

November 21st 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13013-edited.doc).

Title: Vibration stimuli and the differentiation of musculoskeletal progenitor cells – review of results *in vitro* and *in vivo*

Author: Jennifer H Edwards, Gwendolen C Reilly

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 13013

The manuscript has been improved according to the suggestions of reviewers and all changes are labeled on the manuscript by using 'track changes'. The following provides a summary of the changes which have been made.

- 1) Formatting has been updated and some changes to the order of the references presented have been made to improve the flow of the document.
- 2) References and typesetting have been corrected as necessary.
- 3) Revisions have been made as follows according to specific requests of the reviewers.

Reviewer 1:

- The reviewer commented on our reference to reviews during the introduction and requested an increase in primary references in the introductory sections. More key references and pioneer work have been added, as noted in track changes, to improve the information presented within the introduction. Later references have also been updated in this manner where appropriate.
- The section on osteoblastic differentiation has been restructured such that the initial papers discuss direct measures of differentiation and signaling molecules are considered later.
- Updated P2XR to 'P2X7 receptor (P2X7R)' at the request of the reviewer.

Reviewer 2:

- The reviewer noted that we have presented little on the negative effects of LMHFV. We thank the reviewer for this suggestion and have added papers on the negative effects of LMHFV and tried to clarify when other papers reported negative or negligible effects.
- The reviewer asked how it is possible to disentangle the huge amount of information on LMHFV and suggested that we propose standard conditions for future research. However, we feel it is not currently possible to present a standard by which LMHFV could be applied in order to produce beneficial effects *in vivo* or *in vitro*. The purpose of this review was to demonstrate that, despite continued interest in the technique, there are still no standard conditions which are widely used in research and that reported results and outcomes differ greatly between studies. The authors have updated the manuscript to better highlight of common elements between studies where possible.
- The reviewer makes an excellent point about the running title, core tip and abstract in that they implied a focus only on MSCs, while the review focuses on many other cell types. In fact this is what we discovered while writing the review - a surprisingly limited amount of studies have

been performed on stem cells, but since our focus is mostly on osteogenesis we do believe that data on osteoblasts and their precursors is very relevant. We initially conserved the phrase 'stem cells' in the running title since this is what we had given to the editor, but at the request of this reviewer it has been revised. We have also amended the keywords, core tip and abstract to better reflect the final content of the review.

- The reviewer asked for a clarification on the SHAM procedure in discussion of the *in vivo* murine studies. Sham refers to when an operation is replicated without the experimental effect e.g. in the case of OVX the animal is opened to the same extent but the ovaries are not removed. We have now specified that sham means a sham surgical procedure.
- The reviewer requested that we add a reference in regards to allogeneic MSCs and rejection. As the sentence was not of strong relevance to the paper we decided to remove it rather than expand on the topic to improve the clarity of the paper.
- The reviewer felt that we needed to make a 'greater personal contribution to the work in terms of criticism about the studies reported'. This is an excellent point shared by the final reviewer and we have addressed this issue throughout the review. The authors have added in more discussion of the cited papers, particularly in the form of summary text in an attempt to better draw together and comment on the available research. There has also been some restructuring in order to improve the flow of the text and facilitate such discussion.
- All spelling errors and text clarifications specified by the reviewer have been addressed and are shown via track changes.
- The reviewer felt that there were several areas which lacked proper references within the text. Several references have been updated according to the specific direction of the reviewer (noted in the text via track changes) and others have been included to improve the general background, in combination with the comments from the other reviewers.

Reviewer 3:

- The reviewer requested that we 'add comments or criticism on reports. Digest before reaching conclusions, provide summary data, provide analysis, comments or remarks 'within the review. The authors have therefore updated the review to include more summary and discussion of the papers presented. As mentioned above, this has included some restructuring of the text and the addition of discussion and summary sections.

We hope that these changes are satisfactory and feel that we have improved the quality of the paper thanks to the comments of the reviewers. Thank you again for publishing our manuscript in the *World Journal of Stem Cells*.

Sincerely yours,



Jennifer Edwards PhD

Institute of Medical and Biological Engineering,

Faculty of Biological Sciences,

University of Leeds,

Leeds LS2 9JT

UK.

Email: j.h.edwards@leeds.ac.uk

Telephone: +44 113 343 5617