

ANSWERING REVIEWERS

March 23, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).



Name of journal: World Journal of Gastroenterology

ESPS Manuscript NO: 15701

Columns: Editorial

Cell Therapy from Bench to Bed Side: Hepatocytes from fibroblasts-the truth and myth of transdifferentiation

Running Title: The Transdifferentiation Myth

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) 1) The review introduced the several protocols which claim generation of hepatocyte like cells from directed differentiation embryonic stem cells (ES), induced pluripotent stem cells (iPSCs) or other cell types(such as fibroblasts). The authors compared the advantages and disadvantages of the several protocols. It is better guidance to know about the derivation of hepatocyte like cells and therapeutic method for the acute or chronic liver dysfunction.

I have revised the manuscript to include some clinical applications.

2) The review has had a lot of introduction about the generation of hepatocyte like cells from ES and iPSCs. But there is less introduction about hepatocyte like cells derived directly from fibroblasts by transdifferentiation).

I have revised the manuscript to include essential details on transdifferentiation of hepatocytes from fibroblasts.

3) It need supply the content of hepatocyte like cells derived directly from fibroblasts by transdifferentiation. The advantages and disadvantages of generation of hepatocyte like cells by transdifferentiation and the viewpoint of authors should be supplied.

I am afraid, I didn't understand the reviewers concern correctly.

(2) The second reviewer has accepted the manuscript as it is and has no suggestions.

1) (3) It is already 15 years hES cells and 8 years of iPS cells - how much more time is required to evolve a novel protocol for differentiation of ES/iPS cells? It is easy and cheaper

to expand fibroblasts in large numbers compared to iPSC cells - thus the argument that iPSC cells are a better source of fibroblasts is redundant and should be deleted.

iPSC generation protocols are relatively very efficient now compared to transdifferentiation methods. The same is true for generation of hepatocyte-like cells from iPSC/ES compared to transdifferentiation of fibroblasts to hepatocyte-like cells. The main theme of this paper is about the advantages of hepatocyte-like cells derived from iPSC/ES compared to transdifferentiated fibroblasts.

- 2) I would like the author to introduce another player in their article - VSELs which may exist as a sub-population in skin fibroblast culture and may indeed be undergoing differentiation (thus only 0.3% of MEFs convert into iHEP). They may wish to refer to a recent article <http://www.ncbi.nlm.nih.gov/pubmed/25545634>.

I have modified the manuscript to incorporate this suggestion. I will also make a note on the observed similarity between the fibroblasts undergoing trans-differentiation shown in Fig 1a of the manuscript by Sekiya and Suzuki 2011- and VSELs. I have also modified the title to give emphasis to emphasis cell therapy and translational implications (bench to bedside).

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3 References and typesetting were corrected

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

Sincerely yours,



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