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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 82212

Title: Repetitive administration of cultured human CD34+ cells improve adenine-induced kidney injury in mice

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04939204
Position: Editorial Board
Academic degree: PhD
Professional title: Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Japan

Manuscript submission date: 2022-12-13

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-01-30 05:19

Reviewer performed review: 2023-01-30 06:23

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
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
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Takayasu Ohtake et al., showed that repetitive administration of cultured human UCB-CD34+ cells significantly improved chronic tubulointerstitial damage in adenine-induced CKD model in mice via their vasculoprotective and anti-inflammatory effects. The data were interesting and have potential future application in cell therapy, but several points should be addressed, 1) Specific statistical methods used in data analysis of each figure should be mentioned. 2) The language is insufficient and in some parts incomprehensible.

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Reviewer's code: 05196024
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: Japan

Manuscript submission date: 2022-12-13

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-02-01 01:07

Reviewer performed review: 2023-02-09 04:39

Review time: 8 Days and 3 Hours

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

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Language quality	[Y] 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) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Ohtake et al. investigates the ability of three weekly doses of cultured CD34+ cells to improve adenine-induced kidney injury in mice. The culture method, which the authors reported previously, greatly expand CD34+ cells and endothelial progenitor cells (EPC). Overall the manuscript is well written and the work is well performed. I have a few recommendations for improving the manuscript prior to publication. I also have a few questions for the authors that don't necessarily need to be addressed experimentally now, but I would like the authors to consider addressing some of these concerns in the Discussion. Questions for consideration: 1. The authors state that adenine consumption induces a chronic kidney disease. It may be too late to ask this question, since others have published on this model as well, but does a three-week feeding regimen of adenine really mimic CKD? This seems to be a very acute time frame. 2. The authors show very nicely that CD34 cells can blunt the effect of adenine on renal injury (Figure 4). However, it seems that renal injury as measured by serum Cr improves simply by stopping adenine administration in the control animals. Would the animals' renal function return to normal by 6-8 weeks after adenine is

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stopped if no cell therapy was given? Have the authors, or others, examined this? 3. Similarly, can three doses of CD34 given during the period of adenine feeding which the renal injury is still developing be considered therapy for CKD? I suppose one could devise a clinical trial in which CD34 cells were given to earlier stage CKD to see if they prevented progression to ESRD, but a big question is do CD34 cells do anything for true CKD/ESRD, not CKD as it is developing as described in this manuscript. The authors should consider feeding with adenine to allow renal injury (CKD?) to fully develop, then investigate the effects of CD34 cells. 4. Furthermore, are the effects of the cell therapy long-lasting? It is impossible to tell from these studies since the animals were sacrificed only one week after the last dose of cells. Have the authors, or others, waited longer after the last dose of cells before sacrifice? Does the Cr ever return to and remain at baseline, or does renal function worsen again with more time after the last cell infusion? Likewise, do the histologic improvements last? 5. Again, I don't necessarily think the authors need to do more experiments to address questions 1-4 above for this manuscript (unless they already have obtained some data), but perhaps in the Discussion where limitations of the study are reviewed the authors can discuss some of these concerns. It would be acceptable to discuss these topics and say they will be addressed in future research. Recommended changes prior to publication: 1. Can the authors comment on the cell dose used? A cell dose of 10^6/mouse in a 20g mouse is equivalent to about 50 x 10^6 cells/kg in a human, an amount that is probably not achievable clinically, at least in adults. 2. Results, top of page 10, referring to Figure 2B: The text says a 59% vs. a 1% difference; shouldn't this be 59 vs. 1 fold difference, not %? 3. I recommend combining Figures 2 and 3 (e.g., make Figure 3 Figure 2C) since both figures are showing analyses of the cultured CD34 cells. 4. I'm not certain that Table 1 is needed, can just describe in the text. 5. The Y axes in the figures need to be labelled better; labels are either missing (Figures 2, 3) or just a small % sign is given at the top of the Y axis. 6. I

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would consider amending the title to something like “Repetitive administration of human cultured CD34+ cells improve the time course of adenine-induced [chronic – delete?] kidney injury in mice” to better reflect the short-term nature of the experiments as noted in my questions above.