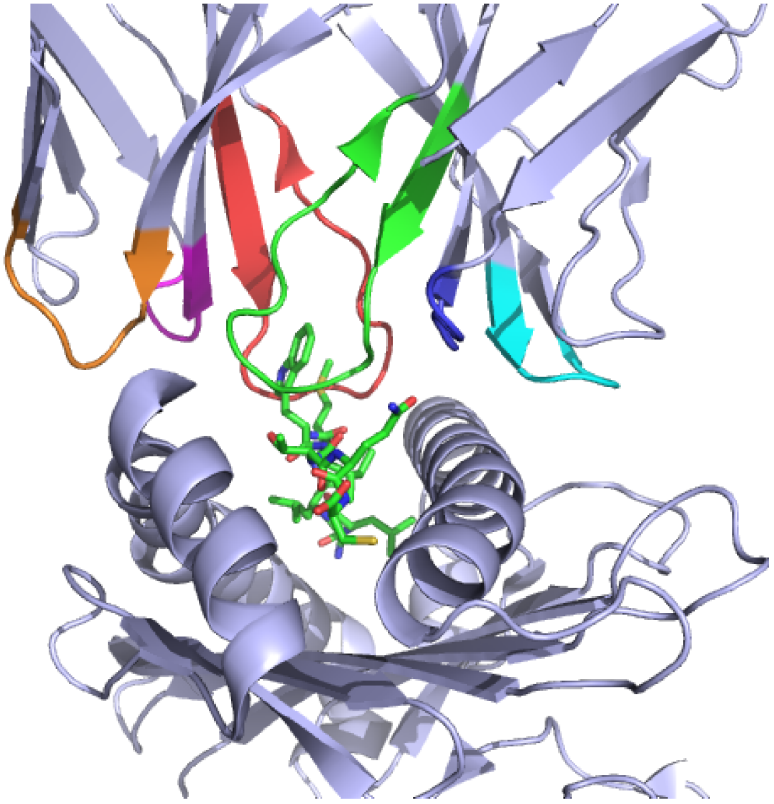
< 1 x $10^{-6}$ of the haploid genome

# T cells recognize short peptides presented on the cell surface by MHC molecules

CD8+

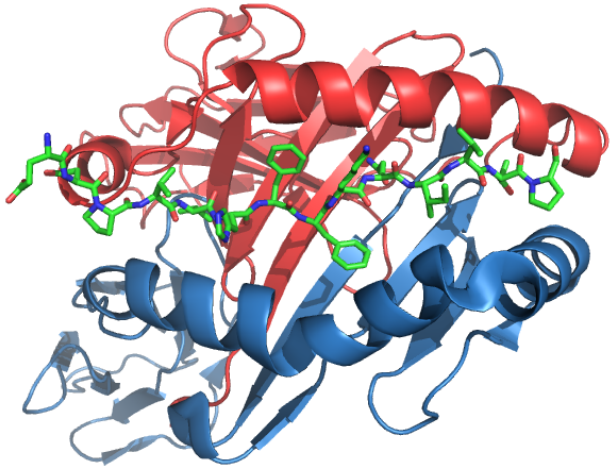
NY-ESO-$1_{157\text{-}165}$
HLA-A*0201



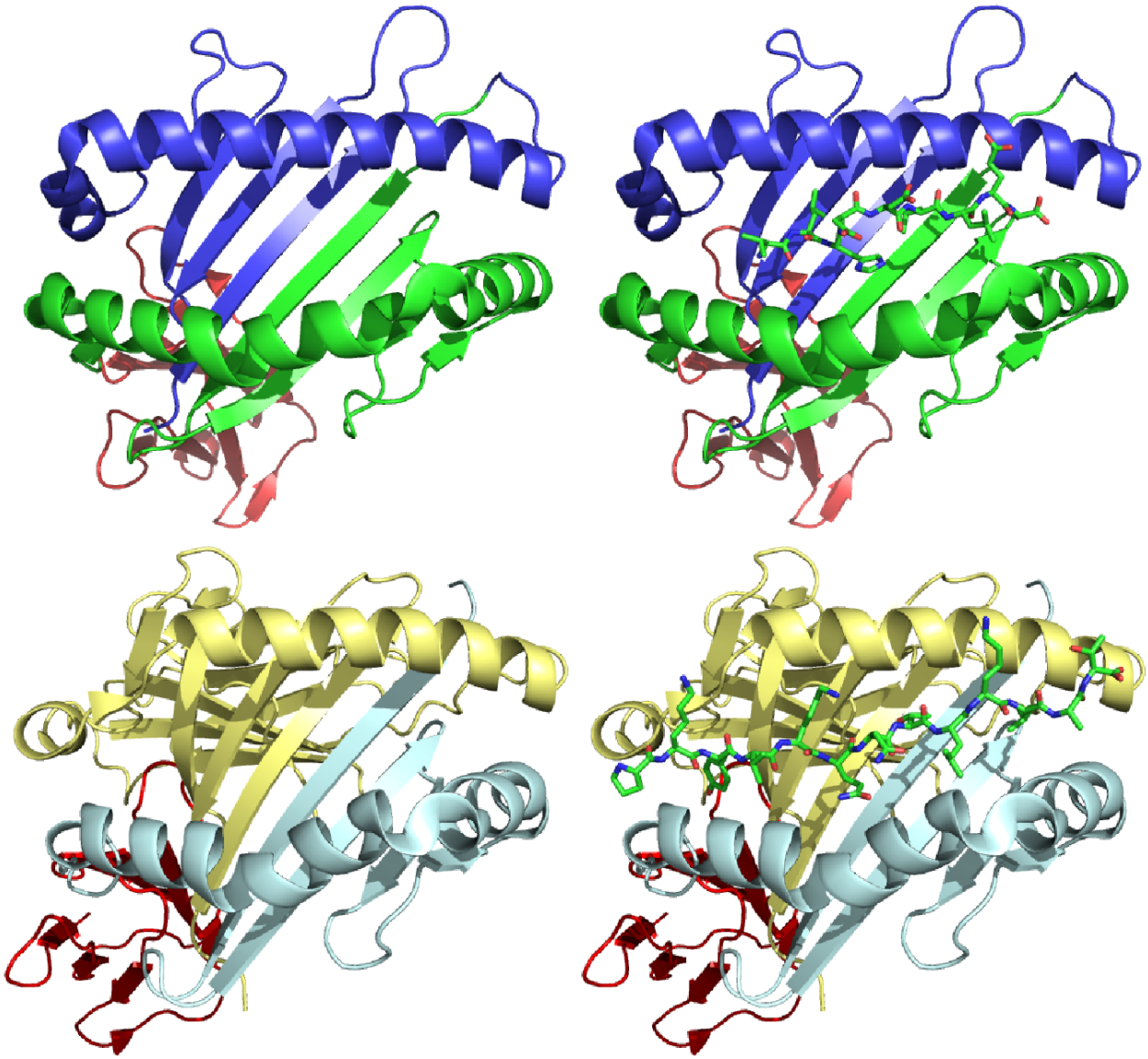


CD4+

$MBP_{217\text{-}230}$
HLA-DR2



# These 1,925 bp encode the peptide binding regions of class I and II MHC molecules

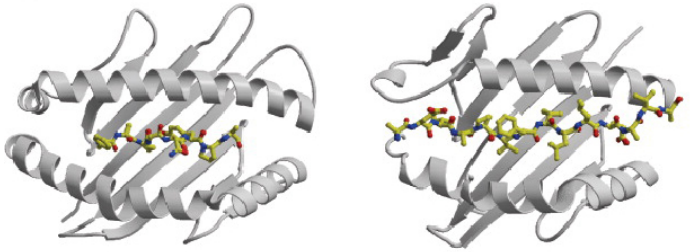


Minor antigen HA-1
VLHDDLLEA
HLA-A*02:01:01

Influenza A HA peptide
PKYVKQNTLKLAT
HLA-DR4

# The composition of the MHC-associated peptidome defines the immunologic identity of a cell

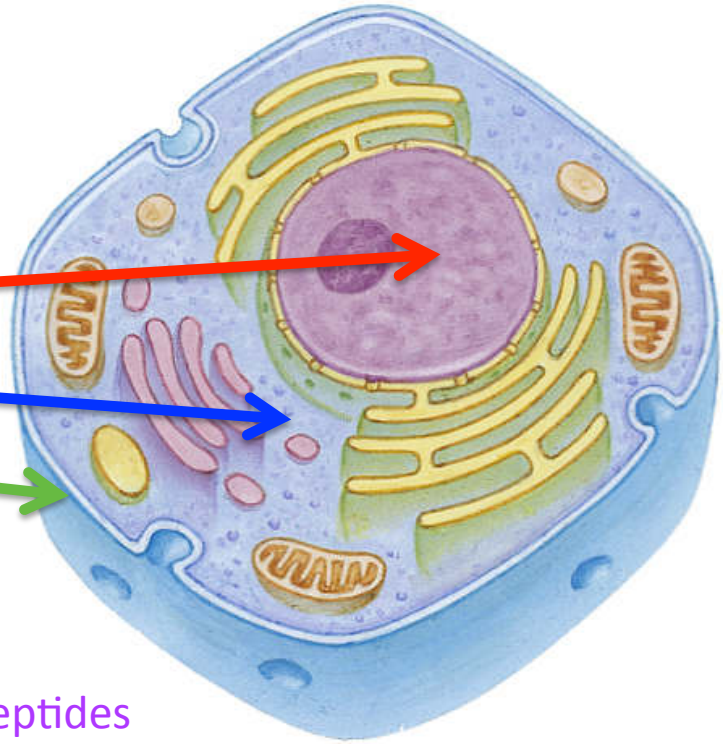
~100,000 MHC class I molecules/ cell (perhaps 1 x $10^6$…)



MHC class II molecules on APC's

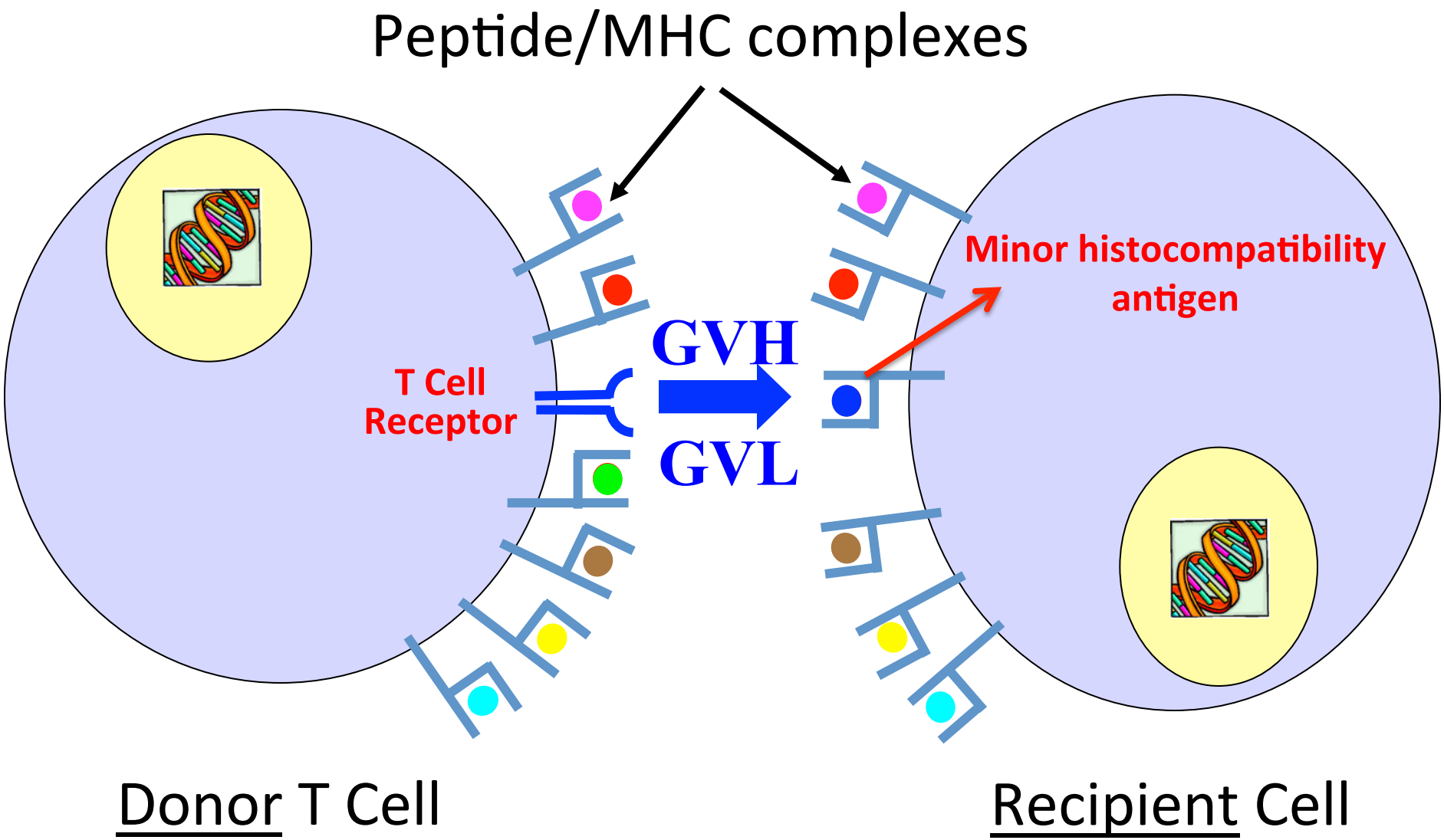
~10,000 distinct peptides derived from:

- nuclear proteins
- cytoplasmic proteins
- membrane proteins
- cryptic proteins…

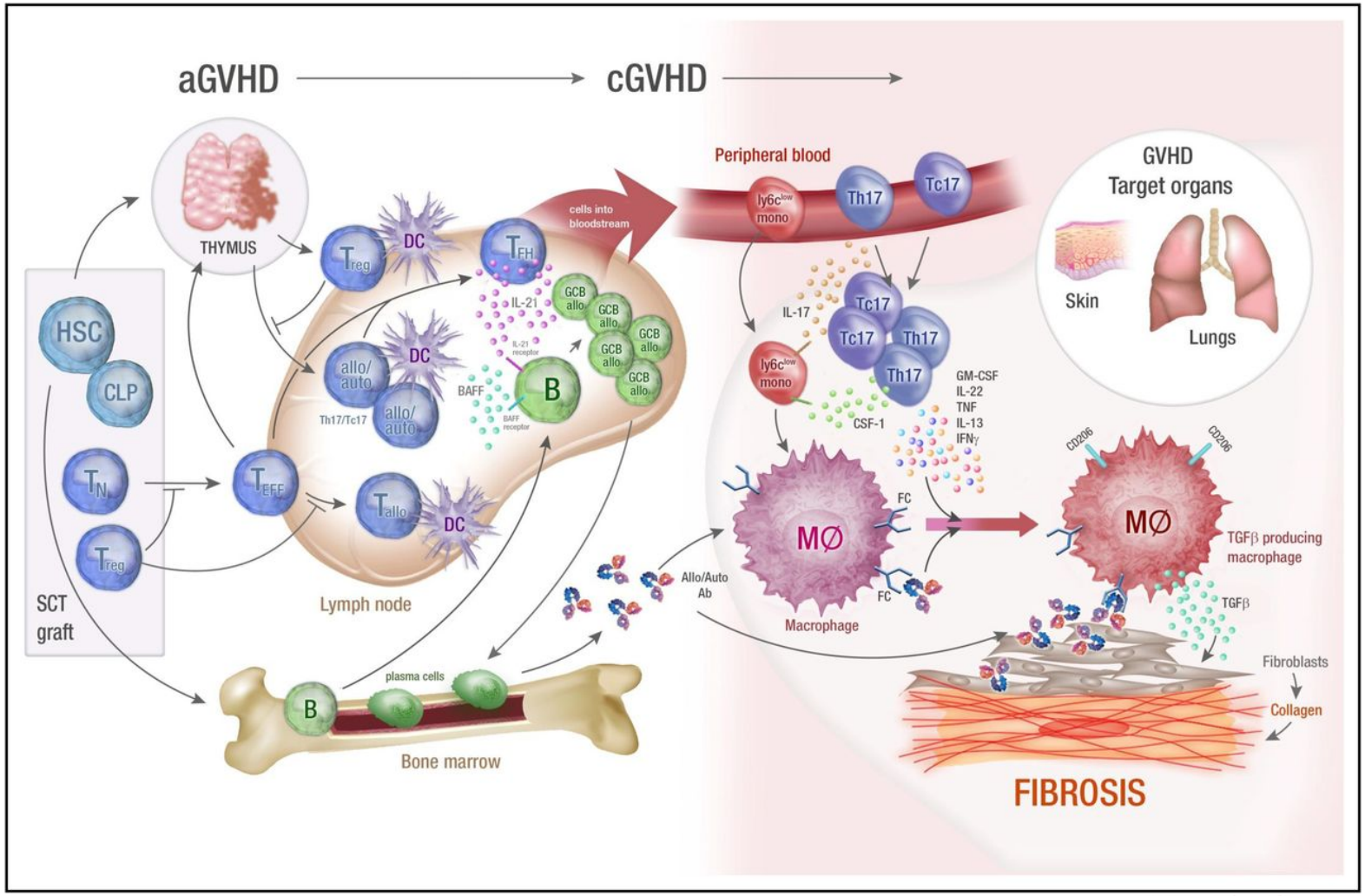


Unexpected translation products; spliced peptides

# The composition of the MHC-associated peptidome is genome- and tissue-specific and very dynamic

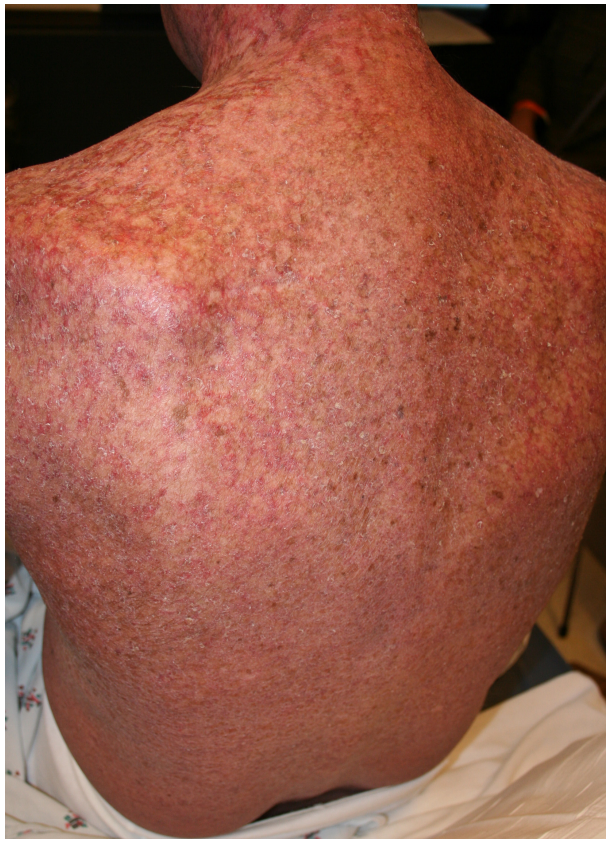


# Schematic overview of the cellular and molecular mediators, known and implicated, contributing to the continuum of acute GVHD and chronic GVHD pathology

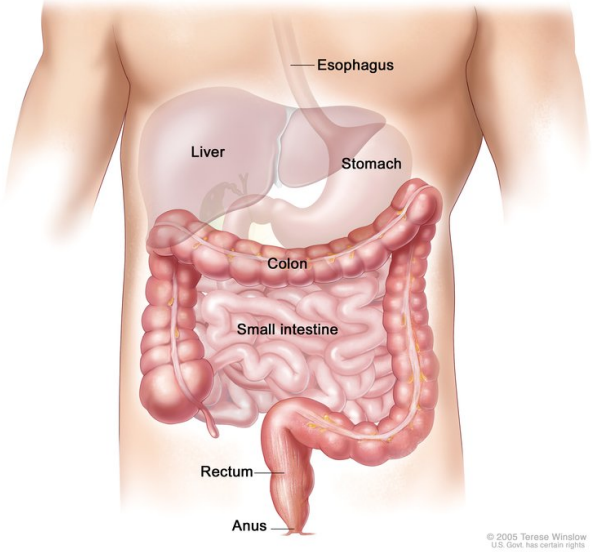



Kelli P. A. MacDonald et al. Blood 2017;129:13-21

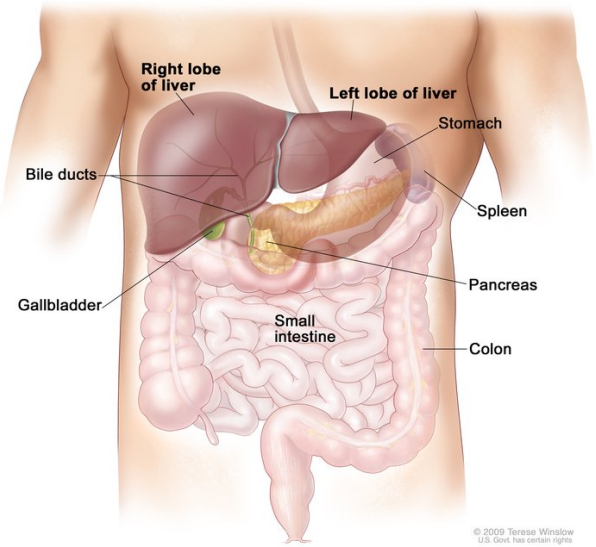
# Major sites of acute graft-versus-host disease



Skin

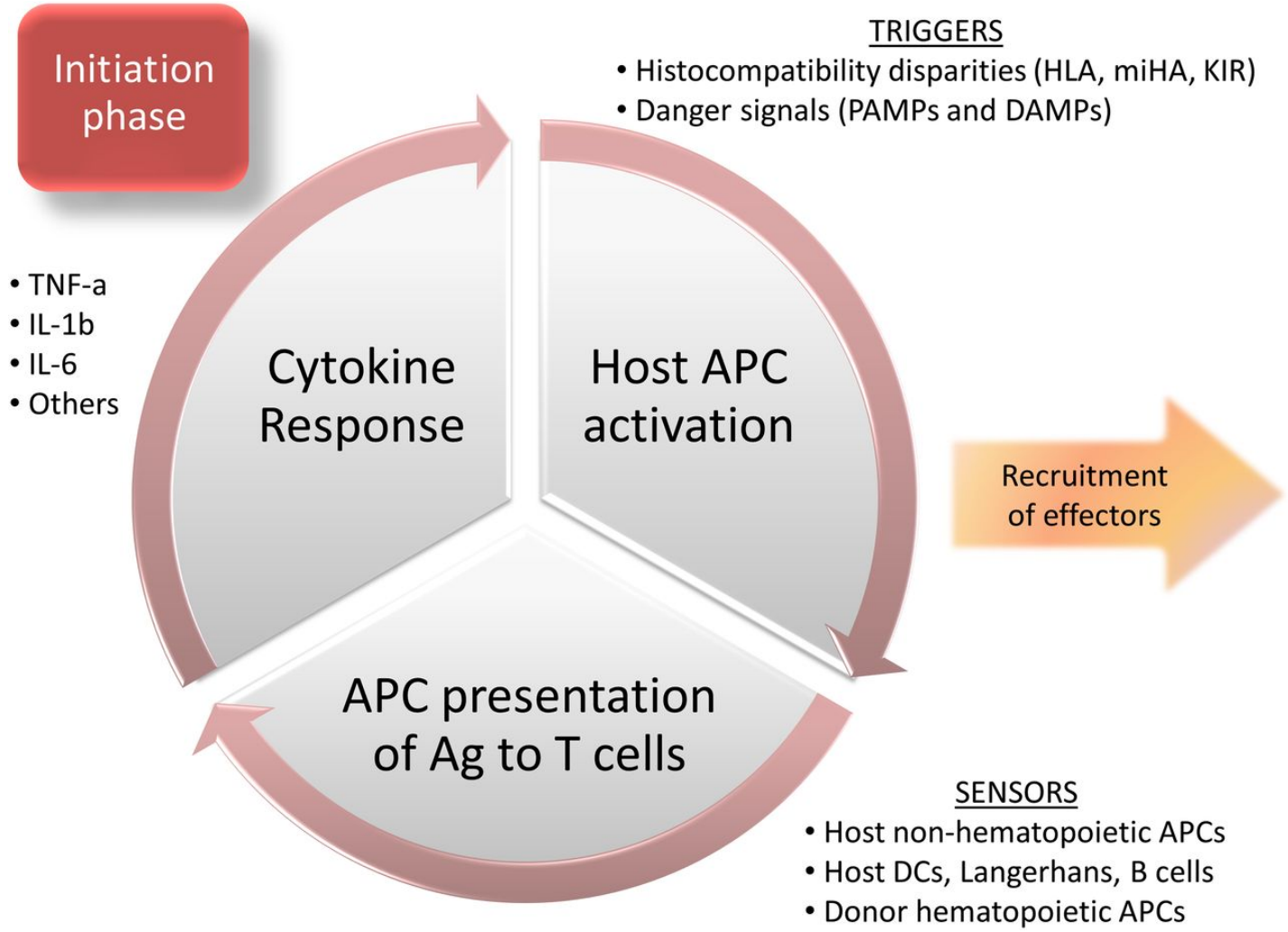



GI Tract



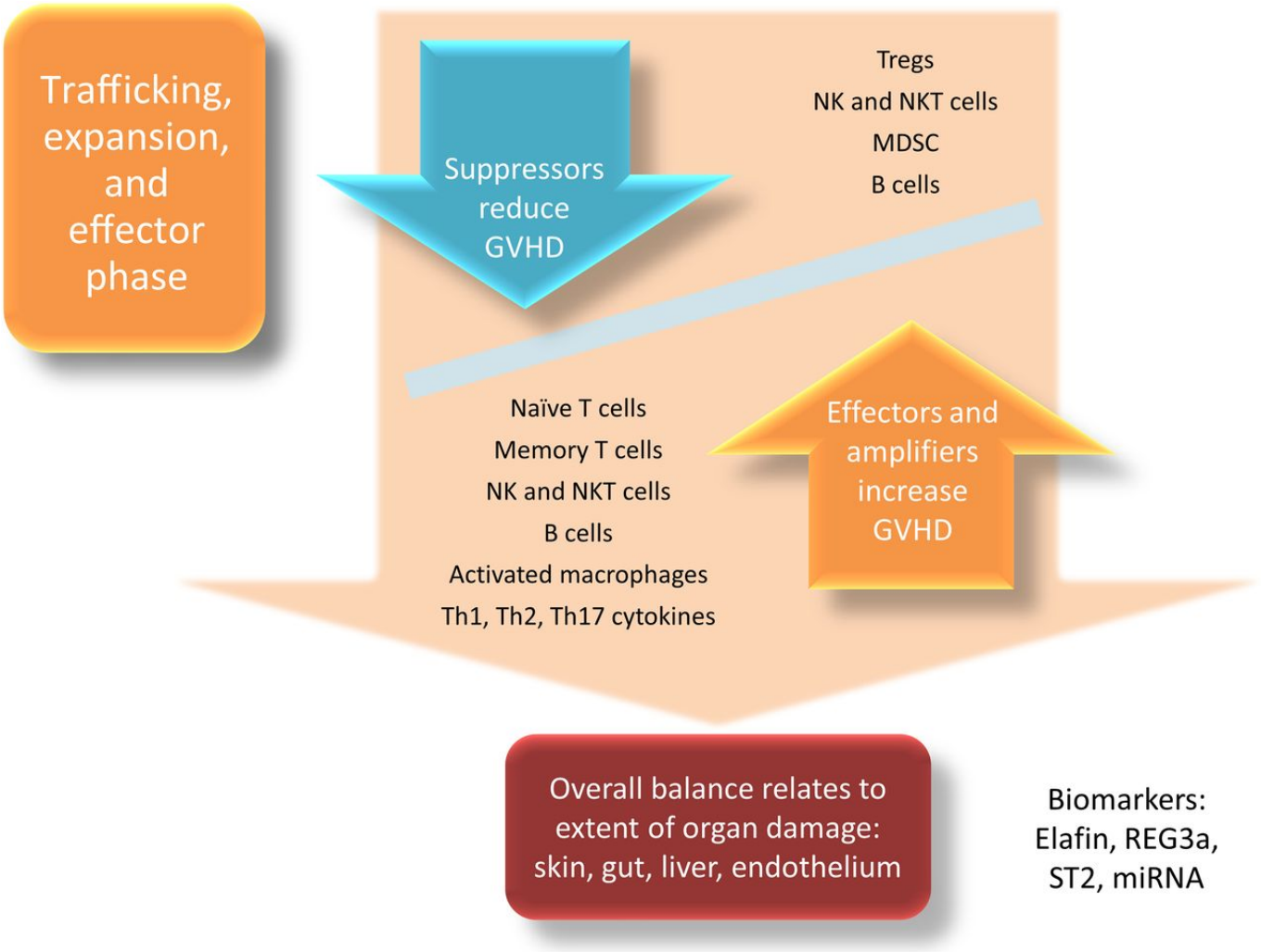

Liver

# Initiation phase of acute GVHD



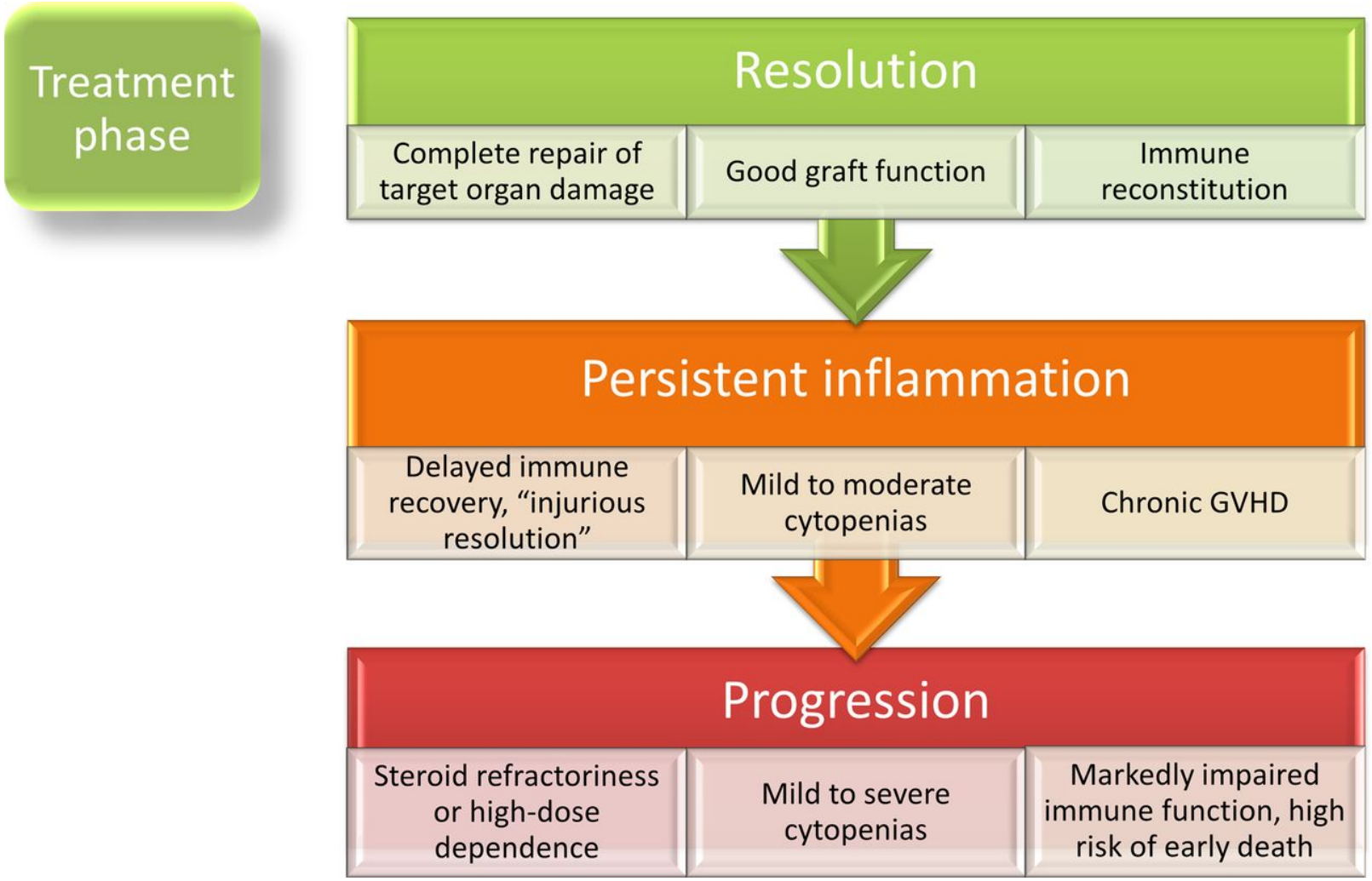

Shernan G. Holtan et al. Blood 2014;124:363-373

# Expansion, trafficking, and effector phase of acute GVHD




Shernan G. Holtan et al. Blood 2014;124:363-373

# Treatment phase of acute GVHD




Shernan G. Holtan et al. Blood 2014;124:363-373

# Approaches to prevention and treatment of acute GVHD

**Table 1. Emerging approaches for the prevention and treatment of aGVHD**

| Treatment or pathway | Potential mechanism(s) of action | Level of evidence | References |
|---|---|---|---|
| **Small molecules** | | | |
| PKC inhibitors, such as R524 (Rigel Pharmaceuticals), and sotrastaurin (Novartis) | Inhibition of PKC$\alpha/\theta$, proteins that maintain immunologic synapse between APC and effector T cell | Preclinical (mouse) Sotrastaurin being investigated in solid organ transplant clinical trials | 125,126 |
| Sphingosine 1-phosphate receptor agonist FTY720 (fingolimod; Gilenya Pharmaceuticals) | Modulates DC function and lymphocyte efflux from secondary lymphoid organs, enhancement of endothelial barrier function | Preclinical (mouse) | 127 |
| Hypomethylating agents azacitidine and decitabine | Induction of FOXP3 expression | Preclinical (mouse) phase 1/2 clinical | 128,129 |
| Retinoic acid signaling | Reduction of T-cell homing, reducing Th1 differentiation, inducing Tregs | Preclinical (mouse) | 130 |
| Tim-3/Gal-9 pathway | Increased activation-induced T-cell death in the absence of Tregs | Preclinical (mouse) | 131 |
| PDL-1 pathway | Coinhibitory molecule, conversion of Th1 cells to Tregs | Preclinical (mouse) | 132 |
| IDO | Rate-limiting enzyme in tryptophan (required for T-cell proliferation) metabolism | Preclinical (mouse, human) | 133,134 |
| Arginase-1 | L-arginine depletion, reducing T-cell signaling and inflammatory cytokines | Preclinical (mouse) | 59 |
| TLR/MyD88 signaling inhibitors | Interfere with danger signaling, especially via inhibitory oligonucleotides against TLR9, to reduce inflammation | Preclinical (mouse) | 135 |
| Notch/notch ligand inhibitors | Detal-like1/4 (notch ligand) inhibitor given peritransplant prevented GVHD, while Notch 1 inhibitor lead to intestinal toxicity | Preclinical (mouse) | 136 |

# Approaches to prevention and treatment of acute GVHD (2)

| | | | |
|---|---|---|---|
| **Cytokine/growth factor modulation** | | | |
| JAK/STAT inhibition | Reduction in inflammatory cytokines | Preclinical, case report | 137,138 |
| IL-17 downregulation | Curcumin downregulates IFNγ and IL-17 production, ameliorating aGVHD | Preclinical (mouse) | 139 |
| IL-21 blockade | Enhances generation of inducible Tregs | Preclinical (mouse) | 140 |
| IL-22 augmentation | Protective factor for intestinal stem cells under immune attack | Preclinical (mouse) | 141 |
| IL-23 blockade | Reduces inflammatory cytokines, T-cell trafficking, gut protection | Preclinical (mouse)<br>Case report, phase 2 (ongoing) | 66,142 |
| **Cell-based therapies** | | | |
| MSCs | Suppress immune effector functions, secrete cytokines/growth factors for tissue repair and angiogenesis, can be obtained from related donors or third party | Phase 3, not yet reported in peer-reviewed literature (NCT00366145) | 124,143 |
| MAPCs | No expression of classical HLA class I markers (distinct from MSC), suppress T-cell activation via prostaglandin E2 synthesis, but only if colocalized with T cells at sites of activation | Preclinical (mouse) | 144,145 |
| Tregs | Expanded from umbilical cord blood, reduced aGVHD grade II-IV incidence from 61% to 43% in double UCB HCT (historical control); in haploidentical-related donors, Tregs reduced GVHD and enhanced immune reconstitution | Phase 1 | 54,146 |
| $TRAIL^+$ T cells | Cytolytic mechanism against both tumor cells and alloreactive T cells | Preclinical (mouse) | 147 |
| NKs | GVHD protection only conferred if infusion was derived from Ly49-mismatched donor | Preclinical (mouse) | 148 |
| NKTs | Invariant NKTs attenuated murine GVHD in association with increased IL-2, IL-4, and IL-5 levels | Preclinical (mouse) | 149 |
| DCs | Tolerogenic DCs enhanced immunosuppressive cytokines in circulation, increased Tregs | Preclinical (mouse) | 150 |
| MDSCs | L-arginine depletion, contact-dependent immunosuppression | Preclinical (mouse) | 59 |

IDO, indoleamine 2,3 dioxygenase; IFN, interferon; JAK, Janus kinase; KGF, keratinocyte growth factor; MAPC, multipotent adult stromal cell; PDL, programmed death ligand; PKC, protein kinase C; STAT, signal transducer and activator of transcription; TRAIL, TNF-related apoptosis inducing ligand; UCB, umbilical cord blood.

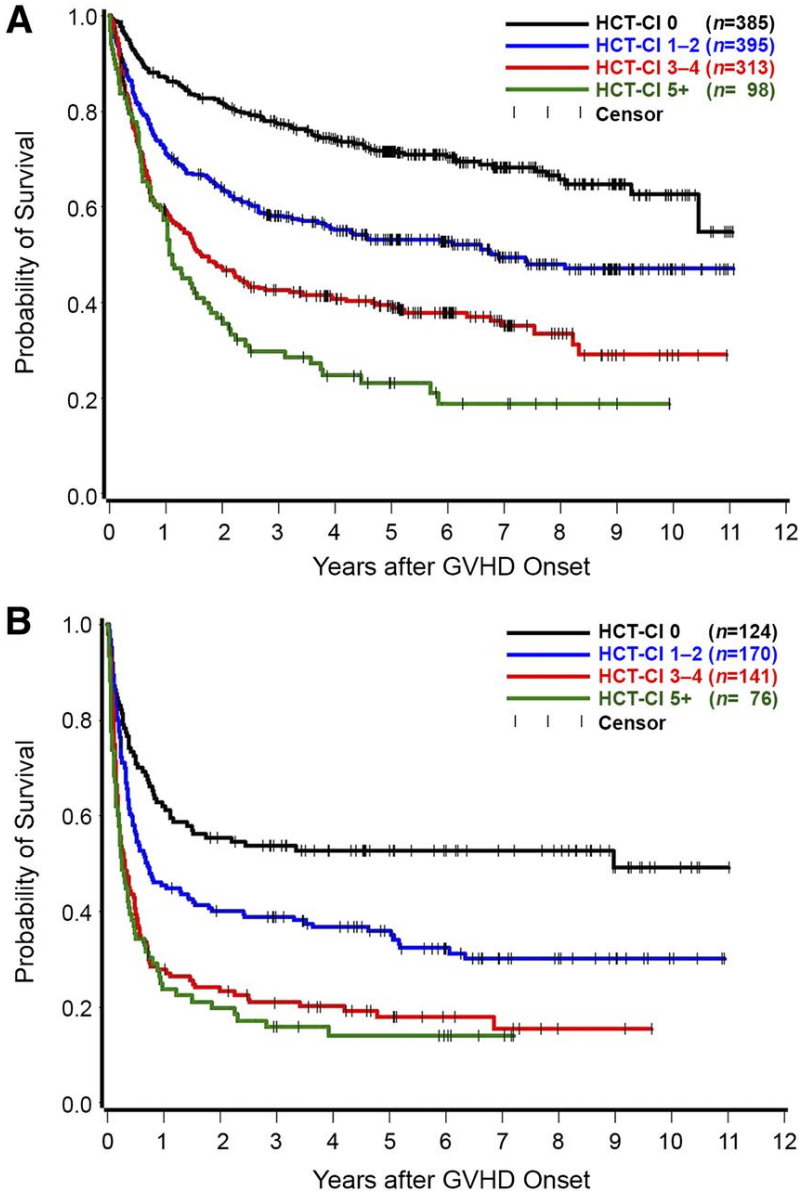
# Approaches to prevention and treatment of acute GVHD (3)

**Table 1. (continued)**

| Treatment or pathway | Potential mechanism(s) of action | Level of evidence | References |
|---|---|---|---|
| **Microbiota** | | | |
| α-defensins | Antimicrobial peptides secreted by intestinal Paneth cells, a target of GVHD | Preclinical (mouse) | 151 |
| Physiologic diversity | GVHD causes increase in *Lactobacillales* and decreases in *Clostridiales*, resulting in loss of physiologic diversity in gut bacteria | Preclinical (mouse and human) | 152 |
| *Candida* colonization | Patients colonized with *Candida* spp. had an increased incidence of grade II-IV GVHD (50% vs 32%) | Preclinical (human) | 153 |
| α-galactosylceramide (RGI-2001; RegImmune) | Produced by microbiome, can bind C1d and activate NKTs, induce Tregs | Preclinical (mouse)<br>Phase 1/2a (ongoing) | 154,155 |
| **Donor-based immunomodulation** | | | |
| KGF (palifermin) | Epithelial, including thymic cytoprotection, inflammatory cytokine response, skewing toward Th2 cytokine response, although there was no reduction in GVHD when recipients were treated with palifermin in a phase 1/2 clinical trial | Preclinical (mouse) | 156,157 |
| Statins | Retrospective study demonstrated reduced grade III-IV GVHD in related HCT from statin-treated donors | Preclinical (mouse, human)<br>Phase 2 (ongoing) | 158 |

IDO, indoleamine 2,3 dioxygenase; IFN, interferon; JAK, Janus kinase; KGF, keratinocyte growth factor; MAPC, multipotent adult stromal cell; PDL, programmed death ligand; PKC, protein kinase C; STAT, signal transducer and activator of transcription; TRAIL, TNF-related apoptosis inducing ligand; UCB, umbilical cord blood.

# Overall survival after diagnosis of acute GVHD, by grade

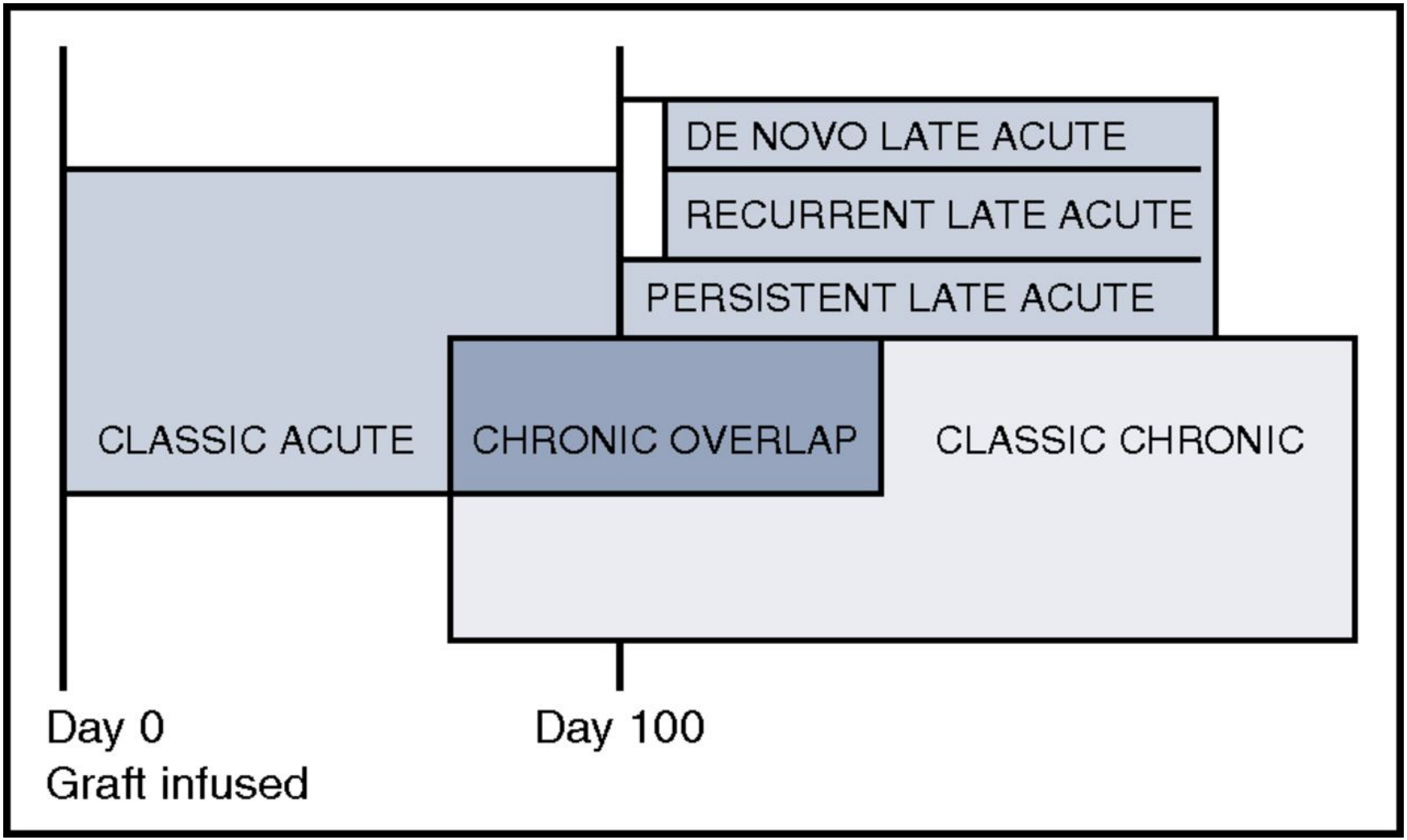



**Mohamed L. Sorror et al. Blood 2014;124:287-295**



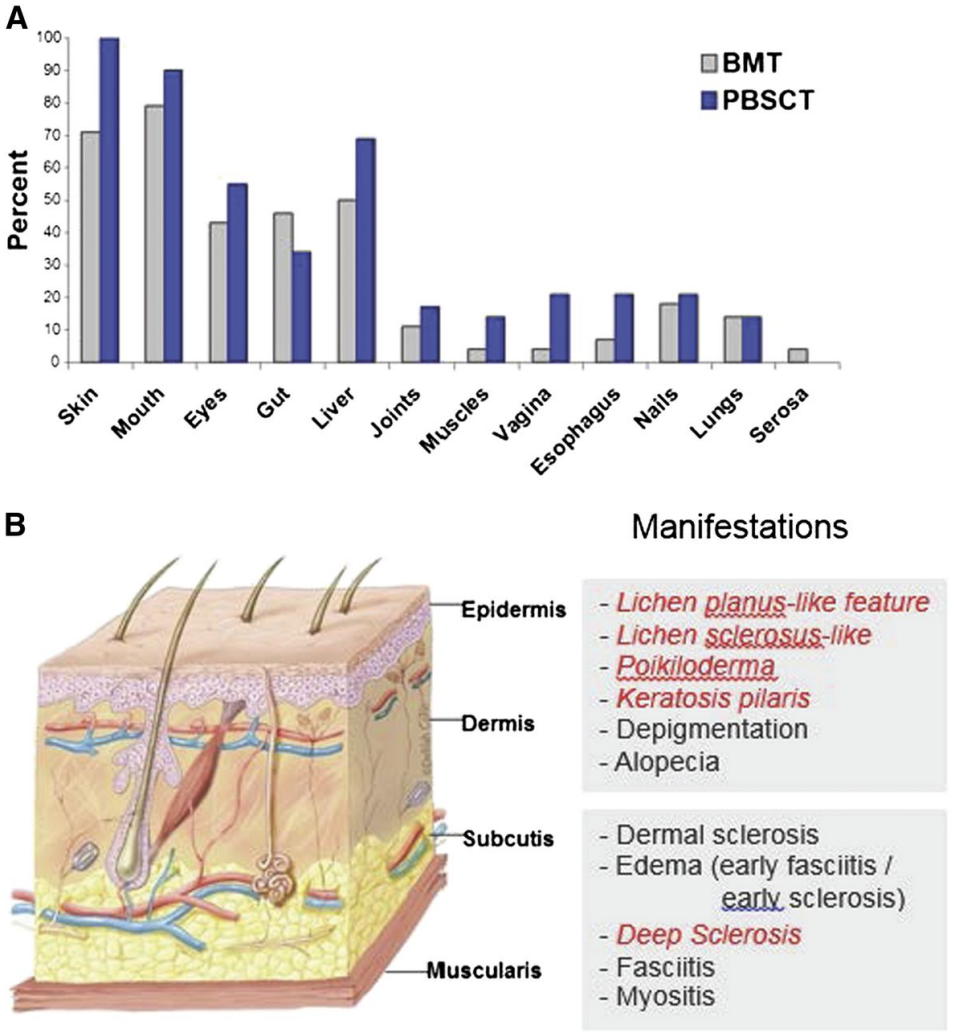
blood

# Acute, late acute, chronic overlap, and classic chronic GVHD



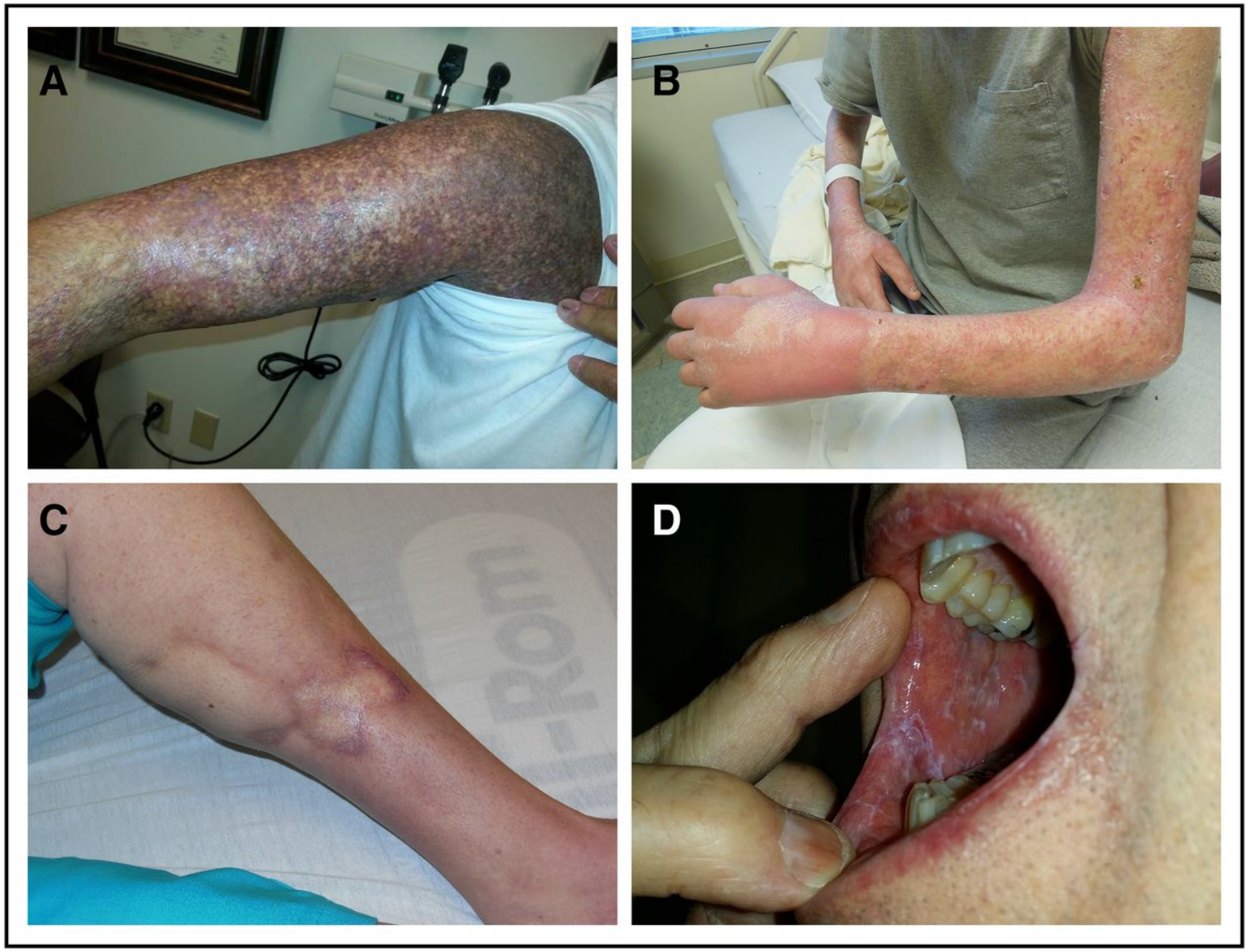

Stephanie J. Lee Blood 2017;129:30-37

# The frequency of involvement by chronic GVHD varies across organs and sites and is higher after HCT with mobilized blood cells as compared with marrow




**Mary E. D. Flowers, and Paul J. Martin Blood 2015;125:606-615**

# Skin and oral manifestations of chronic GVHD

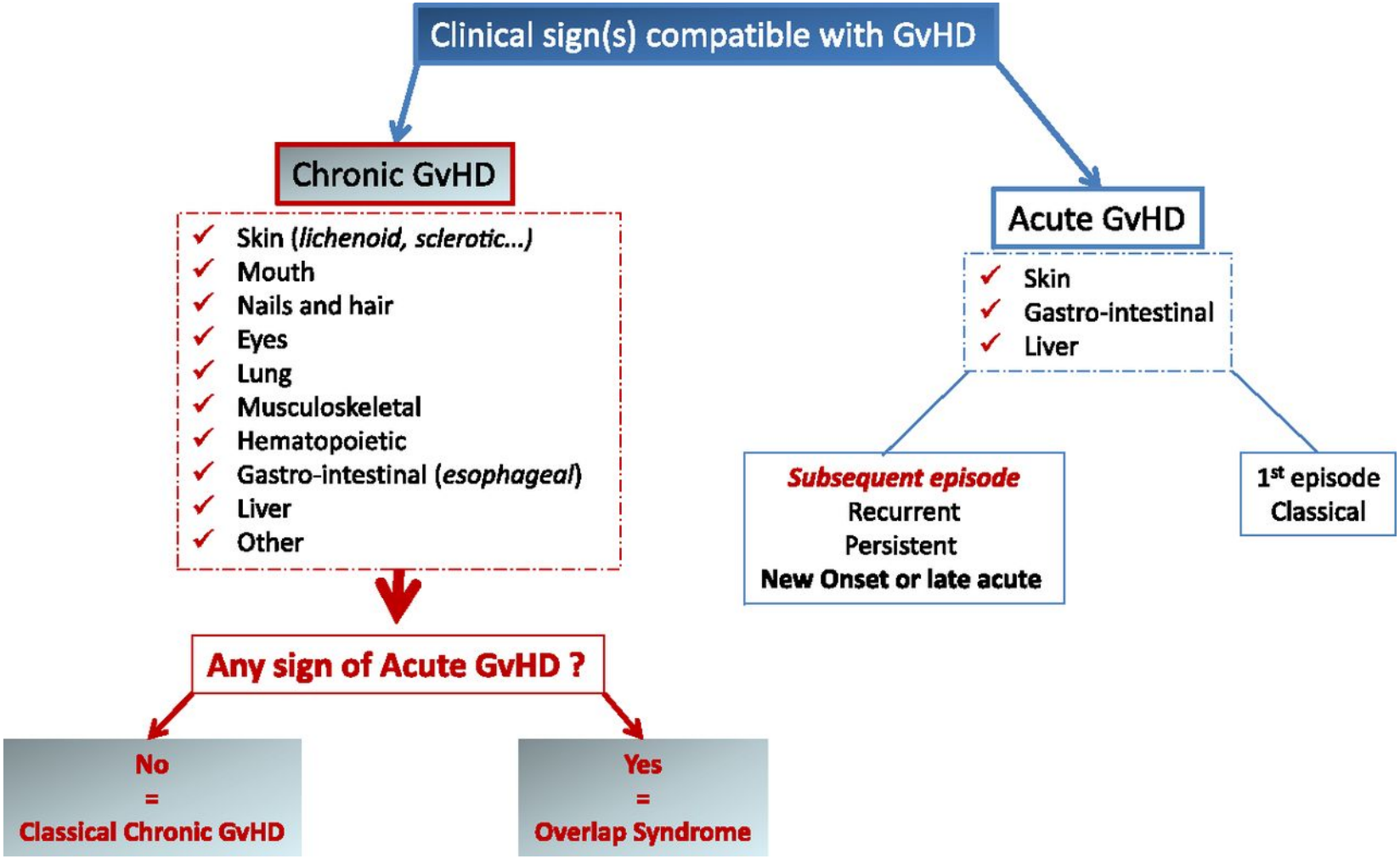



Stephanie J. Lee Blood 2017;129:30-37



blood

# Diagnosis of chronic GVHD, according to the NIH consensus criteria



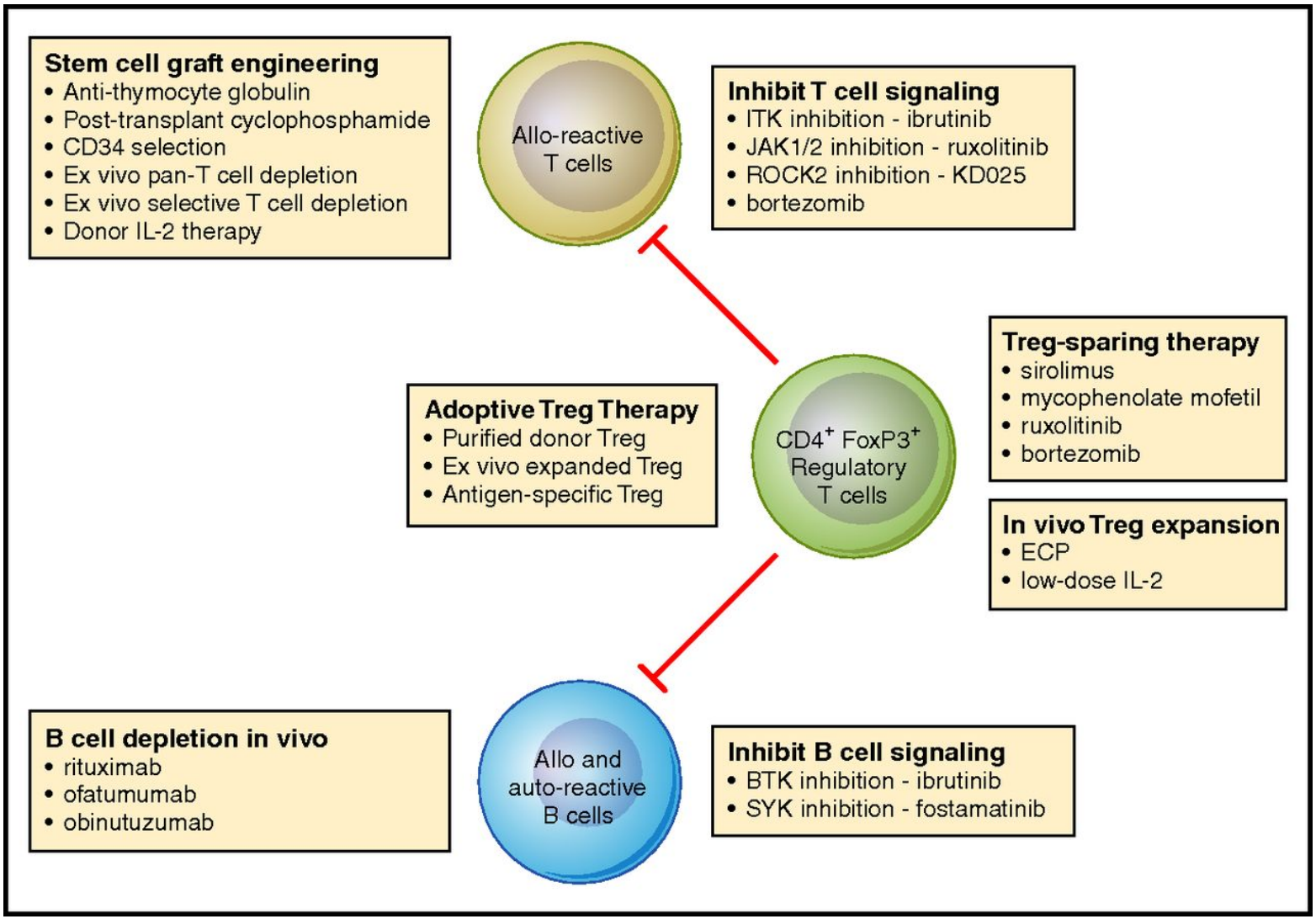

Gérard Socié and Jerome Ritz Blood 2014;124:374-384

# Severity of chronic GVHD: mild, moderate, severe

| | |
|---|---|
| Mild | • 1 or 2 organs or sites (except lung) with score 1<br>  • Mild oral symptoms, no decrease in oral intake<br>  • Mild dry eyes, lubricant eyedrops ≤ 3x/day |
| Moderate | • 3 or more organs with score 1<br>• At least 1 organ or site with score 2<br>  • 19-50% body surface area involved or superficial sclerosis<br>  • Moderate dry eyes, eyedrops > 3x/day or punctal plugs<br>• Lung score 1 (FEV1 60-79% or dyspnea with stairs) |
| Severe | • At least 1 organ or site with score 3<br>  • > 50% body surface area involved<br>  • Deep sclerosis, impaired mobility or ulceration<br>  • Severe oral symptoms with major limitation in oral intake<br>  • Severe dry eyes affecting ADL<br>• Lung score 2 (FEV1 40-59% or dyspnea walking on flat ground) |

Stephanie J. Lee Blood 2017;129:30-37

# Mechanistic interventions for the prevention or treatment of chronic GVHD



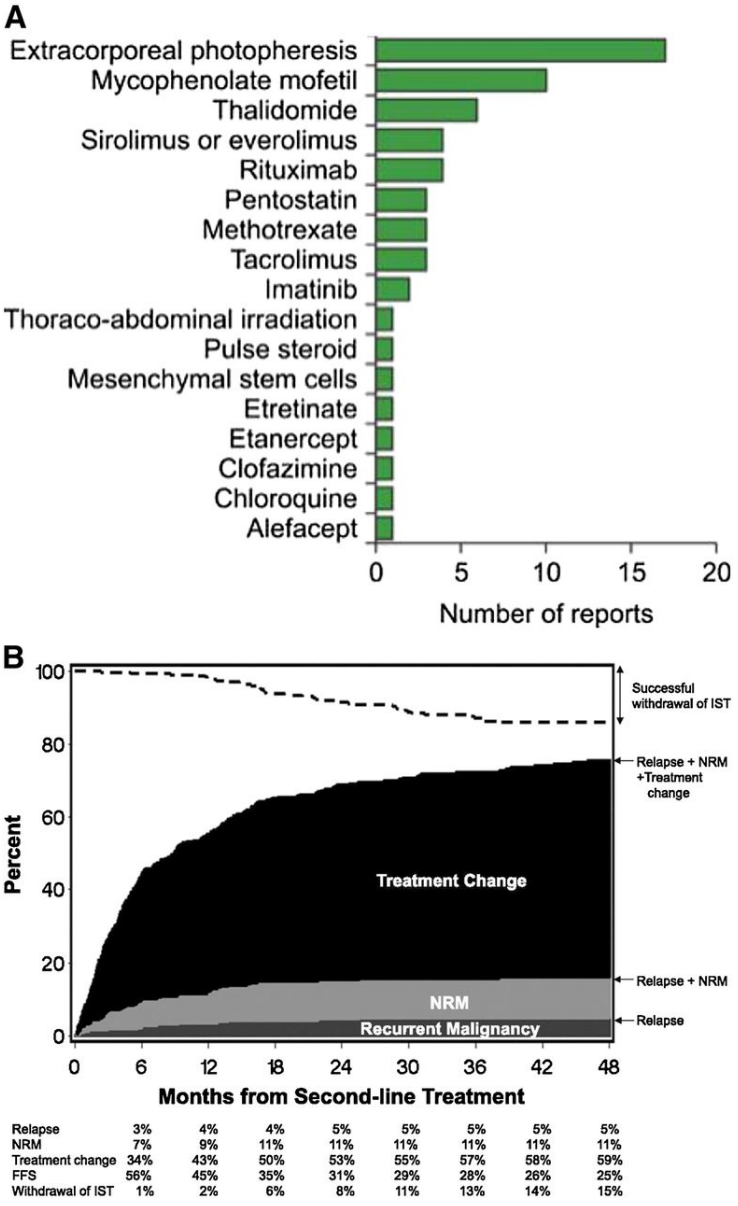

Corey S. Cutler *et al*. Blood 2017;129:22-29

# Prophylactic regimens and treatments for chronic GVHD

**Table 3. Prophylaxis regimens and treatments for chronic GVHD**

| Randomized trial | Main results on chronic GVHD | Reference |
|---|---|---|
| **Acute GVHD prophylaxis** | | |
| Calcineurin inhibitors +/– methotrexate | No effect | 10, 76 |
| Prolonged cyclosporine | No effect | 10, 76 |
| Ex vivo T-cell depletion | No effect | 10, 76, 77 |
| Antithymocyte globulin | Decreased incidence | 72-75 |
| **First-line treatment** | | |
| Prednisone +/– azathioprine | Prednisone better | 79 |
| Prednisone + cyclosporine vs prednisone | Reduced prednisone exposure with combination | 80 |
| Prednisone + cyclosporine vs prednisone + cyclosporine + thalidomide | No benefit of thalidomide | 81, 82 |
| Prednisone + cyclosporine vs prednisone + cyclosporine + mycophenolate mofetil | No benefit of mycophenolate mofetil | 83 |
| Prednisone +cyclosporine vs prednisone +cyclosporine + hydroxychloroquine | No benefit of hydroxychloroquine | 84 |

# Second-line treatment of chronic GVHD




Gérard Socié and Jerome Ritz Blood 2014;124:374-384



blood

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