

Dear **Dr. Fang-Fang Ji**

Baishideng Publishing Group Inc.

We are writing to resubmit the manuscript No. 40480 revised entitled “Hematopoietic Stem Cell Transplantation for Crohn’s disease: Gaps, Doubts and Perspectives” and we are very thankful for the pertinent comments.

Comments to the editor

1. We address answers point to point like Science Editor suggested.
2. Audio recorded core tip was converted to mp3
3. References was revised.
4. PMID, PCMid and DOI was revised and inserted.
5. The references were reformatted and inserted in the final of the phrase or paragraph.

Authors response to the reviewer comments

▪ **Reviewer code 00609371**

SPECIFIC COMMENTS TO AUTHORS

The topic of this editorial is of interest it helps us to put a right Perspective on the Stem cell therapy for Crohn’s disease.

Thank you for this comment

- 1) *the title doesn’t match the content of the article, i.e., Stem cell therapy is a very broad term, which should include all kinds of stem cell, but in the article, the authors focused only on HSCT, even though they also mentioned another kind of stem cells (MSC). The authors need to either **change the title** or addition more content to the text.*

We agree. The Title was changed and now will be “Hematopoietic Stem Cell Transplantation for Crohn’s disease: Gaps, Doubts and Perspectives”.

No more content was added to the text.

- 2) *Editorial is supposed to highlight the main points in the broad-brush style; therefore the first subtitle “the Definition and location of disease” seems in appropriate for this editorial.*

We agree> The subtitle “the Definition and location of disease” was removed

We were very thankful for the pertinent comments of Reviewer #00609371.

▪ **Reviewer code 00573611**

SPECIFIC COMMENTS TO AUTHORS

In this editorial paper, the author described and discussed the aspects and the future of cell therapy in Crohn's disease. This is an interesting editorial paper. The manuscript is well-written. The reviewer has no further comments.

We were very pleased that Reviewer seemed to enjoy our paper.

▪ **Reviewer code 03370303**

SPECIFIC COMMENTS TO AUTHORS

This Editorial is valuable, raising an alarm at an easy decision of taking autologous HSCT as a measure for the treatment of Chron's disease. Showing the unsatisfactory points in the evaluation of efficacy of HSCT and explaining the adverse effects regarding HSCT, authors illustrate the important points that we must consider when deciding which therapeutics we should take.

Thank you for your comments

*Nevertheless, the evaluation of mesenchymal stem cell transplantation (MSCT) seems rather unclear. I speculate that authors have a positive thought for MSCT since it has no adverse effects due to lack of need to use chemotherapeutic and immunosuppressive agents. While HSCT aims a reconstitution (or initialization) of the hematopoietic system, MSCT aims the modulation of immune system (ref S1, S2). One of the important factors that mediate immunosuppressive effects of MSC is prostaglandin E2 (PGE2) (ref S1, S2), which is also known as a mediator for the effect of G-CSF (ref S3). In this sense, it is interesting that G-CSF alone has provided successful outcome for the treatment of Chron's disease as authors mentioned (ref 18). I think that the message of this article would become clearer if authors could add certain comments regarding the evaluation or mechanistic insight for MSCT. Supplemental Reference: S1. Zhao Q, Ren H, Han Z. Mesenchymal stem cells: Immunomodulatory capability and clinical potential in immune diseases. *Journal of Cellular Immunotherapy* 2: 3-20, 2016. S2. F Gao, S M Chiu, D A L Motan, Z Zhang, L Chen, H-L Ji, H-F Tse, Q-L Fu, Q Lian. Mesenchymal stem cells and immunomodulation: current status and future prospects. *Cell Death Dis.* 7: e2062, 2016. S3. Kawano Y, Fukui C, Shinohara M, Wakahashi K, Ishii S, Suzuki T, Sato M, Asada N, Kawano H, Minagawa K, Sada A, Furuyashiki T, Uematsu S, Akira S, Uede T, Narumiya S, Matsui T, Katayama Y. G-CSF-induced sympathetic tone provokes fever and primes antimobilizing functions of neutrophils via PGE2. *Blood* 129:587-597, 2017. A minor point to be corrected: The term "stromal mesenchymal cells" in Abstract in page 2 and in line 13 in page 5 should be corrected as "mesenchymal stromal cells".*

We were very thankful for the pertinent comments of Reviewer #03370303. We agree with you that stem cell therapy is a very broad term, like said before the Reviewer code 00609371 and that the article in truth only deals with HSCT. – Because of this comment and those of Reviewer #00609371, we changed the title to "Hematopoietic stem cell transplantation for Crohn's disease: Gaps, Doubts and Perspectives". We are currently preparing a protocol in respect to the use of mesenchymal stem cells. All mention of MSCT has been removed from our paper. Moreover, we corrected the term "stromal mesenchymal cells" to "mesenchymal stromal cells" as requested by this reviewer.

Final comments

We would like to thank all the reviewers, my apologies to the science editor, and the patience to guide us in the finalization of this relevant editorial in approaching the treatment of Crohn's disease.