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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 67752

Title: Therapeutic effects of menstrual blood-derived endometrial stem cells on mouse models of streptozotocin-induced type 1 diabetes

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04668002
Position: Peer Reviewer
Academic degree: DDS, MSc, PhD
Professional title: Associate Professor, Doctor
Reviewer's Country/Territory: Sweden
Author's Country/Territory: China

Manuscript submission date: 2021-05-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-08 05:51

Reviewer performed review: 2021-05-08 06:15

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] 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 [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Point 01 In the results section: "C57BL/6N mice (n = 40) were adaptively fed for one week and randomly divided into 2 groups: the normal group (n = 10) and the STZ-induced T1D group (n = 40)." The number of mice in each group (10 and 40) do not add up to the total number of mice in the study (n=40). Point 02 How come the authors, already from the start, have chosen to use parametric statistical tests? This is wrong, as the number of mice in each group was so small (n=10), which directly calls for the non-parametric tests, regardless of normality (which, by the way, was not even performed, even though it was not even necessary, due to the small number of samples in each group). Therefore, the authors will have to redo the statistics, now with non-parametric tests. Point 03 I would like to see the precise values of significance for each comparison. $P<0.05$ and $P>0.05$ are not enough.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05387405
Position: Peer Reviewer
Academic degree: MSc, PhD
Professional title: Research Scientist
Reviewer's Country/Territory: Hungary
Author's Country/Territory: China

Manuscript submission date: 2021-05-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-05 09:25

Reviewer performed review: 2021-05-10 17:57

Review time: 5 Days and 8 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] 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 [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Authors of the manuscript investigated streptozotocin (STZ)-induced diabetic mice to compare the effects of menstrual blood-derived endometrial stem cells (MenSC) and umbilical cord-derived mesenchymal stem cells (UCMSC) transplantation. The following issues should be addressed: 1. Please upload and fill a correct ARRIVE Checklist from https://f6publishing.blob.core.windows.net/customuploadedfiles/The_ARRIVE_Guidelines_English.pdf 2. Within the abstract please, resolve UCMSC 3. Should TNFa be TNFα? 4. In core tip: The article is not a review, but an original article. 5. Biochemical and protein assays: Was it n = 5 / group? 6. In methods, I recommend moving the sentence about insulin ELISA to biochemical assays. One-sentence paragraphs should be avoided. 7. Please correct sample sizes within the first sentence of Results. 8. Repeating the STZ- and measurement procedures at the beginning of Result is unnecessary. 9.Figure 2E-F, please correct TNFa and IFNg to TNFα and IFNγ, respectively. 10. Figures suggest large SDs, which with the small sample sizes indicate to use non-parametric tests. What was the rationale behind using parametric tests? 11. Was IL-6 and VEGF of control mice measured? Elevated levels of both of these cytokines are associated with several diseases (diabetes, various autoimmune diseases and cancers, etc.). Authors also discussed that "a low dose of IL-6 can counteract the cytotoxicity of IL-1β", furthermore, the elevation of these markers are usually bad prognostic signs in every conditions. What do authors think, what could be the source of these elevated levels?

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

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Reviewer's code: 02446609
Position: Peer Reviewer
Academic degree: PhD
Professional title: Associate Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-05 12:12

Reviewer performed review: 2021-05-14 22:28

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript by Sun et al. shows that MenSC are able to promote pancreas regeneration and angiogenesis, reduce inflammation, improve glycogen synthesis, and increase area of white pulp in spleens of STZ-induced type 1 diabetes mice, to the same degree as UCMSC. This is an interesting paper, using a novel source of stem cells that may become an effective treatment for T1D. However, the quality of the manuscript can be improved if the authors considered and addressed the following concerns: Major points: 1. I would recommend changing the title to "Therapeutic effects of menstrual blood-derived endometrial stem cells in mouse models of STZ-induced type 1 diabetes" in order to place the focus on MenSC, since that is the new type of SC being tested. Throughout the paper, I think you should rephrase the parts where you say that MenSC and UCMSC help improve type 1 diabetes to instead place the focus on the therapeutic ability of MenSC as compared to UMSC, as information is already known about UCMSC.

2. Subheadings for the results section need to be improved and made more detailed. For the third subheading, only inflammation is mentioned, but the figures discussed here also show data about anti-apoptosis and angiogenesis, so this should be added to the subheading. The last three subheadings all say "morphology" and/or "function." Try to be more specific using the results to come up with better subheadings. 3. The introduction section lacks crucial information. First, information about the usage of UCMSC in the clinic must be added. How/where are they being transplanted? Specifically what improvements do patients see? Merely stating that their usage is limited is not sufficient. Furthermore, it is crucial to differentiate between T1D and T2D, and it is unclear whether MENSC are to be used for one or both. In addition, information

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about the STZ model is required. 4. The figures need a lot of improvement. In Figure 1, the labels (letters) do not match the letters in the legend or in the text. In Fig. 1A, it needs to be clearly stated what * and # refer to. Most of the images (1D, 1E, 4A, 5C) need better labeling. For example, in 1E and 4A, what is shown in the top row and the bottom row? In 1D and 5C, what is shown in the left column and the right column? You should indicate it in the figure legend and also can add the labels to your figures. Also, utilize arrows to label these images. For example, in 1D, point to the islets. Figure 1G needs a better label for the y axis: I would suggest "%CD31+." Overall, your legends can be more detailed. Minor points 1. In the text description about Fig 1A, the authors mention day 43, but in the graph, it appears that it is actually day 42. In Figure 1, what is the significance of increased body weight or food consumption? The text mentions that serum insulin levels were upregulated and it references Fig 1D, E, F, but none of those figures show insulin. Actually, figure 2C is about plasma insulin and that is not even mentioned in the text. I think the insulin figure should be part of Fig 1 not Fig 2. In Fig 1, CD31 is mentioned, but the significance of this marker is never stated. 2. In terms of new experiments, it would be interesting to see the effect of the two types of MSC on WT mice, and include the histology images in each figure. Apart from this, it would be interesting to see the immune cell populations infiltrating the pancreas in normal mice vs T1D mice in the 3 treatment groups, which can be achieved by immunofluorescence experiments. Apart from this, it was mentioned that the UCMSC transplantation is well tolerated by humans, but do they not have MHC molecules that can pose a threat to the recipient? Overall, I think this study is interesting and may pave the path towards using MenSC as treatment for T1D. This paper will be enhanced by the changes mentioned above.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05866045
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Oman

Author's Country/Territory: China

Manuscript submission date: 2021-05-05

Reviewer chosen by: AI Technique

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Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1- The abstract was organised and summarize the finding however, there were a lot of abbreviation in the abstract: - try to minimize the abbreviation - Mention full word for the abbreviation when first time you were writing. 2- Need specific guideline to list the reference

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 67752

Title: Therapeutic effects of menstrual blood-derived endometrial stem cells on mouse models of streptozotocin-induced type 1 diabetes

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04668002
Position: Peer Reviewer
Academic degree: DDS, MSc, PhD
Professional title: Associate Professor, Doctor
Reviewer's Country/Territory: Sweden
Author's Country/Territory: China

Manuscript submission date: 2021-05-05
Reviewer chosen by: Jia-Ru Fan
Reviewer accepted review: 2021-07-30 11:06
Reviewer performed review: 2021-07-30 11:10
Review time: 1 Hour

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

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

SPECIFIC COMMENTS TO AUTHORS

The manuscript now seems to be suitable for publication.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Peer-review model: Single blind

Reviewer's code: 05387405
Position: Peer Reviewer
Academic degree: MSc, PhD
Professional title: Research Scientist
Reviewer's Country/Territory: Hungary
Author's Country/Territory: China

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Authors addresses all my concers in their revision.