

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 84723

Title: Wnt signaling pathway inhibitor promotes mesenchymal stem cells differentiation into cardiac progenitor cells in vitro and improves cardiomyopathy in vivo

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05382654

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Chief Physician

Reviewer's Country/Territory: China

Author's Country/Territory: Pakistan

Manuscript submission date: 2023-03-26

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-04 12:36

Reviewer performed review: 2023-05-14 15:20

Review time: 10 Days and 2 Hours

Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Novelty of this manuscript	☐ Grade A: Excellent ☐ Grade B: Good ☒ Grade C: Fair ☐ Grade D: No novelty
Creativity or innovation of this manuscript	☐ Grade A: Excellent ☐ Grade B: Good ☒ Grade C: Fair ☐ Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No scientific significance
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☒ Minor revision ☐ Major revision ☐ Rejection
Re-review	☐ Yes ☒ No
Peer-reviewer statements	Peer-Review: ☒ Anonymous ☐ Onymous
	Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

This MS mainly investigated the potential of “treatment of hUC-MSCs with IWP-4 for differentiation of MSCs into cardiomyogenic lineage via inhibiting Wnt pathway and their succeeding role in the cardiac function restoration in the rat MI model.” and proposed that preconditioning of MSCs with IWP-4 may be a promising approach for the treatment of this debilitating heart disease, which provided a means for the production of cardiomyocytes from discarded human umbilical cord tissue for cardiac cell therapy. However, below some revisions are still needed before being published in World Journal of Stem Cells. 1. Please refer to recent papers published in World Journal of Stem Cells and correct the format, such as: In page 1, “Running title”, “Author contributions” and “Supported by” section should be added. Before REFERENCES section, ARTICLE HIGHLIGHTS section including Research background, Research motivation, Research objectives, Research methods, Research results, Research conclusions, and Research perspectives section should be added according to the journal’s requirements. In page 1 and 2, “Background”, “Aim”, “Methodology”, “Results”, and “Conclusion” should be changed to “BACKGROUND”, “AIM”,

“METHODS”, “RESULTS”, and “CONCLUSION”. In page 3, 12, and 16, “Introduction”, “Results”, and “Discussion” should be changed to “INTRODUCTION”, “RESULTS” and “DISCUSSION”. In page 4, “[7][8]” should be changed to “[7, 8]”. 2. In page 29, “Figure1:” should be changed to “Figure 1”. In figure legends, all abbreviations should be given in full text according to the journal’s requirements. Additionally, In Figure3 legend, it is suggested that “Cardiac markers gene expression analysis: Cardiac markers gene expression analysis by qPCR” should be changed to “Cardiac markers gene expression analysis by qPCR”. Not *P < 0.05, **P < 0.01, and ***P < 0.001 while aP < 0.05, bP < 0.01, and cP < 0.001 < 0.001 in all bar charts? As shown in Figure 4B, GSK expression was increased in the fourteen days treatment while significant decrease was described in the text. Please check it. In Figure5, it is suggested that Figure 5C should be placed before Figure 5A, and Day 0, Day 7, Day 14 should be put above the picture. Additionally, α -actinin, connexin-43, cTnI, Desmin, GATA-4, Nkx2.5 should be put beside the vertical axis while not under the horizontal axis. There are too many images in Figure 7 and Figure 8. It is recommended to remove some images, and a local enlarged image could be given in the right side of each Masson’s trichrome or HE stained image. In Figure9, in order to facilitate a comparison between the transplanted untreated MSCs and fourteen days IWP-4 treated MSCs group, it is suggested that all alpha actinin images could be listed as Figure 9A, and the corresponding quantification of bar graph could be used as Figure 9B. Similarly, all cTnI images could be listed as Figure 9C, and the corresponding quantification of bar graph as Figure 9D. All GATA-4 images could be listed as Figure 9E, and the corresponding quantification of bar graph as Figure 9F. 3. In references, all authors, PMID and DOI should be provided, and the first author and volume number should be bold. Additionally, all journal names should be abbreviated and italicized. Please check all references including content and format carefully according to the journal’s requirements. Other suggestiones have been listed

in the uploaded revised version.

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Peer-review model: Single blind

Reviewer's code: 05573866

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Pakistan

Manuscript submission date: 2023-03-26

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-04-22 06:50

Reviewer performed review: 2023-05-17 00:27

Review time: 24 Days and 17 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Novelty of this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No novelty
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Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No
Peer-reviewer statements	Peer-Review: ☒ Anonymous ☐ Onymous
	Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

I would like to thank you for your suggestion to review the paper entitled " IWP-4, a potent Inhibitor of the Wnt signaling pathway promotes MSCs differentiation into cardiac progenitor cells in vitro and improves cardiomyopathy in vivo" for World Journal of Stem Cells: According the check list I have added the following comments; The title reflects the main subject/hypothesis of the manuscript Generally, it is an interesting study, however there are some comments and questions the authors should address all were detailed below: Major concerns 1. The components of culture media used for induction of cardiomyocyte differentiate weren't provided. 2. Based on cardiomyocyte phenotype and electrophysiology, cardiogenic differentiation must be confirmed. 3. What was the rational for induction of trilineage differentiation of stem cells? 4. IWP-4 is a well known inhibitor for Wnt, its effect on the expression of cardiac markers and stimulation of stem cell differentiation into cardiomyocytes was previously established in stem cell research by Chen et al. 2015" Development of a scalable suspension culture for cardiac differentiation from human pluripotent stem cells", however the newly added part in this study is the in vivo work, so the authors are

encouraged to focus more on the in vivo results. 5. additional work is needed to highlight the effectiveness of preconditioning on optimizing stem cell therapy. 6. Please, provide more clear figure for differentiated stem cells (figure 5). 7. The abstract must be summarized. 8. introduction is too long. According the check list I have added the following comments; The title reflects the main subject/hypothesis of the manuscript. Generally, it is an interesting study, however there are some comments and questions the authors should address all were detailed below: According the check list I have added the following comments; The title reflects the main subject/hypothesis of the manuscript Generally, it is an interesting study, however there are some comments and questions the authors should address all were detailed below: Major concerns 1. The components of culture media used for induction of cardiomyocyte differentiate weren't provided. 2. Based on cardiomyocyte phenotype and electrophysiology, cardiogenic differentiation must be confirmed. 3. What was the rational for induction of trilineage differentiation of stem cells? 4. IWP-4 is a well known inhibitor for Wnt, its effect on the expression of cardiac markers and stimulation of stem cell differentiation into cardiomyocytes was previously established in stem cell research by Chen et al. 2015" Development of a scalable suspension culture for cardiac differentiation from human pluripotent stem cells", however the newly added part in this study is the in vivo work, so the authors are encouraged to focus more on the in vivo results. 5. additional work is needed to highlight the effectiveness of preconditioning on optimizing stem cell therapy. 6. Please, provide more clear figure for differentiated stem cells (figure 5). 7. The abstract must be summarized. 8. introduction is too long.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 05573866

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Pakistan

Manuscript submission date: 2023-03-26

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-06-02 10:59

Reviewer performed review: 2023-06-03 11:27

Review time: 1 Day

Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☒ Accept (General priority) ☐ Minor revision ☐ Major revision ☐ Rejection
Peer-reviewer	Peer-Review: ☒ Anonymous ☐ Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

authors responded to all reviewer comments