



## PEER-REVIEW REPORT

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

**Manuscript NO:** 83491

**Title:** Different priming strategies improve distinct therapeutic capabilities of mesenchymal stromal/stem cells: Potential implications for their clinical use

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 06286468

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Associate Professor

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

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

**Manuscript submission date:** 2023-01-27

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-01-28 10:22

**Reviewer performed review:** 2023-02-06 16:52

**Review time:** 9 Days and 6 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 Grade E: Do not publish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>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<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 checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" 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

**SPECIFIC COMMENTS TO AUTHORS**

Mesenchymal stromal/stem cells (MSCs) have demonstrated promising therapeutic results in the field of regenerative medicine. In this study, the authors reviewed data on the principal priming approaches for enhancing the therapeutic potential of MSCs. The study is logically designed, the idea is new and very interesting. Although, there are several concerns that need to be addressed. Comments: I think more work is needed in the section of “THE SECRETION OF PARACRINE FACTORS MEDIATE THE THERAPEUTIC FUNCTION OF MSCs”. In the section of “THE SECRETION OF PARACRINE FACTORS MEDIATE THE THERAPEUTIC FUNCTION OF MSCs”, it is better to go into more detail on the introduction of exosomes, some latest references could be cited, “Exosomes as mediators of intercellular crosstalk in metabolism”, “Exosomes Regulate the Epithelial-Mesenchymal Transition in Cancer”, for example, or any other similar references. In the “Priming with 3D culture of MSCs” section, is it “omic approaches” or “omics approaches”?



## PEER-REVIEW REPORT

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

**Manuscript NO:** 83491

**Title:** Different priming strategies improve distinct therapeutic capabilities of mesenchymal stromal/stem cells: Potential implications for their clinical use

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03290608

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

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

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

**Manuscript submission date:** 2023-01-27

**Reviewer chosen by:** Geng-Long Liu

**Reviewer accepted review:** 2023-02-14 11:49

**Reviewer performed review:** 2023-02-20 12:06

**Review time:** 6 Days

<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>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<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 type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" 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

**SPECIFIC COMMENTS TO AUTHORS**

In this review, the authors reviewed the effects of MSC on chemoattraction and modulation of inflammation, angiogenesis, and tissue repair under three priming strategies: inflammatory cytokines, 3D cultures, and hypoxia. The literature is comprehensive but there are several important issues that need clarification. 1. Choosing more specific nouns that summarize article information as keywords would be better. 2. The background is disorganized. After introducing the efficacy of MSC, the clinical trial results can be summarized to explain the current bottlenecks of MSC treatment, such as heterogeneity, low migration to injured tissues, and then to introduce the priming strategies. 3. The dosages form of MSC were suggested to added in the table 1, cells or exosomes. 4.It will goes deeper if a Figure 3 that shows different priming strategies through different signaling pathways regulate MSC is prepared.



## PEER-REVIEW REPORT

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

**Manuscript NO:** 83491

**Title:** Different priming strategies improve distinct therapeutic capabilities of mesenchymal stromal/stem cells: Potential implications for their clinical use

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 06215468

**Position:** Peer Reviewer

**Academic degree:** N/A

**Professional title:** N/A

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

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

**Manuscript submission date:** 2023-01-27

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-02-13 09:55

**Reviewer performed review:** 2023-02-21 09:12

**Review time:** 7 Days and 23 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>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<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 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 checked="" 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

**SPECIFIC COMMENTS TO AUTHORS**

The current review is focused on the specific priming strategies that have been implemented to improve the regenerative and immunomodulatory properties of MSCs. The production of priming type-specific functional factors in MSCs could improve the effectiveness of MSCs in clinics and pave the way toward implementing new MSC-based therapies. Overall, the manuscript is well written and interesting, but still some improvements are required. Comment 1: “Mesenchymal stromal/stem cells (MSCs) have shown significant therapeutic potential and have therefore been extensively investigated for application in the field of regenerative medicine.” is contradictory with “Unfortunately, while MSCs have shown a good margin of safety as a cellular treatment, they have usually been therapeutically ineffective in human diseases.” mentioned in Page 2 Line 2-9. Comment 2: “extracellular vesicles (EVs)” mentioned in Page 5 Line 3 should be changed to “EVs”. Comment 3: The statement in the chapter of “THE SECRETION OF PARACRINE FACTORS MEDIATE THE THERAPEUTIC FUNCTION OF MSCs” should be adjusted appropriately. Otherwise, it looks like each sentence has nothing to do with the next sentence. Comment 4: The format of the Table 1 should be



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

standardized, and it is recommended to classify the contents of Table 1 for easy reading.  
Comment 5: In Page 14 Line 4-38, besides stating your views according to the published literature, please also mention the inference of aggregating sentences to avoid the sentences having nothing to do with the next sentence.



## PEER-REVIEW REPORT

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

**Manuscript NO:** 83491

**Title:** Different priming strategies improve distinct therapeutic capabilities of mesenchymal stromal/stem cells: Potential implications for their clinical use

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03550401

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Professor

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

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

**Manuscript submission date:** 2023-01-27

**Reviewer chosen by:** Geng-Long Liu

**Reviewer accepted review:** 2023-02-13 06:07

**Reviewer performed review:** 2023-02-23 08:07

**Review time:** 10 Days and 2 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>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<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 type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" 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

**SPECIFIC COMMENTS TO AUTHORS**

Specific Comments To Authors: This manuscript focused on the topic “Different priming strategies improve distinct therapeutic capabilities of mesenchymal stromal/stem cells” and reviewed the therapeutic properties of primed MSCs in preclinical models. However, there are some issues that need to be addressed. Firstly, the author published a review titled " Therapeutic Properties of Mesenchymal Stromal/Stem Cells: The Need of Cell Priming for Cell-Free Therapies in Regenerative Medicine" in 2021, which had described three methods for MSCs priming. So, it’s hardly to find novelty in this manuscript. In addition to this, there are some problems: 1. The abstract is lengthy, with 255 words, which is not concise enough. 2. In the second paragraph of the introduction, the clinical products of MSCs should focus more on the controversy section of "MSCs have moderate or poor efficacy, and the results from some studies are controversial". 3. In the section “THE SECRETION OF PARACRINE FACTORS MEDIATE THE THERAPEUTIC FUNCTION OF MSCs”: 1) extracellular vesicles are not soluble factors; 2) The narrative order is a bit out of order, the original text is exosomes - soluble factors - exosomes, it is recommended to adjust. 4. In the



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

section "THERAPEUTIC PROPERTIES OF PRIMED MSCs IN PRECLINICAL MODELS", there is a commonsense error: sepsis is not a chronic disease.



## PEER-REVIEW REPORT

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

**Manuscript NO:** 83491

**Title:** Different priming strategies improve distinct therapeutic capabilities of mesenchymal stromal/stem cells: Potential implications for their clinical use

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03757295

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor, N/A

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

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

**Manuscript submission date:** 2023-01-27

**Reviewer chosen by:** Geng-Long Liu

**Reviewer accepted review:** 2023-02-13 06:49

**Reviewer performed review:** 2023-02-26 21:10

**Review time:** 13 Days and 14 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input 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>Novelty of this manuscript</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<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 checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" 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

**SPECIFIC COMMENTS TO AUTHORS**

The authors reviewed articles to address the impact of different priming treatments, including inflammatory cytokines, hypoxia, and three-dimensional physical cues on the MSCs from different origins and to enhance the therapeutic potential of the MSCs. In addition, the articles included comprehensive tables and figures to summarize and compare the impact differences. Please find below some minor comments and suggestions: - The authors mentioned the impact of MSC heterogeneity on the poor efficacy in clinical trials. However, the authors didn't address the heterogeneity clearly, which was from the tissue differences or within the same tissue. From the recent single-cell articles, we gained insight into the detailed architecture of stromal heterogeneity from different tissues. An example would be Buechler et al. Nature 2021, <https://www.nature.com/articles/s41586-021-03549-5>. Authors may consider further addressing the impact of priming treatment on which specific subpopulations and differences. Some suggested articles include Kosaric et al., Molecular Therapy, 2020 [https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016\(20\)30286-0](https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(20)30286-0); Cai et al. Cell & Bioscience, 2022



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-399-1568

**E-mail:** bpgoffice@wjgnet.com

**https://**www.wjgnet.com

<https://cellandbioscience.biomedcentral.com/articles/10.1186/s13578-022-00848-w>. -  
The authors organized a comprehensive table summarizing the priming treatment effect on the MSCs. However, the order of the cytokine section was neither by MSC types nor priming treatments. I would suggest authors categorize the same MSC type or priming treatment together. - The author might consider using the same citation format in the table. Consider replacing the ['last name'; 'year'] format with the number used in the article, such as Bulati et al. 2020 with "Ref 38" and Garcia et al. 2019 with "Ref 127". Since the references were not ordered by last name, doing so may help readers locate the original article much more quickly. I recommend accepting this article after minor revision.