

## **Reviewer 1.**

Dear Authors, I have gone through the manuscript, which i found to be of importance in the field. I would recommend the following changes to be made in manuscript:

*We thank the reviewer for the positive feedbacks on the manuscript. We provided a point-by-point response to all the comments. All the changes in line with the comments of the reviewer are highlighted in yellow in the revised manuscript. Please find here the detail of the answers:*

**1. The current form of manuscript has to go through the English language edit, as i found many grammatical typos.**

*Answer: We thank the reviewer for the important comment. As requested, the revised manuscript as proof readed.*

**2. The first two paragraphs need to be removed, they provide an impression as if it is a newspaper article reporting on the issue.**

*Answer: We thank the reviewer for the pertinent comment. As requested, we changed the and reduced the size of the introduction and stated a clear research question. We changed the beginning of the introduction section: “In human health, DNA sequencing technologies, including 16S rRNA gene-based amplicon sequence analysis and whole genome shotgun metagenomic analysis were used to discover how exogenous and intrinsic host factors influence gut microbiome composition [1,2]. In large cohorts, scientists investigated the impact of factors such as lifestyle, dietary information, anthropometrics and drugs on the gut microbiome communities [3,4]. They found that age, gender, dietary factors and intrinsic parameters were highly correlated with composition and function of the gut microbiome. They also observed that several drug categories, such as antibiotics, proton-pump, metformin, statins, and laxatives, had a strong effect on the gut microbiome. On the other hand, gut microbiome can affect the bioavailability of oral drugs [5]. Thus, micro-organisms can impact drug absorption and metabolism, that may explain, in part, inter-individual heterogeneity in drug response and disposition [6].”*

**3. There is a need to add a table about each and every microbe found in gut, classification, types etc .. and the association with specific disease... for the indepth coverage and benefit of readers.**

*Answer: Good point for the reviewer. We thank the reviewer, and, as requested, we added a table that summarize the results of the previous studies. A sentence was added in the manuscript: “Several studies reported the profound alteration of the gut microbiota during the aHSCT procedure, as summarized in Table 1.”*

## **Reviewer 2.**

*We thank the reviewer for the positive feedbacks on the manuscript. We provided a point-by-point response to all the comments. All the changes in line with the comments of the reviewer are highlighted in yellow in the revised manuscript. Please find here the detail of the answers:*

**1. Your work related mainly to Allogeneic hematopoietic stem cell transplantation (aHSCT), why you didn't mention it in the title.**

*Answer: Good point. As requested, we changed the title of the manuscript. Please find here the proposed revised title: "The gut microbiome in allogeneic hematopoietic stem cell transplantation and specific changes associated with acute graft versus host disease"*

**2. This review reports the latest compositional and functional changes in what ( must be clearly stated)**

*Answer: We thank the reviewer for the important comment. As requested, I clarified that it is changes in gut microbiome of HSCT recipients. The sentence is changed in the manuscript: "This review reports the compositional and functional changes in gut microbiome of allogeneic HSCT recipients associated with acute graft-versus-host disease that could serve a biomarker for diagnosis and prevention in patients receiving allogeneic hematopoietic stem cell transplantation".*

**3. Too long introduction, need to concise the role of the drugs specially it will be covered later in the main manuscript core, and at the same time need to augment the role of diet. 1)Microbiota and role of diet, lifestyle and drugs (4 paragraphs), 2) Graph versus host disease and Allogeneic hematopoietic stem cell transplantation (aHSCT) (one paragraph), 3)Link between them (one paragraph), 4) Then a clear research question**

*Answer: We thank the reviewer for the pertinent comment. As requested, we changed the and reduced the size of the introduction and stated a clear research question. We changed the beginning of the introduction section: "In human health, DNA sequencing technologies, including 16S rRNA gene-based amplicon sequence analysis and whole genome shotgun metagenomic analysis were used to discover how exogenous and intrinsic host factors influence gut microbiome composition [1,2]. In large cohorts, scientists investigated the impact of factors such as lifestyle, dietary information, anthropometrics and drugs on the gut microbiome communities [3,4]. They found that age, gender, dietary factors and intrinsic parameters were highly correlated with composition and function of the gut microbiome. They also observed that several drug categories, such as antibiotics, proton-pump, metformin, statins, and laxatives, had a strong effect on the gut microbiome. On the other hand, gut microbiome can affect the bioavailability of oral drugs [5]. Thus, micro-organisms can impact drug absorption and metabolism, that may explain, in part, inter-individual heterogeneity in drug response and disposition [6]."*

**4. Will be better to add a table to identify previous studies and their results**

*Answer: Good point for the reviewer. We thank the reviewer, and, as requested, we added a table that summarize the results of the previous studies. A sentence was added in the manuscript: "Several studies reported the profound alteration of the gut microbiota during the aHSCT procedure, as summarized in Table 1."*

**5. refer of what!**

*Answer: Good point for the reviewer. This is the citation for PICRUSt. No change was made in the revised manuscript.*

**6. COMPOSITION CHANGES (what the difference between this title and the above one alteration and composition changes give same meaning) or you mean something else here you will cover the species)**

*Answer: we thank the reviewer for the comment. In fact here we wrote a paragraph on diversity (just above), and here a paragraph on composition changes. We cover here species as specified by the reviewer.*

**7. list the n. of the ref.**

*Answer: good point for the reviewer. We added the number of the reference: “Importantly, in a gnotobiotic model, the authors demonstrated that Enterococcus growth is dependent on disaccharide lactose, and that dietary lactose depletion attenuates Enterococcus outgrowth and reduces the severity of GVHD [28].”*

**8. Must be in separate paragraph**

*Answer: We thank the reviewer for the pertinent comment. As requested, we added a specific paragraph here: “Further studies are needed to confirm or not the controversial role of Akkermansia in acute GVHD. Moreover, some species of the genus Blautia should be investigated as a potential biomarker: high relative abundance at the time of engraftment being protective against GVHD, while low relative abundance could be considered a risk factor for secondary development of GVHD.”*

**9. Observational studies clearly demonstrate that decreased diversity of the gut microbiome and specific species or metabolic pathways are negatively associated with aGVHD and may serve as biomarker for diagnosis and prevention. Need rephrasing**

*Answer: We thank the reviewer for the important comment. As requested, we rephrase the sentence of the conclusion. Please find here the sentences of the revised manuscript: “Observational studies demonstrated that decreased diversity of the gut microbiome and specific species or metabolic pathways were associated with aGVHD. These specific changes could serve as biomarkers for diagnosis and prevention in patients receiving aHSCT”.*

**10. Please fix the the way you mention the authors, if 5, et al, 6,et al or the all authers**

*Answer: we thank the reviewer for the important comment. As requested, we fixed the references section.*