

December 7, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6528-review.doc).

**Title:** Mesenchymal Stem Cells as a Potent Cell Source for Articular Cartilage Regeneration

**Authors:** Mohamadreza Baghaban Eslaminejad; Elham Malakooty Poor

**Name of Journal:** World Journal of Stem Cells

**ESPS Manuscript NO:** 6528

We appreciate the comments and suggestions of the reviewers. The manuscript has been improved according to the suggestions of reviewers.

***Comment 1:** The authors review a various therapeutic options for treatment of articular cartilage regeneration. The authors also review MSCs as a potential treatment for articular cartilage defect. The topic is of considerable interest since injured articular cartilage has a weak capacity for repair and it is a serious disease for which at present no appropriate therapeutic exists. Therefore, review on the treatment options for this disease, and focuses on MSCs to repair articular cartilage disorder is a beneficial. However, there are several concerns about the manuscript which need to be improved. Therefore, I cannot recommend acceptance of the manuscript in its present form. The manuscript needs minor revision.*

*Major Comments: This review is neither complete, nor up-to-date with the latest and most important MSCs information for treatment of this disorder. The authors should add more appropriate up-to-date data to the manuscript.*

**Authors:** The main objective of the current review article is to highlight the major characteristics of MSCs that render them as a potent cellular material for hyaline cartilage repair. There are a

considerable number of studies that focus on the regenerative capacity of MSCs in both animal models as well as human. Here in this review article, we discussed some key and pioneering studies as examples to indicate the MSC capacity for regenerating articular cartilage defects. However, in response to the reviewer comments following data were added to the revised manuscript. 1- Some up-to-date points regarding the profile of surface marker expression on MSCs 2- Some points on MSC chondrogenic differentiation 3- Some data on immunomodulatory function of MSCs 4- A new section entitled “MSCs and cartilage gene therapy” 5- A new section entitled “MSCs-mediated cartilage regeneration in animal models”

**Comment 2:** *Most of the references were old. For example, reference numbers 22 is dated in the 1960's. The authors should delete the old references and add new, more appropriate up-to-date references to the reference section.*

**Authors:** Several old references were replaced with new ones. References 20-23 are the key references regarding historic aspects of MSCs, therefore, the authors prefer not to replace them.

**Comment 3:** *During the first occurrence of an acronym, should spell out a technical term first and then present the acronym abbreviation in parentheses, and then continue subsequent reference by abbreviation only, without switching between two. For example, on page 2 under introduction section, the authors spelled out mesenchymal stem cells and abbreviated (MSCs), and then on the pages 4, again spelled out mesenchymal stem cells and abbreviated, and this repeated again on pages 5. Some more of these examples can be found throughout the manuscript. The authors should go over the entire manuscript for this correction.*

**Authors:** Abbreviations were checked and corrected.

**Comment 4:** *There are some spelling, grammar and syntax errors that require attention. For example, on page 4, line one “osteochondritis dissecans, and other pathologies<sup>[1]</sup>” The end of this sentence needs period. More such examples can be found throughout the manuscript. All of the reference section should be as the same style. For example, reference number 6 title of article is written as capital letter and should be in small letter. More such examples can be found throughout the reference section. The English as written is somewhat difficult and needs revision. The authors should go over the entire manuscript for this correction.*

**Authors:** The manuscript was checked and corrected by the native editor. The references were also corrected.

**Comment 5:** *The authors reviewed from historical knowledge of MSCs to recent papers for use of MSCs to articular cartilage regeneration. Comments 1. This brief review will be improved if the authors add 1) mechanisms of immunomodulation of MSCs, 2) potential pitfalls of use of MSCs, 3) potential reasons why some attempts of use of MSCs failed, 4) author’s comments or new ideas on the use of MSCs to articular cartilage onward, and 5) author’s perspective and future direction. 6. There are many unnecessary abbreviations, which appear only 1 time in the text (OATS, MPCs, MSFs, SOX9, BMPs, IGF1, NO, IDO, PGE2). In addition, the authors showed abbreviations many times (MSCs, ESCs, iPSCs, OA). 7. Page 7. Which TGFb type did they use for promoting chondrogenesis? 8. Many typos and grammar errors. For example, page 3, (MSCs); page 4, chondrocyte-based; page 5, MSCs are considered; page 8, tumors; page 11, chondrocyte-based. 9. The authors need to cite original papers for Chonheim on page 5.*

**Authors:** We thank the reviewer for his/her kind comments. In response to the comments, the following data were added to the revised manuscript.

1-The mechanism of MSC immunomodulation has already been explained in the relevant section. However some up-to-date points were added to this section. 2- A new section entitled “Potential pitfalls of use of MSCs” was added to the manuscript. 3- The potential reason for the formation of fibrocartilage repair tissue at articular cartilage defects was added to the section “Cartilage defects following trauma”. 4 and 5- Author’s comments on the use of MSCs to articular cartilage onward was added to the section entitled “Conclusion, perspective and future direction”. 6-The abbreviations were checked and corrected. 7- Page 7: TGF  $\beta$ 1 was used for promoting chondrogenesis. This was added to the relevant section in the revised manuscript. 8- The manuscripts was checked and corrected by the native editor in terms of typos and grammar errors. 9- The original paper for Chonheim on page 5 was added to the reference list.

We would like to thank the editors of World Journal of Stem Cells for publishing our manuscript.

Yours sincerely,

A handwritten signature in blue ink, reading "M. B. Eslami" followed by a horizontal line.

Mohamadreza Baghaban Eslaminejad, PhD

Royan Institute, P.O. Box 19395, 4644 Tehran, Iran

eslami@royaninstitute.org