Author's response to reviews

Title: Bone Regeneration: Current Concepts and Future Directions.

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Author's response to reviews: see over
To:

The Editorial Board of BMC Medicine

Re: Revised Manuscript submission (ID: 1123130809518435)

Dear Editors,

Please find submitted the revised manuscript entitled: “Bone Regeneration: Current Concepts and Future Directions.” for consideration and publication in the BMC Medicine. We would like to thank you and the reviewers for your important recommendations for improving our manuscript. We have taken into consideration all the comments made and have replied point by point accordingly in the manuscript. Below is our detailed reply to each comment.

We would be most grateful if the article could be reconsidered for further review and potential publication. The authors of this manuscript declare that the article is original, that it is not under consideration by another journal, and that it has not been previously published. All authors have read and agreed to its content.

We are looking forward to hearing from you.

Sincerely

Peter Giannoudis MD

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Reply to reviewers’ comments

I. Reviewer: Britt Wildemann

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. Further illustrations of the article content or tables would improve the manuscript.
Reply to comment: Thank you for your comment. We have included a patient treated in our institution with the induced membrane technique for regeneration of bone defect and we believe that this case will enhance the content of the manuscript.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

2. BMPs and other growth factors, last sentence: The authors should rewrite the last sentence because it is unclear what they try to express with this statement.
Reply to comment: Thank you for your comment. The last sentence has been re-written.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

3. The authors should give more information regarding the importance of mechanical stability and the role of mechanical stimulation on the regeneration process.
Reply to comment: Thank you for your comment. A section on mechanical stability and the role of mechanical stimulation on the regeneration process has been added in the manuscript accordingly.
4. The chapters “Scaffolds..” and “Tissue engineering” have quite a large overlap. The authors should focus in the “Scaffold” section more on different scaffolds and substitutes and exclude the combination with cells. This is part of the section “Tissue Engineering”.

Reply to comment: Thank you for your comment. Changes have been made in the manuscript for both chapters as per your instructions.

5. TE, last para: the discussion about BMPs should be transferred to the BMP section.

Reply to comment: Thank you for your comment. This paragraph has been transferred to the BMP section and has been modified (references’ numbers have been changed accordingly).

6. Fig. 1 needs improvement.

I. The authors must give a more detailed description of what is presented in the Figure.

II. They should highlight the experimental therapies, to allow the reader a discrimination between clinical and research approaches.

III. They should explain if this is a flowchart that a surgeon should follow to stimulate bone regeneration. If yes, what is the option if the mechanical stability is adequate but no healing occurs?

Reply to comment: Thank you for your comment. The initial Figure 1 has been removed completely, as this has been requested from the other Reviewer as a Major Compulsory Revision (see below).
Minor issues not for publication

The authors should write in vivo/in vitro/ex vivo throughout the MS in italics.
This has been corrected in the manuscript.

Introduction, 4th para (page 4): please correct inttamedullary to intramedullary
This has been corrected in the manuscript.

BMPs and other., 2nd para (page 8): please give the year of BMPs approval, and not only state “currently”.
Reply to comment: Thank you for your comment. This information has been added in the manuscript and the word currently has been deleted. The following reference has been added in the reference list:

30. Food and Drug Administration. Medical Devices. Recently-Approved Devices [http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/default.htm]

Systemic enhancement, 2nd para (page 16): please add the abbreviation for receptor activator of NF-κB ligand
The abbreviation RANKL has been added in the text.
II. Reviewer: Hajime Ohgushi

Major Compulsory Revisions

*Figure- 1) They make one figure. It seems they did not well explain this figure and hard to understand this complicated figure. This should be removed. Instead, the actual figures/data from some references may help the readers to understand the strategy of bone regeneration.*

Reply to comment: Thank you for your comment. This figure has been removed as suggested. Another figure has been added demonstrating a clinical case of bone regeneration.

Discretionary Revisions

Introduction 2) *Page 4, line 11. I suppose that the Masquelet technique is not popular and thus the term of “promising method” is over statement.*

Reply to comment: Thank you for your comment. This sentence has been changed to: “An alternative method for bone regeneration and reconstruction of long bone defects is a two-staged procedure, known as the Masquelet technique.”

MSCs 3) *Page 10. Line 6 from the bottom. Reference [44] concerns about culture expanded chondorocytes and not MSCs. Next recent clinical paper is suitable as reference, furthermore this paper discussed about safety issue of the long term implanted MSCs in the 41 patients. They did not find any tumor formation which was discussed in your paper (page 13, line 6 from the bottom).* 

*Wakitani S et.al. “Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months” J Tissue Eng Regen Med. 2011 Feb;5(2):146-50.*
Reply to comment: Thank you for your comment. Reference number 44 has been replaced by the reference that you suggest: Wakitani S et.al. 2011 (Note that the reference number has been changed). Regarding the comment on tumour formation, the following changes have been made in the relevant section of Tissue Engineering: “Cultured-expanded cells may have mutations or epigenetic changes that could confer a tumour-forming potential [44]. However, in vitro and in vivo evidence suggests that the risk of tumour formation is minimal [65]; and no cases of tumour transformation have been reported in 41 patients (45 joints) after autologous bone marrow-derived MSC transplantation for cartilage repair followed for up to 11 years and 5 months. [46].

Tissue Engineering 4) Page 13, line 11; So far, seven human studies have been conducted-----Next paper dealing with bone fracture may be refereed.

Kim SJ et. al., “A multi-center, randomized, clinical study to compare the effect and safety of autologous cultured osteoblast(Ossron) injection to treat fractures” BMC Musculoskelet Disord. 2009 Feb 12;10:20.

Reply to comment: Thank you for your comment. This paper has been added in the reference list and the following changes have been made in the manuscript:

“So far, seven human studies have been conducted using culture-expanded, nongenetically modified MSCs for regeneration of bone defects, with only two studies reporting on long bones and five on maxillofacial conditions [61]. Even though they are rather heterogeneous studies and it is difficult to draw conclusive evidence; bone apposition by the grafted MSCs was observed, but it was not sufficient to bridge large bone defects. Furthermore, the tissue engineering approach has been used to accelerate the fracture-healing process or to augment the bone-prosthesis interface and
prevent aseptic loosening in total joint arthroplasty, with promising results regarding its efficacy and safety [62,63]."

5) Most bone tissue engineering in clinical application have used the composites of MSCs or osteogenic cells and scaffolds. Next paper used in vitro fabricated bone tissue (cultured bone) on the scaffolds. This strategy may be interesting to note in this review paper.


Reply to comment: Thank you for your comment. This paper has been added in the reference list and cited in the manuscript (see previous comment and reply).
