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Prof. Lian-Sheng Ma, M.D.
President and Editor-in-Chief
World Journal of Stem Cells

Re: Manuscript Revision - *World Journal of Stem Cells* - ID (02565821)

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 12911

October 6th, 2014

Dear Prof. Lian-Sheng Ma,

Following your kind invitation to contribute to a review in the World Journal of Stem Cells, I am delighted to resubmit the revised manuscript entitled "Transplantation of stem cell-derived astrocytes in ALS and SCI". We have addressed all of the reviewer comments. We have enclosed along with the manuscript a point-by-point set of response, and we have made all of the necessary changes to the manuscript text. Most importantly, we made modifications to the abstract and to the conclusion section concerning the limitations to clinical translation of stem cell therapy. The whole text was also proof-read by an English native.

We appreciate the reviewer comments, and we feel that the changes based on their input have made for an improved manuscript. I hope that you will be able to send this resubmission back to the original reviewers. If so, I look forward to their comments. If there are any questions that I can answer, please feel free to contact me.

Sincerely,

Charles Nicaise, Ph.D.
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Response to the Reviewers

Reviewer 1

The manuscript reviews a lot of basic information about stem cells, astrocytes, ALS, and SCI. Data are reviewed in two tables for ALS and SCI models. The manuscript has the potential to serve as a useful guide to workers in the field if revised as outlined. Good manuscript, but major revisions are needed.

1. The writing suggests an advertisement pitch for the importance of astrocytes and stem cells and is overall too positive to the point of misleading the reader. The beginning of the conclusions section strikes the proper tone and must be integrated throughout the manuscript and especially in the abstract which is too positive. Say what is the single most specific current limitation to clinical translation in your abstract. There must be more discussion of all of the limitations that make stem cells very difficult to translate. At present stem cells are a research tool but not a viable therapy and may never be one which should be acknowledged. Desperate patients undergo radical and unproven procedures around the world, so there should much more of a cautionary message against these unproven interventions.

The abstract was modified accordingly. The discussion section includes now a longer paragraph about current limitations and major hurdles that must be still solved in preclinical trials before broad clinical translation (page 4 – line 24; page 28 - 1st paragraph).

2. In the review, many instances cite successful stem cell differentiation markers but do not state the percent survival of the injected number of cells (p. 18, p. 21, p. 26). There should be a clear and definitive interpretation that few cells survive after transplanted.

When available, the data about cell survival were added in the text (page 20 – line 21; page 21 – line 1 - line 22; page 24 – line 7, line 10; page 26 – line 16). We also stress out that most of the experimental work assessed the cell viability in a short while after transplantation (usually within few weeks). A sentence raising the issue of limited cell survival was also added in the discussion section (page 28 – line 6).

3. For the recent unpublished findings that are highlighted at the end, is there a meeting abstract to support the data mentioned?

Not yet, these data will be presented at the Society for Neuroscience in next November 2014.

4. Some of the background sections are very basic and do not extend knowledge, draw any interpretations, or make any argument as they should (p. 10, p. 12).

We extended the paragraph on in vivo and in vitro transdifferentiation and mentioned latest studies using cell reprogramming technology in the field of ALS and SCI (page 13).

5. Certain sections do not have references listed but should (p. 15, p. 19, p. 27).

New references 77, 78, 79, 94, 168, 170, 171, 172 were added throughout the manuscript.

6. There is some problems with English and scientific writing style. Proper use of the articles a, an, and the would make it more readable. There are inappropriate adjectives for science throughout the manuscript (e.g., much more p. 8, pretty large p. 8, significant numbers of cells p. 24, etc.). These are meaningless statements.

We corrected all typo's and inappropriate adjectives. The final manuscript was proof-read by an English native.

7. If the authors wanted to make a drawing/diagram pointing out the different methods, then it could be a good complementary illustration, but not necessary.

We than the reviewer for this suggestion but we are not convinced by the added-value of this scheme.

Reviewer 2

Please, check only some small mistakes, for example: page 10: analysis page 18: Feasibility page 28: shown Table 2 page 34: Neonatal

These typo's were corrected.

Reviewer 3

The review by Nicaise et al. gives a comprehensive literature review on the potential use of stem cell-derived astrocytes for ALS and SCI treatment. The review, at times written in poor English, makes a somewhat dry reading as it avoids any critical review of the literature and even when the authors could shed some new insight, they restrict themselves to rather general and uninspiring comments as on p. 13 "Molecular pathways and key transcription factors making transdifferentiation possible are currently under investigation for different (stem) cell types [76]."

We extended the paragraph on in vivo and in vitro transdifferentiation and mentioned latest studies using cell reprogramming technology in the field of ALS and SCI (page 13).

Similarly on p. 25, there is a statement "whereas the Davies and Proschel groups again reported contrasting results [112].", without offering any explanation as to why these differences may have occurred. Unless these critical reviews are added, the present work is of minimal benefit to the literature.

We offer now more interpretations about the discrepancies of outcomes between laboratories using GRP-based cell transplantation, although there are just hypotheses (page 24 – line 9; page 25 – line 4, line 24).

At the very least, the authors should carefully proof-read the manuscript and attend to the points outlined below. p. 2: italicise "N" in N-Methyl-D-aspartate; "D" should be a small cap. p. 6, line 16: insert "transport" after 90% of glutamate p. 6, line 22: exchange rodent by rodents p. 6, line 4 from bottom: "D" in D-serine should be a small cap. p. 7, line 9: delete "so far". p. 7, line 11: insert "knockout' before "mice". p.7, line 4 from bottom: insert "the" before scientific p. 7, line 3 from bottom: delete "to say" p. 7, last line: rodents p. 10, line 11: oligodendrocytes p. 10, line 12: insert "the" before A2B5 antigen. p. 10, line 15: analysis p. 10, line 16: insert a comma after "Further" p. 11, line 5: should this read "…of cells when supplemented…" p. 11, line 7: insert "a" after elicit p. 12, line 7 from bottom: replace "filled" by "fulfilled". p. 12, line 7; "recognize" not appropriate here; establish? p. 13, line spell out "coll." p. 15, first sentence in 3.3 is grammatically not correct. p. 16, last word: astrocyte p. 17, line7: results p. 18, line 7: experiments p. 19, line 2: routes p. 19, line 7 from bottom: insert "the" before "most efficient" p. 21: first sentence is grammatically not correct. P. 21, line 6: insert "a" after "tested" p. 21, line 18: insert "the" after "using" p. 22, line 9: Start with "The" p 23, line 2 from bottom: in (not an) p. 24, line 1: no comma after though p. 24, line 5: insert "the" before "Whittemore" p. 25, line 2: insert "a" before "similar" P. 25, line 7: insert "the" before "above" p. 27, line 8: terms p. 28, line 7 from bottom: insert "the" before "endogenous" p. 29, last line: promote p. 30, line 3: replace "may also likely act" by "are likely to also act" p. 30, line 5: replace "in" by "to" p. 30, line 3 from bottom: astrocyte-mediated.

We corrected all typo's and inappropriate adjectives. The final manuscript was proof-read by an English native.

References: If doi's are given for some references, this should be done for all references as long as they exist. Doi for reference 2, e.g., is 10.1046/j.1469-7580.2002.00064.x

When available, the DOI's were added. Unfortunately, DOI's are not always mentioned in the oldest publications. We apologize for the negligence.