

Oct 31, 2020

Professor Carlo Ventura

Editors-in-Chief

*World Journal of Stem Cells*

Dear Editor:

I, along with my coauthors, would like to resubmit the attached manuscript for publication in *World Journal of Stem Cells*, titled “**Prior Transfusion of Umbilical Cord Mesenchymal Stem Cells Can Effectively Alleviate Symptoms of Motion Sickness in Mice Through IL-10 Secretion**”

The paper was coauthored by Huasu Zhu, Dong Li, Cong Li, Jinxian Huang, Shanshan Chen, Lanbo Li, Qing Shi, Xiuli Ju. The manuscript ID is [58549].

We are thankful for the reviewers’ constructive comments, which have helped us to considerably improve and clarify the manuscript. We have responded to each of the reviewer’s comments in a point-by-point manner. In addition, we have provided a revised version of the manuscript with changes highlighted. We hope that the changes incorporated into the revised manuscript satisfactorily address the reviewers’ concerns.

Thank you for your consideration. We hope our manuscript is now suitable for publication in your journal.

Sincerely,

Xiuli Ju

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**Reviewer #1:**

**Specific Comments to Authors:** good manuscript

R: Thank you very much for your comment.

**Reviewer #2:**

**Specific Comments to Authors:** The content is interesting but interpretation seems to be speculative. The links between effect of stem cells transplantation, IL-10 and pathways should be clear. In this presentation we could to request additional groups inducing IL-10 increase or the application of IL-10, but not only a disruption of IL-10 production or action by AS-101 (which could disrupt other Il-production, as it is known as a a potent in vitro and in vivo immunomodulator, is a novel inhibitor of IL-1beta converting enzyme). Some related papers should be revised and considered to discussion: - Peripheral anti-inflammatory cytokine Interleukin-10 treatment mitigates interleukin-1 $\beta$  - induced anxiety and sickness behaviors in adult male rats. Munshi S, Parrilli V, Rosenkranz JA. Behav Brain Res. 2019 Oct 17;372:112024. - IL-10 Dysregulation in Acute Mountain Sickness Revealed by Transcriptome Analysis. Liu B, Chen J, Zhang L, Gao Y, Cui J, Zhang E, Xu G, Liang Y, Liang Y, Wang J, Gao Y. Front Immunol. 2017 May 30;8:628. Please edit the manuscript to be clear. Limit the speculation and discuss deeply on the obtained results. Please add sentences about the limitations of the study before the suggested experiments and approaches for continuing the putative impact of stem cells in this way.

R: Thank you very much for your comment.

This manuscript aimed to investigate whether UC-MSCs could prevent MS. To assess the involvement of IL-10 in this process, we divided the mice into five groups and transplanted them with UC-MSCs or AS101-treated UC-MSCs. As a mouse model of MS, we used mice subjected to the Morris water maze test, and their dizziness was considered as a sign of MS. IL-10 expression increased in the blood and cochlear tissues of the mice transplanted with UC-MSCs, as assessed via ELISA and RT-qPCR. Further, western blotting analysis results indicated that IL-10RA was upregulated alongside IL-

10 in the transplanted mice, and the protein members of the JAK2/STAT3 signaling pathway, which is involved in IL-10 secretion, were also upregulated. The major point in these findings is that IL-10 secretion by UC-MSCs successfully improved the symptoms of MS since this effect was suppressed by the IL-10 inhibitor AS101. We have provided evidence on several aspects, which suggest that prophylactic transplantation of UC-MSCs can suppress the symptoms of MS in mice, and this effect correlates with increased levels of IL-10 and JAK/STAT3 pathway components in the blood and cochlea.

Regarding AS101, it has been widely used in tumor immunity in recent years to inhibit the tumor-derived IL-10/STAT3 survival signal (kindly see references 1 and 2 below). Immunity is a complicated process. For MS, the involvement of immunity and the effect of immunotherapy still warrant much research. We plan to delve into details in the near future. Nevertheless, we have added the limitation of this study on page 18 line 429-442. We sincerely hope that our responses are satisfactory for you to consider this article for publication.

## **REFERENCES**

1. **Danoch H**, Kalechman Y, Albeck M, et al. (2015). Sensitizing B- and T- cell Lymphoma Cells to Paclitaxel/Abraxane-Induced Death by AS101 via Inhibition of the VLA-4-IL10-Survivin Axis. *Mol Cancer Res* 13(3):411-22;
2. **Hayun R**, Shpungin S, Malovani H, et al. (2007). Novel involvement of the immunomodulator AS101 in IL-10 signaling, via the tyrosine kinase Fer. *Ann N Y Acad Sci* 1095:240-50.

## **Science editor:**

1. I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

**R:** Thank you for bringing this point to our attention. The grant application forms have

been uploaded into the system.

2. I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**R:** We apologize for this oversight. We have added the original figures to a single PowerPoint file and uploaded the file as “58549-Figures.ppt” into the system. In addition, we have uploaded the original data of each image. They are pzf files (prepared using GraphPad Prism 5 Project) or psd files (prepared using Adobe Photoshop Image 12).

3. I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.

**R:** Thank you for your reminder. We have added the “article highlights” section at the end of the main text. Please see pages 19 and 21.

4. please don't include any \*, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as <sup>a</sup>P <0.05, <sup>b</sup>P <0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, <sup>c</sup>P <0.05 and <sup>d</sup>P <0.01 are used, and a third series of P values is expressed as <sup>e</sup>P <0.05 and <sup>f</sup>P <0.01.

**R:** We appreciate your diligence. We have removed these special characters and checked and revised all the statistical significance in the main text and figures. The revised manuscript has been uploaded into the system. The changes have been marked in red font for your convenience. Thank you again for your scrutiny.