

**Manuscript id:** 46603

**Title:** Cell membrane and bioactive factors derived from mesenchymal stromal cells: cell-free based therapy for inflammatory bowel diseases.

**World Journal of Stem Cells**

Dear Editor,

We would like to thank you for the interesting reviewers' comments. You can find our responses to their comments and the revised version of the paper attached to this message. The manuscript has been improved according to the suggestions of reviewers. We expect that, in the revised version, our work is acceptable for publication at World Journal of Stem Cells.

**Reviewers' comments:**

**Reviewer #1:**

**This paper is going to provide useful information for researchers in this field. To overcome the deficiencies of current therapies for inflammatory bowel diseases, the paper addresses cell-free therapy, a topic that is of extreme importance; the usage of bioactive factors and surface proteins of mesenchymal stem cells to avoid the practical issues associated with the use of living cells. Manuscript type: Review article Title. The paper title “Cell membrane and bioactive factors derived from mesenchymal stromal cells: cell-free based therapy for inflammatory bowel diseases.” reflects well what the review article is addressing, as the authors are presenting an overview of the role of bioactive factors and cell membrane proteins derived from MSC to be used as a cell-free therapy to improve inflammatory bowel diseases (IBD) treatment Abstract. The abstract summarizes extensive relevant work described in the manuscript Key words. The key words reflect the focus of the manuscript The article. The manuscript provided an adequate introduction about inflammatory bowel diseases, mesenchymal stromal cells and their use in IBD therapy as well as their use based on their immunomodulatory properties References. The review article reasonably cites the relevant, important and and some of the latest references. Quality of manuscript organization and presentation. The manuscript is well, concisely and coherently presented. The style, language and grammar are accurate and appropriate**

*We thank the referee for the evaluation.*

**Reviewer #2:**

**This is an interesting manuscript to summarize the role of cell membrane and bioactive derived from MSCs for IDB treatment. However, the reviewer has the following comments before it can be considered to be published.**

**1)The manuscript should emphasize in the parts of 3 and 4, but not the other sections as they are basic knowledge for the researchers in this filed. The authors should discuss deeply regarding the use of cell membrane and bioactive factors for IBD treatment as well as the underlying mechanisms.**

*We agree to emphasize parts 3 and 4 and we have done this also by including new bibliography. However, we believe that parts 1 and 2 are also important for this review.*

**2)The authors could use a new table or 1-2 figures to outline these applications to make sure the readers can understand the major meanings from these table or figures. Fig.1 and 2 could not serve this purpose well.**

*Thank you for the suggestion. We included a new table that summarizes data of in vivo studies that used the bioactive factors approach. The table presents MSC origin, used IBD animal model, pathway of infusion and results. We truly believe that the new table improved the data presentation.*

*Figures 1 and 2 were also modified in order to better represent our meanings.*

**3) Additionally, the reviewer suggests the following references should be involved in this manuscript.** Front Immunol. 2018 Nov 9;9:2538. J Cell Physiol. 2018 Nov;233(11):8754-8766. Int Immunopharmacol. 2018 Jan;54:86-94. Int Immunopharmacol. 2019 Mar;68:204-212. J Cell Physiol. 2018 Dec 7. doi: 10.1002/jcp.27934. Inflamm Bowel Dis. 2018 Nov 29;24(12):2501-2509. Am J Transl Res. 2018 Jul 15;10(7):2026-2036. Stem Cells Transl Med. 2018 Jun;7(6):456-467. Stem Cells Dev. 2013 Mar 15;22(6):841-4.

*We thank you for the bibliography suggestion. In fact, J Cell Physiol. 2018 Nov;233(11):8754-8766; Int Immunopharmacol. 2018 Jan;54:86-94; Int Immunopharmacol. 2019 Mar;68:204-212 and Am J Transl Res. 2018 Jul 15;10(7):2026-2036 were already part of our manuscript references.*

*However, we also have read and included your other suggestions.*