Editor in Chief
World Journal of Stem Cells
Editorial Office

Dear Editor in Chief

Re: Manuscript **"hPSC-MSC application in regenerative medicine" (**Manuscript NO: 65810**)**

Based on Editorial Office's and reviewers' comments, the manuscript is revised, all questions from reviewers and Editorial Office are answered point by point. I would like to highlight the following changes in the revised manuscript

1. Language is improved by native English professional
2. Latest references are updated. Of 134 references cited in revised manuscript, 46 references were published after 2018.
3. Clinical trial of hPSC-MSCs is also included.

I hope the revised manuscript meets the high criteria of the journal. I am looking forward to the final decision.

Regards
Tong Ming Liu PhD
Institute of Molecular and Cell Biolgy, Singapore

Responses to reviewers' comments

We are pleased to inform you that, after preview by the Editorial Office and peer review, as well as CrossCheck and Google plagiarism detection, we believe that the academic quality, language quality, and ethics of your manuscript (Manuscript NO.: 65810, Minireviews) basically meet the publishing requirements of the World Journal of Stem Cells. As such, we have made the preliminary decision that it is acceptable for publication after your appropriate revision. Upon our receipt of your revised manuscript, we will send it for re-review. We will then make a final decision on whether to accept the manuscript or not, based on the reviewers' comments, the quality of the revised manuscript, and the relevant documents. Please follow the steps outlined below to revise your manuscript to meet the requirements for final acceptance and publication

Response: Thanks for positive comments on academic quality, language quality and ethics of the manuscript.

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report. Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and make point-by-point responses to the issues raised in the peer-review report(s), which are listed below:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

1.This research focused on hPSC-MSC application in regenerative medicine, very prospective, also Dr Tong Ming Liu have stem cells research experience, in this review also cited 4 papers related with stem cells he publicated.

Response: Thanks for comment on being very prospective and my experience in stem cells. So far, I have 16 years of continuous experience in the field of MSCs and iPSC-MSCs.

2. Have some hPSC-MSC application in clinic until now? Because only animal model from Table 2.

Response: Yes. I have searched "iPSC-MSC", "iPS-MSC", "hESC-MSC", "hES-MSC", "ESC-MSC" and "ES-MSC" in https://clinicaltrials.gov/ and in google, there is one clinical trial using iPSC-MSCs found, I have included it in the revised manuscript and table 2.

3. If can clearly discuss the hPSC-MSC application in regenerative medicine including some signal pathway with a Figure, maybe much more better.

Response: done. Signal pathways related to hPSC-MSC applications are included in Figure 1.

4.References need to be formatted according to the requirements of this journal.

Response: done

5. English need further polish although look very good.

Response: Besides I further polish English, my colleague with native English also helps improve English.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The subject of the manuscript is the application of human pluripotent stem cells-MSC in regenerative medicine. Regenerative medicine covers a wide range, not only bones, cartilage, immune system diseases, kidneys, tumors, etc., but also important applications in organs or tissues such as the heart, lungs, brain (nerves), and teeth. This article only uses a small space to describe the disease model and the current status of its application. Regarding the hPSC-MSC application in regenerative medicine involved in heart, brain, lung, tooth and other systems, no review has been made. It is recommended to add relevant content. A total of 81 references are cited in the manuscript, of which only 14 are published after 2018, which cannot represent the latest progress on this topic.

Response: Thanks for comments on coverage of manuscript. As suggested, I have covered heart, lungs, brain (nerves) and teeth using hPSC-MSCs in the revised manuscript.

Although there are a lot of disease modelling and drug screening using **iPSCs,** there are very limited reports on disease modelling and drug screening using **iPSC-MSCs** as yet. I have included them in the manuscript. Considering this, this review focuses on derivation approaches and various applications of hPSC-MSCs.

I have searched iPSC-MSCs, iPS-MSCs, hESC-MSC, ESC-MSC and ES-MSC in pubmed until June 2021, there are 46, 7, 23, 17 and 7 references found, I have included these in the revised manuscript. Now a total of 134 references in revised manuscript, including 46 references published after 2018.

Reviewer #3:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Rejection

Specific Comments to Authors: You wrote a review on hPSC-MSCs and their several uses in research. 1) Your title, your abstract and your keywords do not reflect the part where you talk about the use of these cells in disease modelling and drug screening.

Response: Thanks reviewer for comments! Besides various derivation approaches and applications of hPSC-MSCs, disease modelling and drug screening is an important application of hPSC-MSCs. To include this part, "disease modelling" and "drug screening" have been added to the abstract and added to key words.

2) Several references are missing: - paragraph 1, lines 2-3 - paragraph 2, line 20 - paragraph 3, lines 7 and 13 - paragraph 4, lines 7 and 22 - paragraph 5, lines 10, 35 and 70

Response: I have gone through the manuscript and tried to include important references. In this minireview, 134 references have been cited. Due to restriction of manuscript, I am sorry that not all references are cited in the manuscript.

3) Table 1 should have references for each line, like Table 2 which is good (it really brings information to the reader).

Response: done.

4) In the "Derivation of hPSC-MSCs" paragraph, you talk about MSCs from paraxial mesoderm but do not give any more information about it.

Response: I have included part of hPSC-MSCs from paraxial mesoderm in the revised manuscript.

5) Even if you talk about important points concerning MSCs, my overall feeling is that it is very hard to gain clear information. Rather than writing lists of items in each paragraph, please try to make links between data / ideas.

Response: Thanks for very useful comments. To make readers easier to understand and follow important issues and challenges related to hPSC-MSCs and discussed in the manuscript, the discussed issues and challenges are listed in a more logic order, all these issues and challenges are linked together with a clue of safety and efficacy of hPSC-MSCs.

6) You should also ask for help for language quality (style, grammar, and spelling).

Response: Thanks for comments. Besides I further polish English, my colleague with native English also helps improve English.

Reviewer #4:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Comments The manuscript 65810 tried to summarize the progress of the derivation of MSCs from human pluripotent stem cells and their various applications in regenerative medicine and discussed the challenges and concerns with hPSC-MSC application. Some points in doubt proposed in my first review as follows before accepted. 1. In Introduction of the manuscript, the author summarized "Mesenchymal stem cells (MSCs) are adult stem cell with fibroblast-like morphology and plastic-adherence, which express MSC surface antigens such as CD73, CD90 and CD105 but lack in hematopoietic markers such as CD14, CD34 and CD45." Here, we should elucidate that the clinical criteria of hMSCs has been updated positive for reactivity to antigens CD73, CD90, CD105, and HLA-DR, and negative for reactivity to antigens CD11b, CD19, CD34, and CD45.

1. We should elucidate that the clinical criteria of hMSCs has been updated positive for reactivity to antigens CD73, CD90, CD105, and HLA-DR, and negative for reactivity to antigens CD11b, CD19, CD34, and CD45.
Response: Thanks for suggestion regarding MSC markers. We have amended part of surface antigen expression based on reviewer's comment and current understanding. According to ISCT minimal criteria for MSCs (DOI: 10.1080/14653240600855905), MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules.

	Positive Markers	Negative Markers
Marker Expression	CD73/5'-Nucleotidase CD90/Thy1 CD105	CD34 CD45 CD11b/CD14 CD79α HLA ClassII
Culture Type	Adhesion to plastic	
Differentiation Ability	Adipogenic differentiation, Osteogenic differentiation, Chondrogenic differentiation after specific stimulation	

Abbreviation: ISCT, International Society of Cellular Therapy.

Based on discussion by Guadix et al (Pharmaceutics 2019, 11, 552; doi:10.3390/pharmaceutics11110552), HLA-DR expression links to clinic, its expression is largely unpredictable during clinical-grade large-scale hMSC in vitro expansion. Therefore, HLA-DR expression should be considered as informative about the quality of hMSCs for clinical use rather than as a criterion to hMSCs identity.

2. Should regenerative medicines for the neurodegenerative diseases, such as (Alzheimer's disease, multiple sclerosis, spinal cord injury, neuropathic pain, stroke, Parkinson's disease, and epilepsy, be included?

Response: Thanks for very suggestion! I have included application of **hPSC-MSCs** in neurodegenerative diseases.

3. The latest references (for 2020) involving with this manuscript should be updated.

Response: The latest 20 references (after 2020) related to this manuscript have been updated in the revised manuscript.

4 LANGUAGE QUALITY
Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

5 EDITORIAL OFFICE'S COMMENTS
Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:
(1) *Science editor:* 1 Scientific quality: The manuscript describes a review of the hPSC-MSC application in regenerative medicine. The topic is within the scope of the WJSC.
Response: Thanks for comment of within the scope of the WJSC.

(1) Classification: Grade C, Grade C, Grade C and Grade E; (2) Summary of the Peer-Review Report: The authors summarize the progress of the derivation of MSCs from human pluripotent stem cells and their various applications in regenerative medicine and discussed the challenges and concerns with hPSC-MSC application. However, the English need further polish. The questions raised by the reviewers should be answered; and

Response: Thanks for very useful comments. Besides I further polish English, my colleague with native English also helps improve English. The questions raised by the reviewers are answered point by point in the "Responses to reviewers' comments"

(3) Format: There are 2 tables.
Response: done

(4) References: A total of 81 references are cited, including 13 references published in the last 3 years;
Response: In the revised manuscript, of 134 references, there are 46 references published after 2018.

(5) Self-cited references: There are 4 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B, Grade B, Grade B and Grade C. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJSC.

Response: Of total 134 references in the revised manuscript, only 4 of my publications closely related to the topic of the manuscript are cited, the self-referencing rates are only 2.98%.

5 Issues raised:
(1) The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240;
Response: Thanks for comments. Besides I further polish English, my colleague with native English also helps improve English.

(2) The "Author Contributions" section is missing. Please provide the author contributions;
Response: As the sole author and corresponding author of manuscript, I draft the manuscript, including tables and figure.

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and
Response: done.

(4) The column should be minireviews.
Response: done

6 Recommendation: Conditional acceptance.
Response: Thanks for conditional acceptance

(2) *Editorial office director:*

(3) *Company editor-in-chief:* I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thanks for conditional acceptance of manuscript. I have improved the manuscript and answered question from reviewers point by point.