

Point-to-point reply

Geerman & Nolte, WJSC 29741

Title: *Impact of T cells on HSPC function: good guys or bad guys?*

Our manuscript was reviewed by 3 reviewers: #2446114, #2104609, and #1851506. We thank the reviewers for their effort. The first two reviewers had no comments and accepted the manuscript in its original form. The third reviewer (#1851506) was also positive, but did pose several constructive remarks and made some helpful suggestions. Below are the comments of this reviewer, and our reply in blue font.

General comments

This review discusses the issues relevant to the successful hematopoietic stem cell transplantation, in particular, the yin and yang features of T cells in the donor cells. In general the text is well written. However, the lack of figures has significantly lowered the quality of this review.

We agree with the reviewer, and we have therefore included a table and a figure summarizing the most important content of the review.

Major concerns:

It will be difficult for those who are not expert in the field to follow the context without figures. Therefore, I strongly recommend the authors to provide some figures to facilitate reader's comprehension. For example:

- a figure depicting the problems and the advantages using UCB and MPB in HSPC transplantation is nice to illustrate the status quo.
- Another figure will illustrate what issues should be resolved, how they can be resolved (i.e. what type of T cells is desirable or should be eliminated to have a safe and efficient HSPC transplantation in the context of tumor eradication, or of GvHD, etc?).
- Furthermore, the authors can add another figure illustrating the different combination of HSPC (UCB alone, UCB combined with CD34+ cells from haploidentical grafts) pointing out the constraints, limitations, advantages, and disadvantages, if any.
- Regarding the effects of CD8 and/or CD4 (TCR $\gamma\delta$) T cells on HSPC transplantation, it is highly desirable to put a figure illustrating possible interactions among the putative players with the effectors such as cytokines and cell adhesion molecules.

The suggestions made by the reviewer for new figures are interesting, though we feel that they do not necessarily reflect our main message and they are partly beyond the scope of this review. Instead, we decided to add a table in which we summarize the impact that T cell depletion of an HSPC graft, or selective donor lymphocyte infusion, can have on the clinical outcome of an HSPC transplantation (Table 1). Moreover, we added a new figure that graphically summarizes potential mechanisms on how CD8⁺ T cells improve HSPC engraftment (Figure 1). We feel that these new displayed items recapitulate the most important concepts that we have discussed in the text, and thereby enhance the readability and quality of the review.

Minor points

1. How do the authors distinguish HSC from HSPC? It is not clear for me whether or not the authors intentionally use these different terms. If it is, please clarify the difference. The term HSC was used when we refer to the long-term, self-renewing hematopoietic progenitor population that is at the top of the hematopoietic hierarchy. We use the term HSPCs when we refer to the mixture of HSCs and progenitor cells, which provides respectively long and short-term repopulation following transplantation. We clarified this on page 5.

2. The following sentence is difficult to follow. Therefore, I recommend authors to modify or restructure the sentence so that general readers could understand. Page 4 Allogeneic HSCT is regarded as a more precarious procedure, as HSPCs from a non-self origin are transplanted, which are thus subject to rejection.
[We agree and we modified this sentence.](#)
3. What does "it" mean? Grafts depleted of T cells or simply it should be "they"? Page 6 While grafts depleted of T cells minimize the risk of developing GvHD, it also compromises the engraftment of transplanted HSPCs.
[We agree and we modified this sentence.](#)
4. " is " should be " are ". Page 6 Further examination on the CD8+ TCR β + cells, which is more predominately present in the BM, revealed that they express CD44 (Gandy et al. 1999).
[We agree and we modified this sentence.](#)
5. The following sentence is difficult to follow. Therefore, I recommend authors to modify or restructure the sentence so that the general readers could understand. page 7 This indicates that the impact that T cells can have on the behavior and function of HSPCs is complex and not only dependent on the T cell subset, but also on its activation status and the cells it interacts with.
[We agree and we modified this sentence.](#)
6. There is inconsistency in the format referring the literature at the beginning of sentence. For example, Stemberger and colleagues (line 3) vs. Rutella et al., 2000 (line 12), both in page 11. Although the format is at the discretion of the authors, it is better use the same one throughout the manuscript.
[These inconsistencies have been addressed.](#)

[We thank the reviewer for the insightful comments and constructive remarks. We feel that our revisions to address these issues have considerably improved the manuscript. We hope that the reviewer and editor agree with these improvements, thereby enabling rapid publication of this manuscript.](#)