

Format for ANSWERING REVIEWERS



August 1st 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4277-review.doc).

Title: Molecular mechanisms of mesenchymal stem cell differentiation towards osteoblasts

Author: Maya Fakhry, Eva Hamade, Bassam Badran, René Buchet, David Magne

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 4277

The manuscript has been improved according to the suggestions of reviewers. Modifications in the revised article are highlighted in blue:

1 Format has been updated, and the English language checked by an English native speaker.

2 Revision has been made according to the suggestions of the reviewer

(1) Response to reviewer 00646562: as suggested by reviewer 00646562, we now discuss the fact that the ISCT criteria should be discussed and improved. We indicate that although these criteria are widely accepted, they may still be imperfect. Indeed, the three markers we initially proposed are co-expressed in a wide variety of cells, and may therefore not be able to indentify a single MSC population *in vivo* (Lin CS, *Histol Histopathol* 2013). Moreover, we further explain that differences appear to exist between MSC populations from different tissues presenting a an additional challenge to devise a universal definition (Keating A, *Cell Stem Cell* 2012).

(2) Response to reviewer 02445937: we thank the reviewer for his first remark. We have included in page 3 this more relevant reference (Caplan AI, *J Pathol* 2009). We also agree with his second remark. We have added two paragraphs to propose mechanisms that may be responsible for the contradictory reports concerning PPAR γ effects during osteoblast differentiation.

(3) Response to reviewer 00998752: We acknowledge that several laboratories use dexamethasone instead of vitamin D3 to trigger osteoblast differentiation. We have added a sentence in page 3 to mention this point. We also agree with the reviewer's second comment. We have included this paragraph:

Several excellent reviews on osteoblast differentiation have been published in recent years. To our knowledge however, none has focused on the interactions between transcription factors and microRNAs in human mesenchymal stem cells specifically. We believe that it is particularly important since significant differences are well acknowledged between osteoblastogenesis of human and mouse MSCs. For instance, while vitamin D3 binds to a vitamin D response element (VDRE) in the *osteocalcin* promoter in humans and rats, the mouse *osteocalcin* promoter is devoid of any VDRE and vitamin D3 exerts an indirect inhibitory effect on osteocalcin transcription (Zhang, *J Biol Chem* 1997; Clemens, *J Bone Miner Res* 1997).

(3) Response to reviewer 00504800: as mentioned above, we acknowledge that several laboratories use dexamethasone instead of vitamin D3 to trigger osteoblast differentiation. We have added a sentence in page 3 to mention this point. We also agree with the second remark. We have added two paragraphs to propose mechanisms that may be responsible for the contradictory reports concerning PPAR γ effects during osteoblast differentiation.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in purple ink, appearing to read 'D Magne'.

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