Manuscript NO: 39955

Title: Stem cell therapy for faecal incontinence: current state and future perspectives.

RESPONSE TO THE EDITORIAL BOARD:

Dear editor,

Thank you very much for your commentaries and suggestions.

We have taken them into consideration and have made a thorough reading of reviewers' appreciations.

In this new version we send, the changes to the text appear highlighted to answer the reviewers. You will be able to find them also in this document.

Changes suggested by BPG are the following:

- We added the Audio Core Tip.
- We have modified, signed and attached the "Conflict-of-interest" statement in PDF format
- We have erased tables 3 and 4, included their contents to the main text and renumbered the other tables.

We hope that with these modifications our manuscript accomplish all BPG criteria to be accepted for publication.

Thank you very much.

Kind regards.

Manuscript NO: 39955

Title: Stem cell therapy for faecal incontinence: current state and future perspectives.

Reviewer's code: 03550192

Reviewer's country: Ukraine

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not Publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Peer Review of Manuscript NO: 39955 Title: Stem cell therapy for faecal incontinence: current state and future perspectives

GENERAL COMMENTS: The research is important because faecal incontinence is an illness which affects adults and children. It is associated with disabling consequences, considerable embarrassment, anxiety and poor quality of life. The research findings are significant. Literature data analyzed in the review give the evidence that stem cell therapy is safe, stimulates the repair of both acute and subacute anal sphincter injuries and gives some encouraging functional results. The research is innovative. There are no similar "exhaustive" research in the literature. The manuscript's presentation is of high quality and readability.

SPECIFIC COMMENTS FOR THE VARIOUS ARTICLE SECTIONS: The main and short titles adequately reflect the major topic and content of the study. The abstract provides a clear delineation between the research background, objectives results, and conclusions. However there is no information about the methods used in the study in this section. The abstract presents the innovative and significant points related to the background, objectives, materials and methods, results, and conclusions. The materials and methods

are sufficiently described for the results and conclusions of the review. The method used in the study is adequate to its aim and will allow other investigators to reproduce the study. The study design is adequate to its aim. The results' data draw firm scientific conclusions. The discussion is well organized and conclusions appropriately reflect the reviewed literature. The discussion describes findings based upon systematic theoretical analyses of the results and provides valuable conclusions. According to the text, healthcare costs for faecal incontinence treatment amounted to 2897$ or 2169€ per year. It would be appropriate to mention in the discussion the authors' opinion about the potential cost of stem cell treatment of faecal incontinence. Will it cost more or less than treatment without stem cells? The references are appropriate to the topic of the review, relevant, and up-to-date. The tables fully reflect the results of the study. The tables present the maximum of information in the clear manner.

LANGUAGE EVALUATION B: Minor language polishing is required: There are several mistakes, for example: Indirect cost are… repair is the most successfully… and health levator ani… rectal mucosa and EAS was approximated… so findings not respond… authors objective that… all of them evaluated at… and many associate high morbidity rates… variable on literature…and the like.

CLASSIFICATION OF THE MANUSCRIPT B: Very good

RESPONSE TO REVIEWER 03550192:

Dear reviewer,

Thank you very much for your appreciations. We have taken all of them into consideration and modified our manuscript to answer your queries.

We have added some information about the methodology of our study in the abstract, highlighted in the new version ("A narrative or descriptive review is presented").

Your commentary about the potential costs have been very interesting for us. Performing a real analysis is very difficult because there are no clear evidences about the type of SC, dosage, allogeneic or autologous use, etc. so it is impossible to know the cost SCs will have as a "drug" in the market. However, our research group has a long experience conducting clinical trials with ASCs and we know the costs in our country (Spain), using ASCs for research. We have added that information to the discussion as it can be seen highlighted on the new version:

"It is very difficult to estimate the real potential cost of this kind of therapy for humans because there is no consensus in the type of SC, autologous or allogeneic use, the required dose, etc. The real efficacy needs yet to be clarified, but if a cure could be

achieved, direct and indirect costs mentioned before, could disappear and probably hospitalization costs might be lower due to less invasive procedures to implant SCs compared with FI surgery. Based on our previous experience in clinical trials for anal fistula[22-29], approximated costs in Spain are the following: 1500-2500€ (1727.8 to 2879.73 US $) for closed system SVF, 2800-4000€ (3225.48-4607.83$) for $40x10^6$ autologous ASCs and 3500-5000€ (4032.88-5761.26$) for $100x10^6$ allogeneic ASCs; the costs for other MSCs are equivalent. It must be taken into account that these costs are for SCs produced and dedicated to research, and not for commercial use (maybe higher at least during the firsts years). Between 2018 and 2019 is expected the first allogeneic ASCs medicine product for fistula marketing so we will be able to know real costs on a large scale production."

Concerning language mistakes, we are very disappointed because we have paid a professional language editor to correct it, and still you could find a relevant number of remaining mistakes. We have corrected all of your suggestions and reviewed the text from the beginning.

Thank you very much for your wise commentaries, we are sure that with the newly added information to the manuscript answering your questions, it has gained scientific quality.

Kind regards.

PEER-REVIEW REPORT

Manuscript NO: 39955

Title: Stem cell therapy for faecal incontinence: current state and future perspectives.

Reviewer's code: 03478635

Reviewer's country: Japan

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not Publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This study is very important in terms of investigating the faecal incontinence in clinical stem cell therapy. In abstract, the muscle-derived or mesenchymal stem cells are needed to be defined more clearly.

RESPONSE TO REVIEWER 03478635:

Dear reviewer.

Thank you very much for your gentle commentary about our work and for recommending our manuscript for publication. We hope it can be finally published and continue working on this field of knowledge.

In response to your answer, we have modified the abstract when it refers to muscle or mesenchymal Stem Cells: "Preclinical studies have demonstrated that cellular therapy, mainly in the form of local injections of muscle-derived (muscle derived stem cells or myoblasts derived from them) or mesenchymal (bone-marrow or adipose derived) stem cells".

As you might know, muscle SCs are not as clearly defined as MSCs, with two consensus statements from ISCT. We have reflected this issue on the text: "There are two mostly employed SCs: muscle progenitors (including MDSCs and myoblasts, more committed and derived from the previous, 15 studies) and bone marrow cells (10); allogeneic or autologous use is similar (17 and 11 studies respectively, one uses both types). Muscle

progenitors are less defined on literature than MSCs; there is no consensus defining MDSCs and myoblasts as opposed to MSCs and ASCs, so the cellular products employed on publications could be more heterogeneous and could combine different cell lines."

Kind regards.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 39955

Title: Stem cell therapy for faecal incontinence: current state and future perspectives.

Reviewer's code: 00573611

Reviewer's country: Taiwan

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this review article, the authors reviewed the published literature related to faecal incontinence and stem cell therapy and currently ongoing clinical trials. The authors tried to identify and summarize the existing published knowledge of stem cell utilization as a treatment for faecal incontinence. Comments This is an interesting review article. This manuscript is well-written. The format of this manuscript may need to be modified. The reviewer has no further comments.

RESPONSE TO REVIEWER 00573611:

Dear reviewer.

Thank you very much for your gentle and positive commentaries about our work and for recommending our manuscript for publication. We hope it can be finally published.

Related to the commentary about the manuscript´s format, the journal Editorial Board has not mentioned us any indications different to the published on *Instructions for authors*, and we have followed them. However, concerning your commentary we have made some minor modifications in the general format of the paper, such as in the headings, as it can be seen on the new version.

Thank you very much for your appreciations.
Kind regards.