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2020 NIH Chronic GvHD Consensus Project on Etiology and Prevention

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KMW – none

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Purpose of the WG1 document

- **Etiology & Prevention** – Identify knowledge gaps needed to approach how best to assess risk and to prevent cGVHD
  In patients who have not yet developed signs or symptoms of cGVHD
- **Reaching Consensus** – Held a series of meetings/discussions and many written drafts, we reached general agreement about etiology & prevention.
  This is not a review article or a guide to treatment
- **Major objective** – Set the Next Gen Research Agenda
  What future research will be both scientifically and clinically impactful

What do we know and what do we need to know about the Etiology and pathogenesis that informs us regarding the risk of cGVHD and the intervention points

Introduction to the WG1 document

***Key Point**: Moderate to severe cGVHD leads to excess morbidity and mortality and should be prevented.*

- Despite the advent of effective cGVHD prevention strategies, further scientific and clinical research is needed.
- T-cell depletion strategies decrease the risk of cGVHD but can also impair immune reconstitution and anti-tumor effects after HCT.

Etiology & Prevention: What We Know

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What we know:

- From clinical trials, we know certain T cells subsets are needed for cGVHD development
- From preclinical studies, we know that donor-derived T cells, antibody-producing B cells, monocytes and recipient-derived fibroblastic reticular cells (FRC) contribute to development of the disease.
- Studies with 3 different methods show improvement re cGVHD prevention (ATG, PTCY, naïve T depletion) – encouraging results! TABLE 1 is a summary of such progress…

So, are we done?…

Etiology & Prevention: Gaps in Knowledge

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What we don't know that is critical for risk stratification:

- Risk of infection, cancer are significant issues
- Morbid forms of cGVHD still develop

Coordinated effector pathways leading to cGVHD poorly understood

Host factor contributions and second insults remain poorly understood

How do we best approach design of Prevention Trials?

Outline of the WG1 document

I. Primary Insults – Immune cell-driven etiology of chronic GVHD and potential points of intervention

II. Secondary Insults in cGVHD - Damage/dysfunction of host immune tissues/organs in cGVHD development and potential points of intervention.

III. Based on what we know about cGVHD etiology, how might we assess risk of cGVHD development?

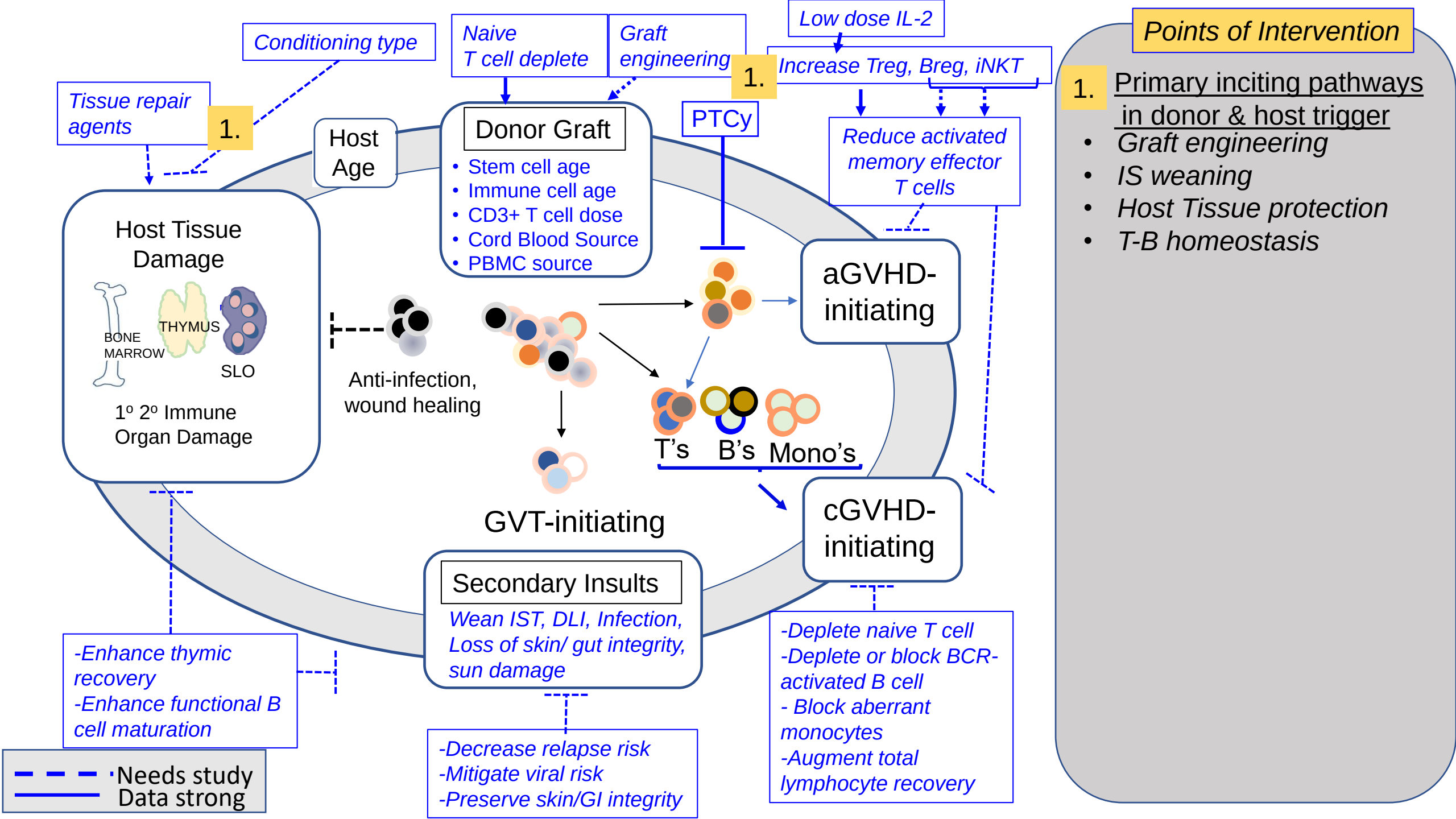
IV. How do we best consider the risk of recurrent or progressive malignancy as we consider prevention of cGVHD?

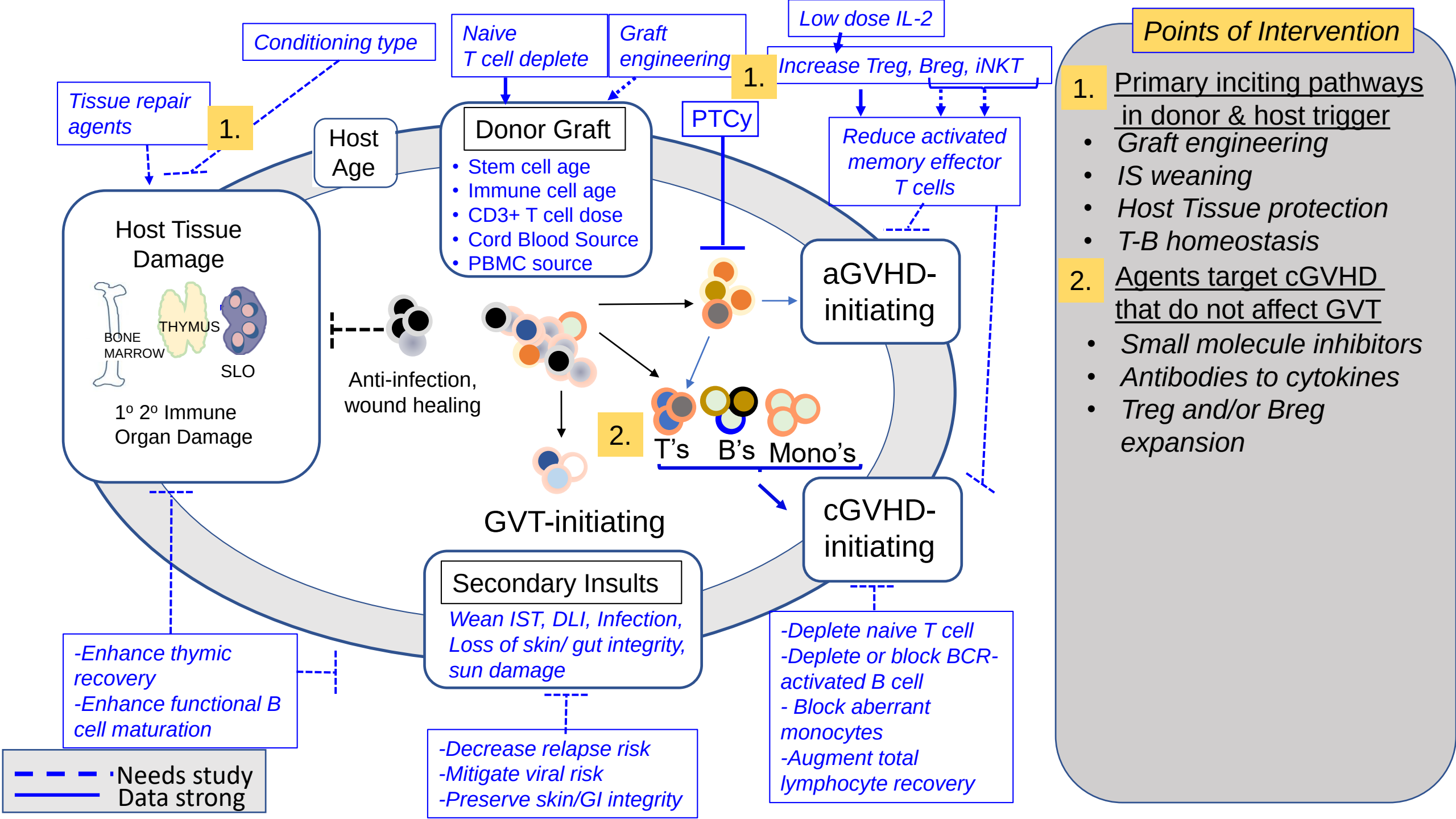
V. Critical questions and answers about cGVHD prevention trials

Factors (aside from acute GVHD) that confer risk of cGVHD

From patients

Donor factors	**HLA mismatch**[126]
	Unrelated donor (except CB)[7, 126]
	Older donor age[126]
	Female donor for male recipient[7, 126]
	Parity of female donor[126]
	Mobilized blood cell graft[7, 126]
	Cord blood graft (low risk)[7]
	Genetic polymorphisms[127-129]
Recipient factors	Older patient age[7, 126]
	Genetic polymorphisms[127-130]
	Radiation for sclerotic GVHD[131, 132]
	Busulfan for BOS[133]


Conditioning type
Naive
T cell deplete
Graft
engineering
Low dose IL-2
Increase Treg, Breg, iNKT
Tissue repair
agents
1.
1.
Host
Age
Donor Graft
• Stem cell age
• Immune cell age
• CD3+ T cell dose
• Cord Blood Source
• PBMC source
PTCy
Reduce activated
memory effector
T cells
Host Tissue
Damage
BONE
MARROW
THYMUS
SLO
1º 2º Immune
Organ Damage
Anti-infection,
wound healing
aGVHD-
initiating
T's
B's
Mono's
cGVHD-
initiating
GVT-initiating
Secondary Insults
Wean IST, DLI, Infection,
Loss of skin/ gut integrity,
sun damage
-Enhance thymic
recovery
-Enhance functional B
cell maturation
-Decrease relapse risk
-Mitigate viral risk
-Preserve skin/GI integrity
-Deplete naive T cell
-Deplete or block BCR-
activated B cell
- Block aberrant
monocytes
-Augment total
lymphocyte recovery
Needs study
Data strong
Points of Intervention
1. Primary inciting pathways
in donor & host trigger
• Graft engineering
• IS weaning
• Host Tissue protection
• T-B homeostasis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1. Primary inciting pathways in donor & host trigger
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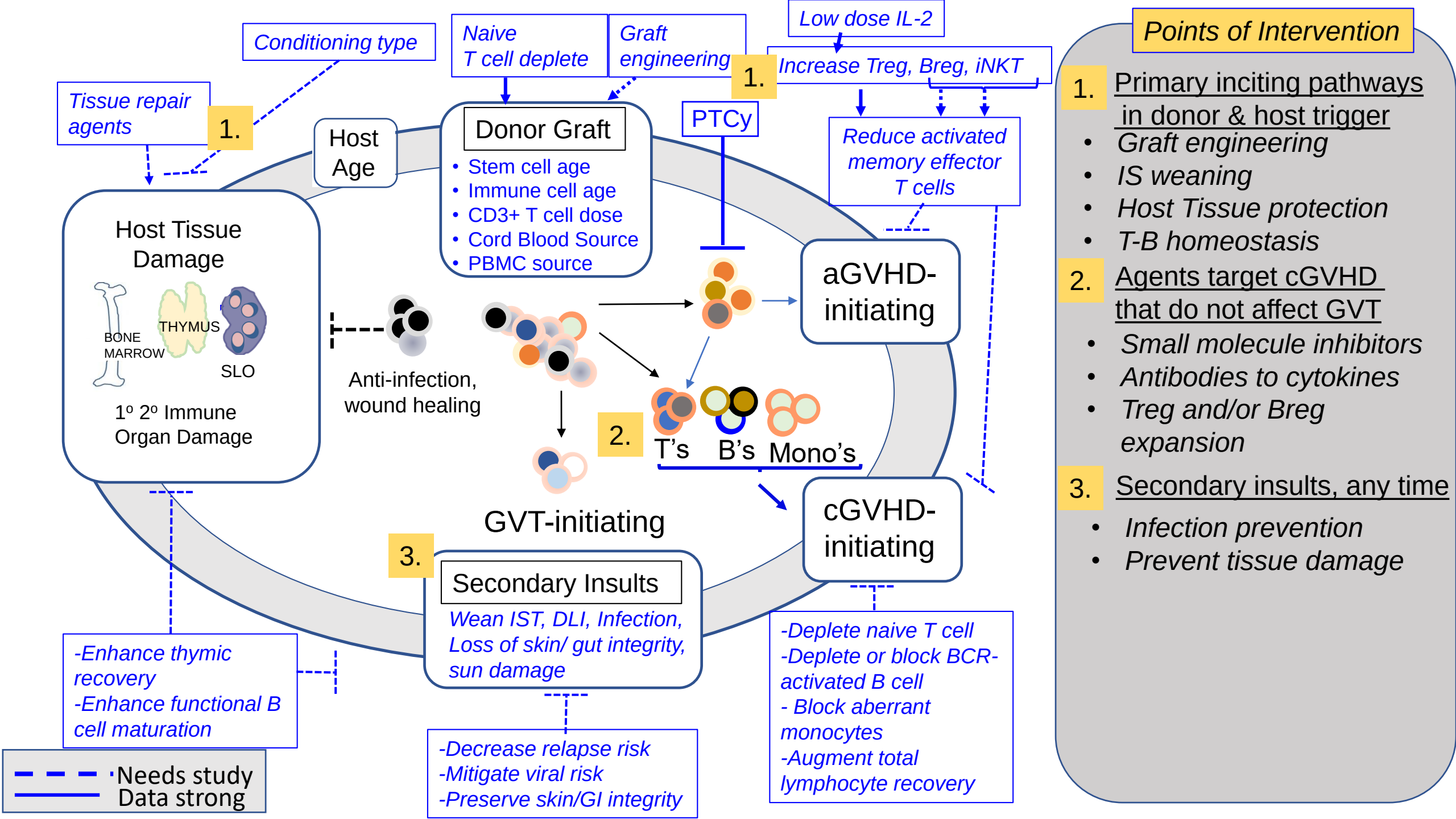
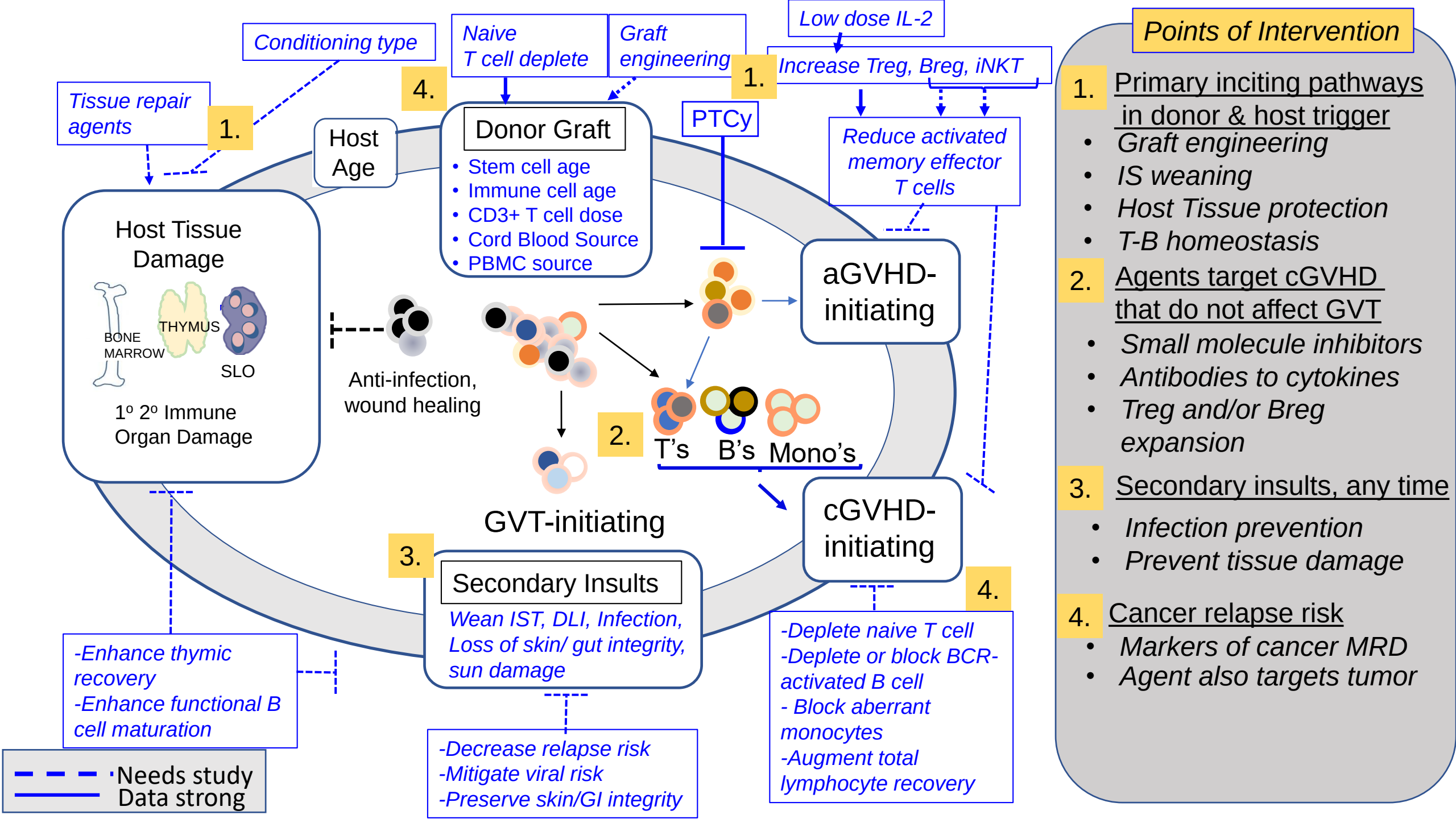
2. Agents target cGVHD that do not affect GVT
• Small molecule inhibitors
• Antibodies to cytokines
• Treg and/or Breg expansion



Points of Intervention

1. Primary inciting pathways in donor & host trigger
   - *Graft engineering*
   - *IS weaning*
   - *Host Tissue protection*
   - *T-B homeostasis*
2. Agents target cGVHD that do not affect GVT
   - *Small molecule inhibitors*
   - *Antibodies to cytokines*
   - *Treg and/or Breg expansion*
3. Secondary insults, any time
   - *Infection prevention*
   - *Prevent tissue damage*


Conditioning type
Naive T cell deplete
Graft engineering
Low dose IL-2
Increase Treg, Breg, iNKT
Tissue repair agents
1.
4.
1.
Host Age
Donor Graft
• Stem cell age
• Immune cell age
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• PBMC source
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BONE MARROW
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aGVHD-initiating
2.
T's
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cGVHD-initiating
GVT-initiating
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Secondary Insults
Wean IST, DLI, Infection, Loss of skin/ gut integrity, sun damage
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-Enhance thymic recovery
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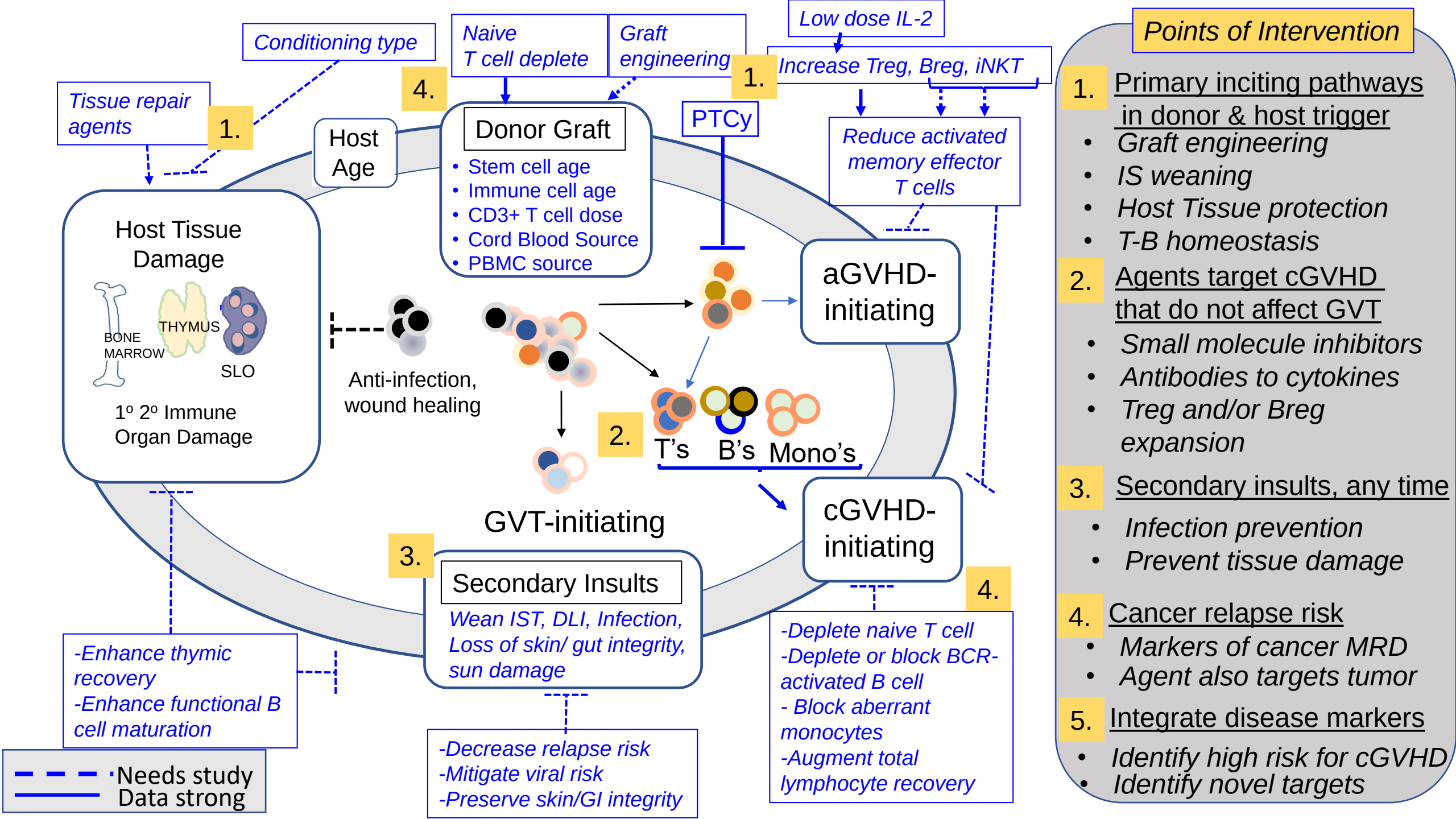
3. Secondary insults, any time
• Infection prevention
• Prevent tissue damage
4. Cancer relapse risk
• Markers of cancer MRD
• Agent also targets tumor



Points of Intervention

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   - *Small molecule inhibitors*
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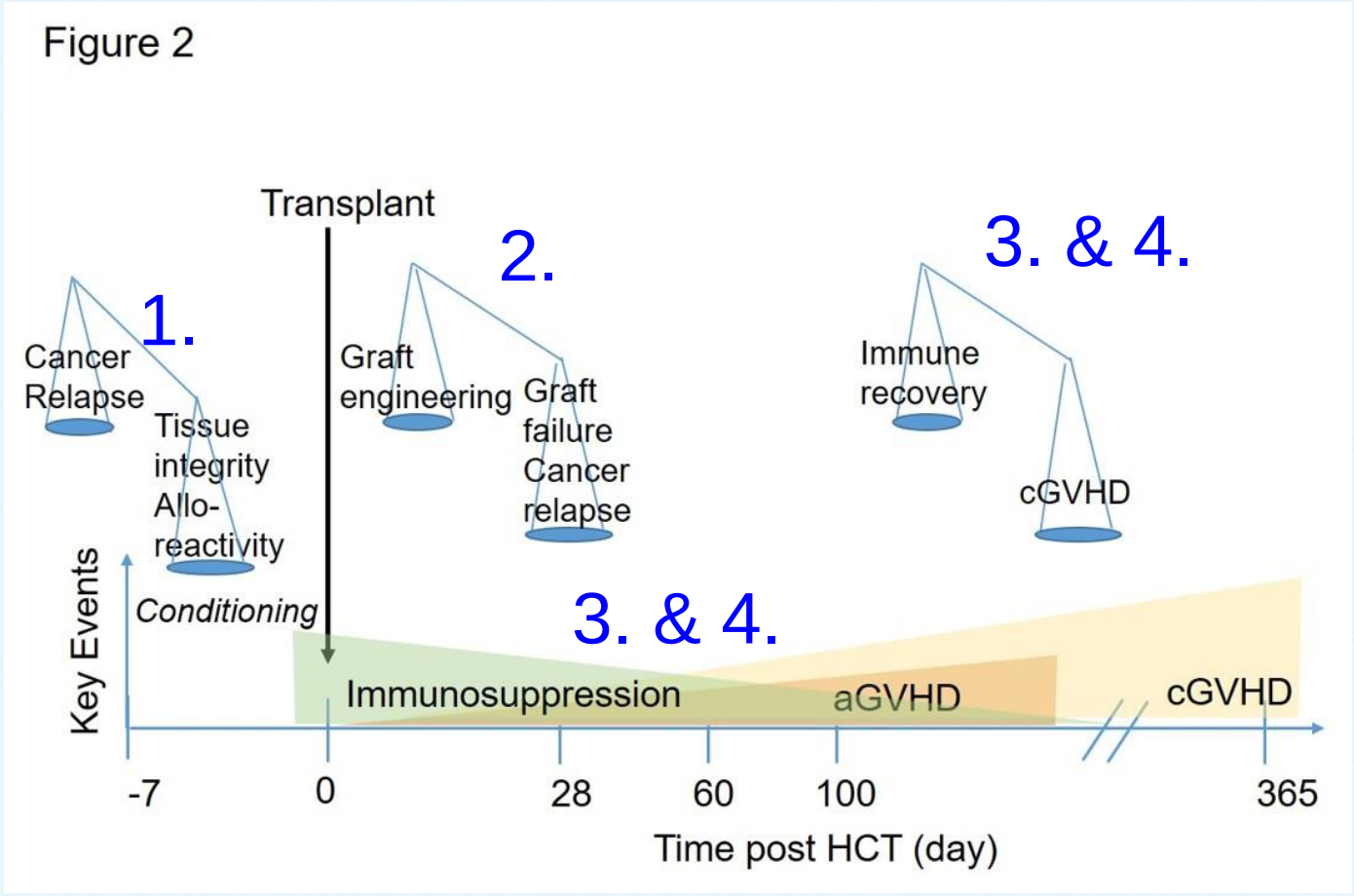
3. Secondary insults, any time
   - *Infection prevention*
   - *Prevent tissue damage*
4. Cancer relapse risk
   - *Markers of cancer MRD*
   - *Agent also targets tumor*
5. Integrate disease markers
   - *Identify high risk for cGVHD*
   - *Identify novel targets*

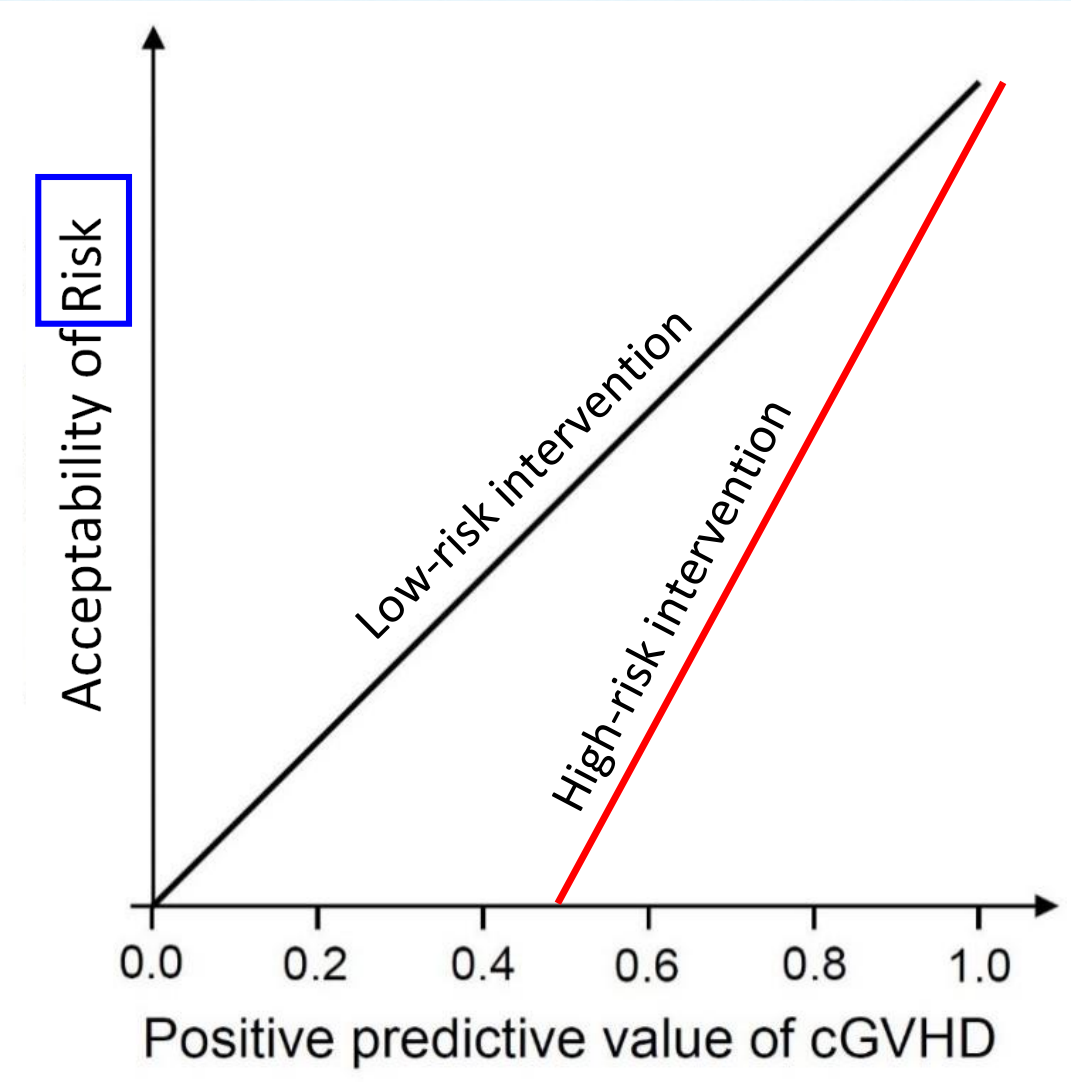
Figure 2 – Balancing risks and benefits of interventions



1. Type of conditioning
2. Type of Graft
3. Immunosuppression (IS) type
4. IS weaning strategy

Figure 3 – Consideration of risk as we develop cGVHD prevention trials

Risk –
-Graft rejection
-Infection
-Delayed immune recovery
-Recurrent Cancer

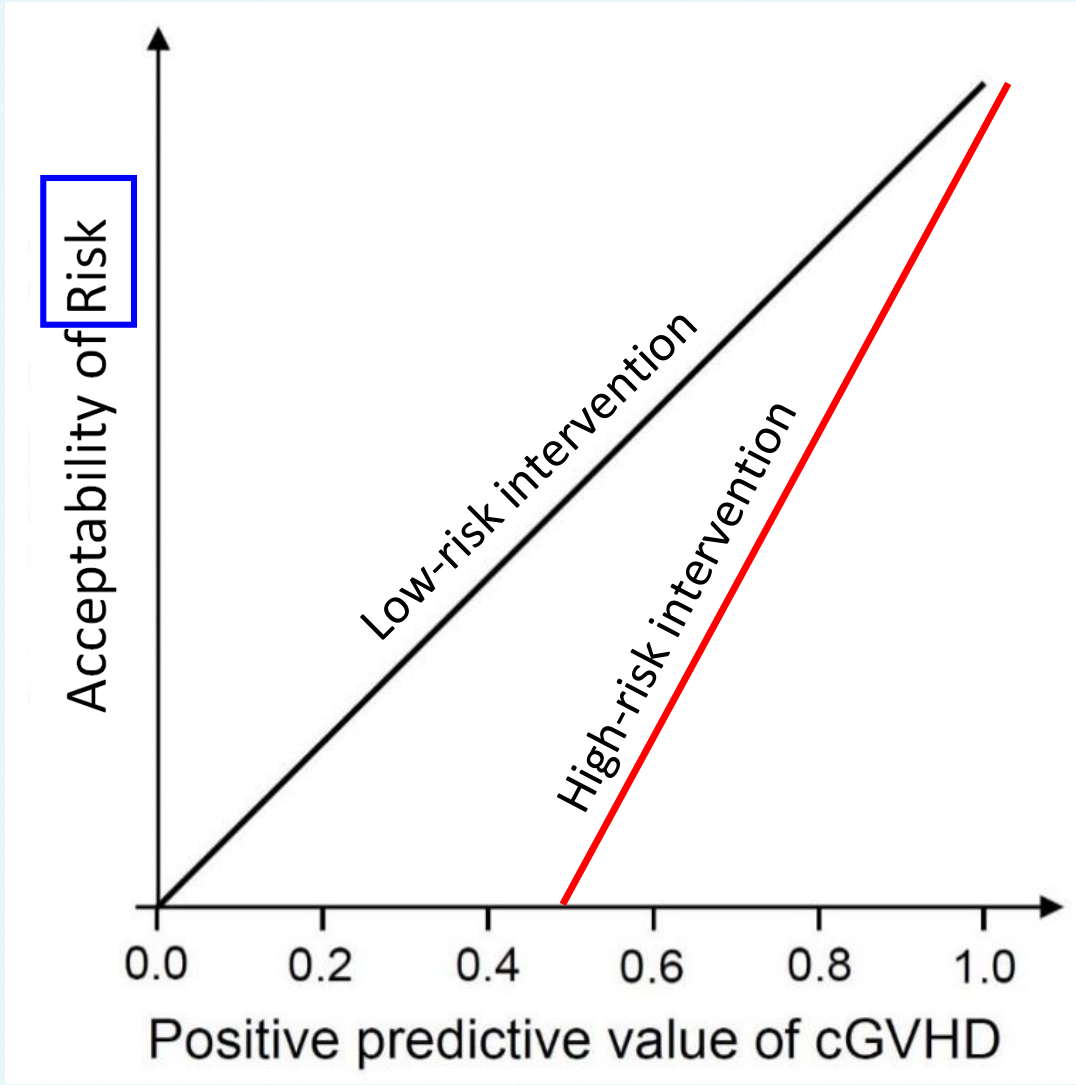


Potential benefit is proportional to **PPV (y-axis)**

Figure 3 – Consideration of risk as we develop cGVHD prevention trials

Risk –
-Graft rejection
-Infection
-Delayed immune recovery
-Recurrent Cancer

- *High-risk interventions are acceptable only for patients at high risk of cGVHD*
- *Lower-risk interventions may be acceptable for patients at lower risk of cGVHD.*



Potential benefit is proportional to **PPV (y-axis)**

QUESTION: Is the study intervention efficacy high enough to warrant effort and cost of a given prevention trial?

As shown on x-axis - eligibility criteria should be defined to select patients at **high risk of mod-severe cGVHD**

Etiology & Prevention: Etiology Major Points of Discussion

- From clinical trials, we know that certain T cells subsets are needed for chronic GVHD development
- From preclinical studies, we know that donor-derived T cells, antibody-producing B cells, monocytes and recipient-derived fibroblastic reticular cells contribute to development of the disease.
- Studies with 3 different methods show improvement re chronic GVHD prevention (ATG, ALG, PTCy, naïve T depletion) – encouraging results! TABLE 1 in the manuscript is a summary of such progress…

Do we have more to learn?

Can we use what we know to risk stratify?

Etiology & Prevention: Clinical Trials- Major Points of Discussion

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What is the most appropriate primary endpoint in prevention trials?

- We would propose moderate-severe chronic GVHD-free survival.

How well do pre-transplant risk factors predict the probability of moderate-severe chronic GVHD-free survival?

- No studies have addressed this question.

What are the most promising avenues to explore in future prevention trials?

- No consensus has been reached. **Further trials are needed!**

Open issues

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- Has the problem of mod-sever chronic GVHD development been solved—*Do we need chronic GVHD prevention trials?*
- Given what we know about etiology – *Can we risk stratify and apply strategies to prevent Moderate-Severe disease? Can we apply multi-omics approaches?*
- Re Host behaviors - *Can secondary insults be points of intervention?*
- Re Age: *What can we learn from host age (pediatric patients) about cGVHD etiology?*
- Risk stratification should include cGVHD-GVT link: *Without cGVHD do we get sufficient GVT needed for some patients?*

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Commentator

Paul Martin

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Panel Q and A

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Audience Discussion