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Manuscript NO: 53339

Title: Stem cell homing, tracking and therapeutic efficiency evaluation for stroke treatment using nanoparticles: A systematic review

Editors-in-Chief: Dr Tong Cao

The World Journal of Stem Cells

Dear Editor

We would like to thank the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve considerably the quality of this manuscript.

We are sending the revised version of the manuscript entitled, *Stem cell homing, tracking and therapeutic efficiency evaluation for stroke treatment using nanoparticles: A systematic review*, Manuscript NO: 53339, with point-by-point corrections (see below) suggested by you and the reviewers.

Thank you again for your time and consideration. We hope the paper is now suitable for publication in *The World Journal of Stem Cells*. We are looking forward to hearing your decision.

Sincerely,

Lionel Gamarra

Reviewer #1 (code: 00906911)

Generally, the analysis of this study appears to be sound. However, the further analysis according to the source of stem cells (MSC vs NSC) and of source (human vs animal, bone marrow vs others) might be needed to present the more advanced review.

Answer: Thank you for your observation. We added more information in the discussion section of the manuscript to improve this analysis about the source of stem cells and their repercussions in cellular therapy.

Reviewer #2 (code: 03478635)

This is a comprehensive review article about stem cell homing, tracking and therapeutic efficiency evaluation for stroke treatment using nanoparticles.

Answer: Thank you for your time and dedication in the manuscript review, as also for the recognition of our effort in preparing this manuscript.

Reviewer #3 (code: 02446101)

This study was designed to evaluate stem cell migration homing, tracking and therapeutic efficacy in the treatment of stroke using nanoparticles. The results show that cellular therapy demonstrated considerable efficacy with regard to the functional and structural evaluation. The manuscript provides a comprehensive, up-to-date evaluation of the stem cell migration and efficacy of cellular therapy for brain injury to the readers. It's well organized and easy to read. So, acceptance should be recommended for this manuscript.

Answer: Thank you for your time and dedication in the manuscript review, as also for the recognition of our effort in preparing this manuscript.

Reviewer # 4 (code: 03086928)

This review by Nucci et al, consists on a bibliographic review of different works covering the areas of stem cell tracking techniques using nanoparticles and stem cell based stroke

treatments. The tracking techniques are aimed to analyse the homing and engraftment efficiency of transplanted stem cells.

Major Comments.

- 1) *Overall I think this kind of review is interesting for the scientific community although I believe that in this particular case it tries to deal with several issues at the same time making it somehow confusing. Imaging techniques, tracking systems to evaluate homing and engraftment, effectiveness of stroke treatments based in stem cells, etc.... There should be a conductive thread that keeps all sections together and I am not able to find that. Instead, all sections seem somehow disconnected. In each of the sections a short introduction talking about the relevance of the section and how this fits in the global picture should be given. The aim and the connections between the sections are clear in the article highlights, but this is not reflected while reading the text.*

Answer: Thank you for your comments, but as the review is systematic and not narrative, we need to detail each aspect involved in the process of stem cell homing and tracking evaluating. The manuscript has a logical sequence with details in each step of the process, but always bearing in mind that our final objective is the assessment of CTM's homing a tracking. Thus, the sessions followed the logical sequence of firstly providing information where the studies were carried out (3.1. Overview of the reviewed literature) and then starting to survey the characteristics of the cells that were used in tracking and therapy (3.2 Stem cell characteristics). In order to track the cells, some contrast agents were used (3.3 Contrast agent characteristics used in the stem cell labeling, homing and tracking analysis). These contrast agents were internalized into the cells through the labeling process and the cellular viability was analyzed before implantation (3.4 Stem cell labeling process with the contrast agent). After all cell preparation, the disease model induction for cell therapy was analyzed (3.5 Stroke model and brain injury evaluation, the target of stem cell migration), and the characteristics of each molecular imaging technique and parameters used in the image acquisition after cell administration (3.6 Techniques used to detect stem cell migration). Concluding the review analysis with the effective evaluation of cell homing and tracking after administration in stroke model and the result of cell therapy after the arrival of the cell at the target (3.7 Stem cell administration strategies after stroke induction, their migration analysis, and the therapeutic effect). Therefore, for a better understanding of this whole process, a brief complement of information was added at the beginning of some sessions and titles as requested by the reviewer.

- 2) *In the introduction, when different imaging methods are compared, it would be much more didactic to use a table to represent the advantages and disadvantages of each of these methods. The authors are way too succinct in their explanation about the relevance or role of magnetic nanoparticles in these techniques or other concepts very specific of this research area. For example, the rationale of using magnetic nanoparticles and a brief explanation of how they are used is a must do the work can reach a wider readership.*

Answer: We elaborate Table 1 with the major characteristics of molecular imaging modalities according to the reviewer's request and added more information to improve the comprehension. In addition, we added the complementary information about magnetic nanoparticles as a contrast agent used in MRI technique

- 3) *I do not understand the logic of this sentence "Because of population growth, particularly among the elderly, the total number of stroke events and mortality have dramatically increased worldwide in the last two decades.". To measure impact of stroke on the population on absolute terms does not make sense. The authors should provide percentages to support the growth of these events worldwide over the last few years.*

Answer: We modified the first paragraph of the introduction section of the manuscript with more precise data about worldwide population changes and its relationship with stroke events.

Minor Comments.

- 4) *Latin words such as "in vivo" and "in vitro" should always be in italics.*

Answer: Thank you for your suggestion. We modified all Latin words of the manuscript for italics form.

- 5) *Core tip is highly similar to the abstract. This should be re-written to avoid redundancy.*

Answer: Thank you for your comment. We modified the core tip.

- 6) *The sentence "the efficacy of stem cell therapy depends on the stem cell homing ability and engraftment into the injury site over a long period of time and tracking stem cells from their niche to the target tissues. " which is used both in the abstract and core tip does not make sense. Is there a missing link between the first part of the sentence and the second part (and tracking stem cells.....)?*

Answer: Thank you for your observation. We modified both sentences to improve the comprehension of information.

7) *Use economic burden instead of economic cost in the introduction.*

Answer: Thank you for your suggestion. We modified the term in the introduction section of the manuscript.

8) *A full stop after reference 5 should be included.*

Answer: We corrected according to your suggestion.

9) *In paragraph 3 of the introduction, what is exactly what the authors call stem cells “derivatives”.*

Answer: The word “derivative” is referring to the different types of stem cells according to their sources such as embryonic or fetal neural, umbilical mesenchymal, bone marrow-derived mesenchymal, or peripheral blood hematopoietic. In addition, this word is commonly used in studies^[1-3] about stem cell transplantation.

References

1. Tocci A, Forte L. Mesenchymal stem cell: use and perspectives. *Hematol J*. 2003;4(2):92-96.
2. Phelps J, Sanati-Nezhad A, Ungrin M, Duncan N, Sen A. Bioprocessing of Mesenchymal Stem Cells and Their Derivatives: Toward Cell-Free Therapeutics. *Stem Cells International*. 2018;2018:1-23.
3. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. *Stem Cell Res Ther*. 2019;10(1):68.

10) *In some cases the verb “tracking” is used several times in the same sentence. You could substitute tracking by following or a similar verb to avoid being repetitive.*

Answer: Thank you for your suggestion. We modified the verb “tracking” for a similar verb to minimize the repetition.

11) *I do not see the usefulness of the chapter entitled Stem cell characteristics. It would be much more useful if it would have described the nature of the stem cells used in addition to identify if they are murine or human.*

Answer: In a systematic review it is necessary to carry out a survey of all information that comprises the objective of the study, in the case of the present review, ranging from obtaining stem cells with all their characteristics to the process involved in them so that they can be detected in the stem cell homing and tracking process, as well as the stroke model process, focus of the analysis application. Detailed tables were elaborated with a comprehensive amount of data, in order to have a broad comparative process of the studies related to the theme treated in the present review, without losing the focus of the proposed analysis, which is the evaluation of the homing and tracking of stem cells applied to the stroke.

This type of information is common in published systematic review papers, both from our group and from other authors.

However, when a narrative-type review is carried out (No systematic review), these data are not reported, and data related to the homing and tracking process is evidenced and discussed, in a continuous, but superficial way, without much detail of all the processes involved. so that there is an effective analysis, as was done in the present review, which followed all the methodological and informative rigor with a high degree of detail, as it is being placed, where the reader has the possibility to evaluate the studies since the beginning of the elaboration process of a cell tracking evaluation.