February 7, 2014

Dear Editor,

Please find enclosed the edited manuscript in PDF format.

Title: Mesenchymal Stem Cells in the Treatment of Spinal Cord Injuries: A Review

Authors: Venkata Ramesh Dasari, Krishna Kumar Veeravalli, Dzung H. Dinh

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 6992

We appreciate the Reviewer's comments on this manuscript. We have addressed each concern in this revision – and we believe that this has substantially strengthened the manuscript. The changes are summarized below on a point-by-point basis. The changes in the manuscript have been made in green font.

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 reviewers
   a) 00504441

   Comment: The authors organized the review according to the source of the MSC, while this approach may provide a glimpse of the type of MSCs used for treating SCI, it however failed to pinpoint the clinical significance of each treatment. This will leave the audience, especially those who are new to MSCs, confused.

   Response: We have included clinical significance wherever possible. Please look at the revised article and also Tables 1, 2, 5 and 6.

   Comment: The review is up to date and includes many latest articles on SCI and MSCs, however the authors failed to elaborate and comment on the findings. For eg. page 14 "Zhou et al., (2013) compared mesenchymal stromal cells from human bone marrow and adipose tissue for the treatment of spinal cord injury and suggested that hADSCs would be more appropriate

for transplantation to treat SCI than hBMSC." The reader is left wondering why AdSC is more appropriate.

Response: Please refer Table 2.

There are some typos and grammatical mistakes. Abbreviation should be expanded on first use in the text.

Response: These corrections have been done.

b) 00901006

Comment: It is not clear what audience the review is aimed at.

Response: We included the text regarding suitable audience. Please refer Introduction section in page 2.

Comment: Many of the reviewed papers are presented are with very little commentary as to the larger pictures and while this might be useful for workers in the field of SCI a less sophisticated reader will find it hard to weigh the relative significance of the different work. This is perhaps even more pronounced in the case of the different cell types. It is unclear whether the authors value one source of MSCs over any other or if they have different functionality. In some cases it is as much what is not discussed as what is which may lead to some confusion. For example bone marrow MSCs are discussed as having immunosuppressive properties while this is not mentioned in the discussion of adipose cells. The reader is left wondering if adipose cells do not have immunosuppressive effects. The review would be of additional use to the field if the authors provided a general synopsis at the end of the review regarding the effects of the different types of MSCs on the different stages of pathology of SCI. In this way the reader will be provided with a framework in which to place the detailed discussion of the biology.

Response: Please refer tables 1, 2, 5 and 6.

c) 00609371

Comment: Even though this article mentioned both advantages and limitations of the MSC-based treatments, it failed to stress that one of the biggest or the most important obstacles that is currently hindering the clinical application is the uncontrollable heterogeneity of so called MSCs. Failing to properly address this fundamental uncertainty will likely mislead the readers.

Response: Please refer page 6.

Comment: This article evaluated several potential sources of MSC, including bone marrow, adipose tissue, umbilical cord (Wharton's Jelly & Umbilical Cord Matrix) derived MSCs, but failed to clearly portrait the major profiles of these different cell-based treatment paradigms. As a result, most readers would likely still left in confusion in the end. Thus, I ask the authors to summarize the main features of each treatment paradigms, including all the limitations of each paradigm, in a table so the readers could have a bird's eye view of this specific field.

Response: Please refer Tables 1, 2, 5 and 6.

Comment: There are some obvious typos and possible error of grammar, indicate the bad scholarship. For example, "Immediate microvascular injuries with central gray hemorrhage and disruption of cellular membrane and blood-spinal cord barrier is followed by edema, ischemia, release of cytotoxic chemicals from inflammatory pathways, , and electrolyte shifts, triggering the secondary injury cascade that compounds the initial mechanical injury with necrosis and apoptosis that are injurious to surviving neighboring neurons, further reducing the chance of recovery of pre-numbra neurons and render any functional recovery almost hopeless (McDonald and Sadowsky, 2002, Vawda and Fehlings, 2013)."(page 3-4) "They . Intramedullary posttraumatic cavities were filled by a neoformed tissue containing several axons, together with

BMSC that expressed neuronal or glial markers."(page 11).

Response: These corrects have been done.

3. Grammatical mistakes were corrected

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

Sincerely yours,

Dzung H. Dinh, MD, MBA
Professor of Neurological Surgery
Department of Neurosurgery
University of Illinois College of Medicine at Peoria
Peoria, IL-61656
USA
(309)655-2642
ddinh@uic.edu