

## **# Reviewer 1. SPECIFIC COMMENTS TO AUTHORS**

This review summarizes several of the most recent approaches, providing an up to date view of the main developments in MSC-based regenerative techniques. This review can reflect the main research progress of this research direction and has reference value for the readers. The writing is fluent, logical and readable. In conclusion, acceptance should be recommended for the manuscript.

We thank the reviewer for his/her kind words and are delighted to hear that this reviewer thinks that our manuscript “*provides an up to date view of the main developments in MSC-based regenerative techniques*” and that it “*has reference value for the readers*”. We would like to transmit our gratitude for supporting acceptance of the manuscript.

## **# Reviewer 2. SPECIFIC COMMENTS TO AUTHORS**

A well organized , interesting work focusing on the direct contribution of mesenchymal stem cells in regenerating bone tissue. A large part of the manuscript is dedicated to describing general methods of improving culture condition and/or delivery and only a relatively small part presents about proposed methods of enhancing osteogenesis. Maybe the title/abstract/core tip of the manuscript should reflect this situation accordingly or readjust the importance and length of respective chapters if the title needs to be maintained. An important question regarding osteogenic potential of MSCs is their intended use. Constructing bone grafts in vitro for transplanting them into bone defects is one challenge that needs to address specific requirements (such as interfaces problems, graft vascularization among many) while treating delayed fracture consolidation or non union is another problem. To add to this already distinct matters, groups are trying to treat systemic bone loss (osteoporosis). It is important to acknowledge that for each and every specific application one or another of the contribution of MSCs is preferred (engraftment and motility is crucial for example for treating osteoporosis but

has no relevance whatsoever when one tries to build bone grafts in vitro)

We are pleased to read that this reviewer thinks that our manuscript is interesting and well organized. Upon consideration, we fully share the reviewer's comment regarding the convenience to change the title in order to reflect more appropriately the content of the manuscript. We have suggested a new title that we hope the reviewer finds more adequate.

Regarding the reviewer's comment about the intended use of the MSCs, we totally agree and apologize for not making the purpose of this work clearer from the introduction. Although our manuscript certainly mentions other uses of MSCs, the main focus of this review is the use of MSC-based regenerative techniques to promote local bone regeneration in critical size and non-union fractures, mainly by using a combination of MSCs and scaffolds. It was not our intention to fully cover bone grafts building in vivo or the treatment of systemic bone loss, as we believe those are very specialized areas which development and application involves a wider variety of factors that could not be covered in this current work. We have now added two paragraphs in the introduction trying to highlight this fact and to introduce the reviewer's comment, which we believe, would certainly improve the manuscript. These additions are indicated in RED in the text of the original manuscript.