Format for ANSWERING REVIEWERS

October 21, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6079-review.doc).

Title: Neural Differentiation from Pluripotent Stem Cells: the Role of Natural and Synthetic Extracellular Matrix

Author: Yan Li, Meimei Liu, Yuanwei Yan, Shang-Tian Yang

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 6079

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

1. Format has been updated
We added the running title (less than 6 words) which is required by the format. The abstract is revised to meet the word limit based on journal format (>200 words). However, we keep the current title (14 words) because we cannot reduce it to 12 words.

2. Revision has been made according to the suggestions of the reviewers

Reviewer #1
(1) As the reviewer suggested, we rephrase the statements in the text that "3-D matrix scaffold could recapitulate the neural stem cell niches and PSC-derived progenitors in it could mimic the in vivo development of neural stem cells." We intended to indicate the difference of 3-D matrix in comparison to 2-D monolayer culture. But we agree with the reviewer that "recapitulate" is a strong word to reflect the complex interactions of all the niche factors. PSC-derived progenitors can be used to study the early embryonic tissue development. But we also agree with the reviewer that 'mimic" overstates the complex process of in vivo development of neural stem cells. So these statements have been corrected throughout the main text.

Reviewer #2
(1) All abbreviations have been checked.

(2) As the reviewer suggested, we modified the text to distinguish therapeutic effects of autologous, allogeneic and xenogeneic cells in in vivo models. The use of human embryonic stem cells in human is usually allogeneic model. The use of human induced pluripotent stem cells can be autologous, but no clinical trial has demonstrated the autologous transplantation. The animal studies using human cells are xenogeneic models. The discussion using human embryonic stem cells was limited with the approved lines and the approved trials by Food and Drug Administration (FDA). We did not include any discussion about the human embryonic stem cell line derivation.

(3) As the reviewer pointed out, sensitivity of permanent or in vitro growing cell lines to various drugs is often different from the sensitivity of primary cell cultures. We mentioned this in section 7.

Reviewer #3
(1) As the reviewer suggested, on page 7, we rephrased the sentence, which now reads "However, the variability of iPSC lines due to different tissues of origin and reprogramming methods may account for the difference".

(2) On page 8: the spelling of "oligodendrocytes" has been corrected. Other minor spelling errors have also been corrected in the text.

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

Sincerely yours,

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