



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 55168

**Title:** Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine

**Reviewer's code:** 03472014

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Senior Lecturer

**Reviewer's Country/Territory:** Malaysia

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-03-15

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2020-03-16 05:02

**Reviewer performed review:** 2020-03-18 11:33

**Review time:** 2 Days and 6 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
<b>Conclusion</b>	<input checked="" type="checkbox"/> Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
<b>Re-review</b>	[ ] Yes [ ] No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

Authors have provided a scholarly written work capturing potential of mesenchymal stem cell-derived exosomes as a cell-free therapeutic strategy in accelerating regeneration. A review on their application for various degenerative diseases is very commendable and the highlight on the contribution of this manuscript. The article provides an essential reference for researchers in this field.



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 55168

**Title:** Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine

**Reviewer's code:** 00505755

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Senior Research Fellow

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-03-15

**Reviewer chosen by:** Jin-Zhou Tang (Quit in 2020)

**Reviewer accepted review:** 2020-03-23 00:32

**Reviewer performed review:** 2020-03-23 06:15

**Review time:** 5 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

This is an interesting study about mesenchymal stem cell-derived exosomes. The MSC-derived exosomes may have great potential for regenerative medicine. The differences of exosomes among differentiation stages of MSCs may be added for the section 4 MSC-derived exosomes.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 55168

**Title:** Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine

**Reviewer's code:** 00504800

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-03-15

**Reviewer chosen by:** Jin-Zhou Tang (Quit in 2020)

**Reviewer accepted review:** 2020-03-21 17:27

**Reviewer performed review:** 2020-03-27 20:37

**Review time:** 6 Days and 3 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

The manuscript by Ma et al. provides a fairly comprehensive review of the potential of MSC-derived exosomes for regenerative therapies. The authors briefly review the history of MSC and MSC-derived exosomes, including their biogenesis, characteristics, techniques of isolation, properties, and potential advantages over their parental MSC. The authors then provide a relatively comprehensive review of the animal data on exosomes to treat various diseases. My main critique of the manuscript is that it is very heavily focused on in vitro and animal models and essentially fails to mention any human clinical trials which have either completed accrual or are in progress. A brief literature search revealed two recent (2019) papers reviewing exosomes for clinical use, which cover similar material as the current manuscript, but also review a number of current clinical trials utilizing exosomes (Yin K et al., Biomarker Research 2019; Mendt M et al., Bone Marrow Transplant 2019). The Yin paper in particular is similar in format to the current manuscript. A brief search of ClinicalTrials.gov shows 83 registered interventional therapeutic studies (not including basic science, biobanking and biomarker studies) using exosomes. The authors need to both incorporate the findings from published clinical trials, and summarize disease processes being investigated in active clinical trials for their manuscript to provide benefit to the scientific community over what has already been published. Second, the writing of much of the manuscript related to therapeutic potential of exosomes is not terribly exciting for the reader. Much of the second half of the manuscript is “these authors showed this; those authors showed that”. I think that many of the in vitro and animal study data could be shortened, which would leave room for the authors to mention any clinical trials which pertain to the disease process. Minor comments: Section 2.1: Reference 25 refers to the International Society for Cellular Therapy position paper. To my knowledge,



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neurogenic differentiation was not a required characteristic to define MSC in this paper. Figure 1: Please define M1 and M2 cells (macrophages) at first use of the abbreviation. Section 2.2.2: First sentence should be revised to refer to “lodging” of MSC in non-specific tissues. What is meant by “homing to natural ‘walls’”? Table 2: There are some contradicting statements in the table that need to be corrected, such as Membrane filtration: keeps exosomes intact is an advantage, but deformation is a disadvantage – which is correct? “High yield” is listed as both an advantage and a disadvantage for Precipitation. Section 4: First line, should maybe say “ease of isolation” instead of “non-invasive isolation”. Line 4, differentiation of MSCs MAY induce ossification – ossification is a rare event and certainly does not happen in all cases. Section 4.2.1: Can the authors give an example or a reference for exosome production on a large scale using specialized cell lines? Section 4.2.2: Do the authors intend to say that MSC are not stable at -80C, or that exosomes are more stable at -80C than MSC (which should be kept frozen in LN2 or vapor phase)? Section 5.2.1: Top line p. 19, please define HuES9.E1 as a human embryonic-derived MSC line Section 5.3.2, third paragraph middle of p. 23, please revise the sentence containing “acting as a ceRNA to sponge miR-138-5p can regulate Sirt1” – this is unclear.