

August 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.
(file name: ESPS Manuscript No12794-MiniReview.doc).

Title: Renal Stem Cell Reprogramming: Prospects in Regenerative Medicine

Author: Elvin E. Morales and Rebecca A. Wingert

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 12794

The manuscript has been improved according to the suggestions of reviewers as follows:

1 Format has been updated to meet the writing requirements of minireviews.

2 Revisions have been made to the content of the manuscript based on the suggestions of both reviewers. In brief, the introduction and conclusion sections were revised to add information about renal stem cells and the use of mesenchymal stem cells in clinical trials for renal disease. A figure was also added for visual interest.

3 References and typesetting were corrected and are complete. In some cases, an article does not have a DOI due to its publication date.

Thank you again for publishing our manuscript in the *World Journal of Stem Cells*.

Sincerely yours,



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REVIEWER #1

Manuscript Number 12794

Manuscript Title Renal Stem Cell Reprogramming: Prospects in Regenerative Medicine

Review Time 2014-07-28 21:04

COMMENTS TO AUTHORS:

This is a very well written review which focuses on the hot topic that is iPSCs. Overall the quality of the review is high but it does lack detail in places and could be more critical rather than simply summarising.

We thank the reviewer for the evaluation of our manuscript. The manuscript has been reviewed to address each of the major and minor points, as described below.

CLASSIFICATION: Grade B

LANGUAGE EVALUATION: Grade A: priority publishing

CONCLUSION: Minor revision

Major Points:

1. Introduction - the authors identify 9 review papers that look at the identification of renal stem cells but then immediately jump into iPSC instead. I feel the introduction would be much stronger if a better justification for why iPSC rather than renal stem cells (other than just avoiding immunosuppressant drugs) was written. For instance, do those reviews show a lack of success in finding human renal stem cells? Are they rare in the tissue and therefore difficult to isolate or culture?

The introduction has been revised to include the topic of renal stem cells. At present, this remains a controversial subject and there is no consensus in the kidney field as to whether adult renal stem cells exist. The introduction has also been revised to better explain why this review focuses on the current work with iPSC.

2. The authors should also refer to how many cells are thought to be needed for a therapy as this will help

but the low differentiation efficiencies into context for the reader.

The conclusion has been revised to give readers a sense of how many cells are used in clinical trials with stem cells, and we also provide references to relevant articles that further discuss this point.

3. The authors should also acknowledge the work that is ongoing looking at the use of other stem cells (e.g. MSCs) to treat kidney diseases and make reference to any clinical trials ongoing or completed in this space.

The conclusion has been revised to include the topic of mesenchymal stem cells and the current hypotheses about the utility of these cells for the treatment of kidney diseases.

4. Again - taking this work into account, what is the justification for focusing on iPSCs?

We focused on iPSCs in this mini-review to highlight recent advancements in the induction of kidney cell types. Other topics related to renal reprogramming have been extensively reviewed in other current articles. We do reference a number of other current reviews where readers can go to learn more about related topics.

5. Forward thinking section : here the authors talk about several studies that have used small molecules but fail to mention what the reprogramming efficiencies were (or highlight that these were not determined). Given this is a key issue highlighted earlier in the text this is odd.

The efficiencies were not explicitly stated in the studies discussed in this section, and we have added a notation to the manuscript to indicate this.

6. General - the authors have not addressed/acknowledged the issue of cell quality - if the patient has an acutely or chronically damaged kidney, are these cells suitable for reprogramming?

Good point – the conclusion has been revised to acknowledge the issue of cell quality. This is also incorporated into the newly added figure (Figure 2).

7. They have also not mentioned the issue of downstream processing which is integrally linked to the issue of low differentiation/reprogramming efficiencies - ie do you need to isolate the successfully reprogrammed/differentiation cells and if so how and at the appropriate scale?

This was also a useful suggestion – the conclusion has been revised to acknowledge the issue

downstream processing. This is also incorporated into the newly added figure (Figure 2).

Minor Points:

8. Abstract - "stem cell therapy is a promising alternative" ...to what? Sentence is odd in this context.

This sentence has been revised to read: "Stem cell therapy is a promising future enterprise for renal replacement in patients with acute and chronic kidney disease..."

9. Introduction - bottom paragraph pg 1 is under-referenced.

The referencing has been fixed in the aforementioned introductory paragraph.

10. Introduction - pg 4 "produced (evidenced by....". Bracket is never closed, sentence rambling.

The missing bracket has been added, thus eliminating the problem of sentence rambling.

11. Throughout - it would be useful if the authors could make it clear when studies used human rather than e.g. mouse cells as this helps the reader identify the relevance of the work described.

The manuscript has been edited throughout to clarify when mouse or human cells were used for various studies.

12. Reference list: this seems inconsistent as not all references have DOIs. Perhaps the editor could comment on whether or not this is an issue.

The reference list has been carefully edited to meet the publishing guidelines of the journal. In some cases, a DOI is not available for an article, due to its date of publication. All existing DOIs are reported.

13. Although well written the review is heavy going as it is mostly text with only 1 figure and a large number of abbreviations. More figures or tables could be helpful here.

We have added another figure to the manuscript. The new Figure 2 accompanies the discussion. The abbreviations are organized for the audience and provided at the beginning of the article.

REVIEWER #2

Manuscript Number 12794

Manuscript Title Renal Stem Cell Reprogramming: Prospects in Regenerative Medicine

Review Time 2014-08-11 10:10

COMMENTS TO AUTHORS: None

CLASSIFICATION: Grade A

LANGUAGE EVALUATION: Grade B: minor language polishing

CONCLUSION: Accept

We thank the reviewer for the evaluation of our manuscript. The manuscript has been revised throughout to improve language and perform minor language polishing.