

December 05, 2018

Manuscript NO: 42912

Title: Triple-modal imaging of stem-cells labeled with multimodal nanoparticles, applied in a stroke model

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, Triple-modal imaging of stem-cells labeled with multimodal nanoparticles, applied in a stroke model, Manuscript NO: 42912, with point-by-point corrections (see below) suggested by you and the reviewers.

We believe that the contents have been more clearly and appropriately transmitted, a native English speaker carried out an English language review and the manuscript was carefully formatted following the guideline.

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: 02728252)

It is a comprehensive basic study with two arms, in vitro and in vivo. The authors aimed to determine the sensitivity of triple-modal imaging of stem-cells labeled with multimodal nanoparticles in vitro and to confirm their results with in vivo stroke model. They highlighted the importance of quantification of multimodal nanoparticles internalized into cells and their efficacy in signal detection for the triple image modality in stroke model.

Observation no. 1: Despite the great efforts that were done, the abstract and the introduction sections were poorly written and should be checked by Language Service Company to improve the manuscript and to be of high quality

Answer no. 1: We modified the abstract and the introduction sections and after, we sent the manuscript for English language review by Language Service Company (biomedical editing company “American Journal Experts”), in which was emitted a Certificate Service Editing by AJE Company, whose certificate verification key is 0FB9-08D7-A4BE-4A99-6389.

Observation no. 2: *In the result section; • Please write the degree of positivity for CD90 in the text. • Positive markers surface should be written positive surface markers and the same for negative markers surface should be written negative surface markers. • In some instances, logarithmic scale pH was written correctly and in others as ph?*

Answer no. 2: Thank you for your observation. We done all modifications suggested:

- The degree of positivity for CD90 was added in the results section “CD90 (94.7%)”
- We modified the phrase “Positive markers surface” by “positive surface markers”, as well as “Negative markers surface” by “negative surface markers”.
- We modified all “ph” written for "pH" in the manuscript

Reviewer #2 (code: 03947685)

The manuscript is good and worthy of publication as it focuses on a good goal the importance of quantification of MNP internalized into cells and the efficacy in signal detection for the triple image modality in stroke model but there are some minor things:

Observation no. 1: *The authors should review the abbreviations. There are abbreviations without expressing them. The item must be written in full and the abbreviation should be written in parentheses.*

Answer no.1: **We review the manuscript and corrected the abbreviations without the full expression.**

Observation no. 2: *The other thing, is that the authors mentioned that MSCLuc implanted in the animal after submitted to stroke induction; they have to write the method they have induced this stroke in the experimental animals*

Answer no. 2: **The item 2.14 of the method section, we reported in detail the stroke model induction, followed of the item 2.15 about the cell implantation procedure. In addition, the item 2.12 of method section, we reported all experiment design carried out in the animal model (Experiment 1 and 2) to clarify the steps of research.**

Reviewer # 3 (code: 02728252)

The manuscript addresses an important area of research relevant to fate determination of stem cells post transplantation.

Observation no. 1: *My comments for the improvement of the quality of the manuscript include: 1. The manuscript contains too much of unnecessary text and details. Redundancy of the text is distracting for the reader from the real message. For example, both Introduction and discussion part can be cut down to remove unnecessary details. Similarly, inclusion for 100 references for a research paper are a little too many and need to be reduced significantly.*

Answer no.1: **Thanks you for your observation. We removed the repeat information of the introduction and the discussion. In addition, we adequate the number of references according to request.**

Observation no. 2: *The text needs extensive revision for language, grammar and spellings. There are many words which are not used in English language at all. Please extensively revise the paper.*

Answer no. 2: **We sent the manuscript for English language review by Language Service Company (biomedical editing company “American Journal Experts”).**

Observation no. 3: *The authors claim that the Triple modal approach will help to morphofunctionally assess the fate of the transplanted cells. It remains less evident from the provided data how the labels will help in assessment of the differentiated cells from the undifferentiated cells and similarly if the cells proliferate, how the label will assess the derivative (daughter) cells. Similarly, if the cells undergo apoptosis, how the label will discriminant between the immune cells picking up the released label from the dying/ apoptotic transplanted stem cells.*

Answer no. 3: **Studies that used multimodal images approach also reported the morphofunctional aspects during analysis with different image modalities for treatment or diagnoses and highlighted these important aspects allowed by image acquisition combined (Martí-Bonmatí L, et al. 2010, Misri, R, et al., 2013; Zhao J. et al., 20118; Lee DE. et al., 2012; Yang HM. et al., 2018). The proposal of this study was to detect the stem cell signal labeled with multimodal nanoparticles by the triple modal images**

(bioluminescence, fluorescence and magnetic resonance) and to analysis their localization, proliferation, apoptosis and biodistribution. In addition, we analyzed the quantification of the iron load internalized in the cells, as well as the correlation of quantification results between the techniques.

References:

- Martí-Bonmatí L, Sopena R, Bartumeus P, Sopena P. Multimodality imaging techniques. *Contrast Media Mol Imaging*. 2010 Jul-Aug;5(4):180-9. doi: 10.1002/cmml.393. Review. PubMed PMID: 20812286.
- Misri, R. (2013). Multimodality imaging. *Molecular Imaging Techniques: New Frontiers*, 162–176. doi:10.4155/ebo.13.186.
- Zhao J, Chen J, Ma S, et al. Recent developments in multimodality fluorescence imaging probes. *Acta Pharm Sin B*. 2018;8(3):320-338.
- Lee DE, Koo H, Sun IC, Ryu JH, Kim K, Kwon IC. Multifunctional nanoparticles for multimodal imaging and theragnosis. *Chem Soc Rev* 2012;41(7):2656-2672.
- Yang HM, Park CW, Park S, Kim JD. Cross-linked magnetic nanoparticles with a biocompatible amide bond for cancer-targeted dual optical/magnetic resonance imaging. *Colloids Surf B Biointerfaces* 2018;161:183-191