

Dear Dr Fang-Fang Ji,

Thank you for your letter inviting us to submit a revised version of our manuscript entitled: 'iPSC, are they a small step or a giant leap for mankind therapeutic applications?'. We are pleased to hear that the Reviewers found our review interesting and well positioned in the field. The Reviewers' comments and the Editor's guidance have helped us to improve the manuscript and to make it more complete. Detailed responses to the Reviewers' comments are enclosed.

We are confident that we have sufficiently addressed all Reviewers' and Editor's comments and very much hope that you will now consider our manuscript suitable for publication in *World Journal of Stem Cell*. We look forward to hearing from you.

Kind regards,

José Bragança

Reviewer: 1

Reviewers comments: *"In their manuscript the authors describe the state of art regarding iPSCs. The question on the iPSC is very complex because although they seemed a great alternative for cell therapy in therapeutic field many problems arose as a result of their use. These problems are highlighted in the manuscript but sincerely, although the title asks a question, the feeling is that the authors do not take a position in this argument although there are many doubts that they highlight in the iPSCs use. In my opinion after reading their manuscript, the position relative to iPSCs is not favorable because many problems related to their use will have to be solved. If it were possible I would like the authors not to limit themselves to exposing the data reported in literature, but, considering the title, that they make a conclusion paragraph with strenght and weaknesses of iPSCs well highlighted."*

We are grateful for the comments and suggestions made, which helped to complete our manuscript and to clearly establish our position on the matter. Please note that the proposed changes and/or additions to the text of the original

manuscript to address the comments of both Reviewers and Editors are indicated in **RED**.

The Reviewer's comments are addressed below:

1 - *"In my opinion after reading their manuscript, the position relative to iPSCs is not favorable because many problems related to their use will have to be solved."*

AUTHORS' ANSWER/MODIFICATIONS:

We thank the Reviewer for this comment. Indeed, we have made the point to present some of the weaknesses still hampering the full use of iPSC for therapies. However, our vision is that the iPSC technology has a great future for multiple approaches. Moreover, despite the problems that remain to be solved, iPSC-derived cells have entered clinical trials already.

Indeed, the title has been changed to *"iPSC, a giant leap for mankind therapeutic applications"*

We have also added the following paragraph to the conclusion section;

*"Although many technical hurdles remain to be surpassed for iPSC technology to fully reach its potential. In just over ten years after its first development this technology has remarkably led to several clinical applications, and provide new ways of obtaining disease models *in vitro* to better study the mechanism of human pathologies and to improve patients' treatment in a more adequate and personalized manner. Thus, iPSC technology has already been "a giant leap" in terms of obtention of human cells with incredible versatility and potential for therapeutic applications. "*

2 - *"If it were possible I would like the authors not to limit themselves to exposing the data reported in literature, but, considering the title, that they make a conclusion paragraph with strenght and weaknesses of iPSCs well highlighted."*

AUTHORS' ANSWER/MODIFICATIONS:

We thank the Reviewer for these suggestions. We have partially addressed some of these points by modifications exposed in the point above.

We have also prepared a Table (Table 1) to be part of the manuscript, which exposed the weaknesses and strengths of iPSC technology, and presents some suggestions on potential improvements or corrections that could be made to overcome these limitations. Please see Table 1.

Reviewer: 2

Reviewer's comments: *"The manuscript entitled "iPSC, are they a small step or a giant leap for mankind therapeutic applications?" by Bragança and colleagues represents a very interesting review on iPS cells. The title reflects the main subject of the manuscript. The abstract summarizes the work described and the key words reflect the focus of the manuscript. The introduction adequately describes the background and significance of iPSC. The topics selected in this are appropriately highlighted and clearly presented. While the figure presented in the conclusion could have been presented earlier in the manuscript. But in a simple diagramatic way summarized the main topics of the review. This reviewer has noticed several typos that should be corrected."*

We thank the Reviewer for finding that our manuscript is interesting, well written with an accurate description of the findings which are relevant for the research field.

The changes and additions made to address the reviewer's and editor's comments and suggestions are indicated in **RED** in the text of the original manuscript.

The Reviewer's comments are addressed below:

1 - *"While the figure presented in the conclusion could have been presented earlier in the manuscript."*

We have introduced the Figure earlier in the text.