Jan 6, 2024
Name of journal: *World Journal of Stem Cells (WJSC)*
Manuscript NO.: 90578
Title: **Unlocking the Versatile Potential: Adipose-derived Mesenchymal Stem Cells in Ocular Surface Reconstruction and Oculoplastics**

Dear Editor-in-Chief of WJSC,

I would like to extend my gratitude for the efforts and time spent reviewing the submission. The Reviewer makes excellent points and offers valuable suggestions to improve the manuscript. **Please find the responses in bold font under each of the comments made by the reviewer below, which can also be found highlighted in the modified/added contents with yellow color in the revised manuscript**.

Science Editor and Company Editor-in-Chief:

Science Editor: *Specific comments: (1) In the "Ref." column of Table 1, it is necessary to add the cited reference number.*

The references have been cited in Table 1, as requested.

Company editor-in-chief: *I have reviewed the Peer-Review Report, full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted.*

When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the Reference Citation Analysis (RCA), of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/ or visit PubMed at: https://pubmed.ncbi.nlm.nih.gov/.

We have found the RCA tool to be quite useful in preparing the modified manuscript.
The following has been added in lines 85-87 :
"The review was performed by using PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com)."

Reviewer 1 (number ID: 03813908):

This manuscript reviewed the use and potential use of adipose-derived MSCs in ocular surface reconstruction and oculoplastics. The review is beneficial to researchers in this field. However, some concerns need to be addressed. 1. Although the author claims to be a native speaker. The language still needs polishing. There are many distinguishable language mistakes.

Many thanks for the positive comment about our paper. The paper has been edited and polished to enhance the flow and correct the grammar.

2. The author tried to review the use of adipose-derived MSCs. However, many conclusions or references are not limited to adipose-derived MSCs. I suggest the author to change the subject to MSCs and add more data, thus changing the manuscript to REVIEWS. Alternatively, they can keep the structure, and just add a section to refine and discuss other kinds of MSCs.

The Reviewer raises a good point. In accordance with the second suggestion made by the reviewer, a new section entitled "Other kinds of MSCs" has been added to lines 444-459 as follows:

8. OTHER KINDS OF MSCs

MSCs are highly heterogeneous multipotent stromal cells which can be found in various tissues throughout the body. Autologous adult stem cells have consistently served as the primary cell type employed in various applications due to their immunocompatibility, and their utilization poses minimal ethical concerns[136]. This stands in stark contrast to the use of embryonic stem cells (ESCs), umbilical cord mesenchymal stem cells (UCMSCs), and induced pluripotent stem cells (iPSCs), each of which has encountered substantial limitations in clinical practice[137]. These constraints primarily revolve around issues concerning cellular regulation and the potential for teratoma formation, ethical dilemmas, immunogenicity (in the case of ESCs), genetic manipulation complexities (associated with iPSCs), and difficulties related to the long-term preservation of UCMSCs[138,139]. In this review, we included studies about different sources of MSCs to support the wide array of functions that MSCs can potentially express in the field of ocular surface reconstruction and oculoplastics. However, the main focus stays on adipose-derived MSCs, since adipose tissue offers a more abundant supply of MSCs cells and is relatively easier to access compared to other sources. [38]

3. The serial numbers of subtitles are in a mess.

We apologize for the messy formatting. The numbering for the headings and subheadings has been corrected to enhance the flow of the manuscript.

4. The readers also care about the clinical use status of adipose-derived MSCs. The author should add a section to discuss it and provide suggestions on how to accelerate the clinical use of adipose-derive MSCs.

As suggested by the Reviewer, a new section entitled "Accelerating the clinical use of MSCs" has been added to lines 460-468 as follows:

"9. ACCELERATING THE CLINICAL USE OF MSCs

As of today, the primary issue in the application of MSCs appears to be their inability to survive at the site of administration. We should likely focus on this aspect to assess their actual clinical efficacy. Various factors contribute to this challenge and understanding them is crucial for developing strategies to enhance the survival and therapeutic potential of MSCs in clinical settings. Further investigation into the survival mechanisms, interaction with the host microenvironment, and optimization of delivery methods may provide valuable insights for addressing this critical concern in MSC-based therapies. Various clinical trials are ongoing."

5. It is better to discuss more in the CONCLUSION section. For example, the limitations of the research.

The Conclusion section has been expanded, as requested. Mention regarding strengths, limitations, and future perspectives has been added to lines 464-474 to read:

"While the current evidence suggests their promising role in various clinical scenarios, further studies are warranted to elucidate the precise mechanisms of action and functions of MSCs, particularly in the context of wound healing, inflammation, and regenerative and reconstructive procedures in ophthalmology and plastic surgery. Optimizing and standardizing protocols for the application of MSC-based cell therapy will be crucial for unlocking their full therapeutic potential in addressing the intricate challenges posed by ocular surface and periocular conditions. Moreover, the main issue to untangle consists of their effective survival in the donor area. Many unsatisfactory clinical results may be due to the poor survival rate. Further high-quality basic and clinical studies are needed to finally be able to apply MSCs successfully in our daily clinical practice."

The valuable comments and assistance with the manuscript are greatly appreciated. I look forward to your final decision regarding our modifications, with the hope that all concerns have been addressed appropriately.

Kind regards,
Marco Zeppieri