

October 19th 2018

Ying Dou,

Science Editor, Editorial Office

BPG Editorial Office

Dear Editor,

We thank you for considering the manuscript “**Cancer Stem Cell impact on clinical oncology**” for possible acceptance for its publication in *World Journal of Stem Cells*. We appreciate the comments made by the reviewers, since they improve the understanding of this review to the readers. We present our response to each reviewer and we address each concern separately according to the comments we received.

Reviewer 01:

“Toledo-Guzmán ME et al. have submitted an interesting mini-review about impact of Cancer Stem Cells on clinical oncology. Supported by an up to date bibliography, it is a fluently written manuscript which provides some basic information regarding CSCs to the reader. My one suggestion to break the monotony of continuous text is that the authors should consider to provide some information in the form of small tables such as table for surface markers, a summary of CSC characteristics etc. This will help the readers to keep their focus.”

We are grateful for your comments, which are helpful for improving the present manuscript. Based on the suggestion about adding tables in order to facilitate the manuscript reading, we included Table 1 in which we present some publications where cancer stem cell markers were identified in several tumor types using different study models.

Reviewer 02:

“The manuscript by Toledo-Guzman et al is a minireview on Cancer Stem Cells and their role in clinical oncology. The title is appropriate and it well reflects the subject of the paper, as well as both the abstract and the keywords. The review is exhaustive and well written, with authoritative references. The subjects is really interesting, with a detailed and up to date part on cancer stem cells markers and overall the current approach to target these cells. The reviewer just has a few suggestions: - Schematic diagrams and/or tables would be helpful for the reader, so the suggestion is to include them into the review. - Although the English is acceptable, the review should be revised according to a more formal style (it is vs it's)”.

We appreciate your comments about the manuscript; we included Table 1 in which we summarize some relevant cancer stem cells markers mentioned in the manuscript in different tumor types and highlighted the study model used to identify them.

Reviewer 03:

“Authors review the CSC research history, characteristics and application for cancer therapy. Actually, CSC is new concept and critical for the cancer management nowadays and future, and we can take this message from this review. I suggest some points needed to be corrected. <Major points> I think that both 2 figures which authors created is very important in this review, because this is just overview of 2 main parts, “CSC CHARACTERISTICS WITH CLINICAL RELEVANCE” and “CSC IDENTIFIED IN PATIENTS: PHENOTYPE AND TYPE OF STUDIES”. So that citation of Fig.1 should be

written before the detail of “Surface marker” and “Functional markers”. Moreover, key concept of Fig.1 should be explained. It may be following things. i) One marker is found in different organ cancer. ii) Several markers are positive for one type of cancer In case of Fig.2, there is no citation in the document. Citation and explanation of this figure also should be written in the main document. <Minor points> · In the last paragraph of INTRODUCTION, authors wrote that, “Despite the well-documented role of CSC...” Purpose of this review to explain the CSC character and its meaning. Therefore, I think it is not suitable to use “well-documented” here without detail explanation. · In the first paragraph of “CSCs AND THRAPPY RESISTANCE”, authors wrote “.they have been found over expressed...” I think the word “overexpressed” is normal”.

Thank you very much for your useful comments, we considered each point mentioned before. We cited Figure 1 as you suggested before “surface markers” and “functional markers” in the CSCs generalities section, “**It is very important to note that although the CSC model is widely reported in several cancer types (Figure 1), there are also...**” moreover, a table that summarizes known CSC markers in several cancer types as well as the model or models in which each marker was validated was added as Table 1 and cited together with Figure 1 at the beginning of section CSCs characteristics with clinical relevance “**To date, several CSC markers from distinct tumor types have been proposed and validated through different experimental models (Table 1, Figure 1). Some of these markers are discussed below**”.

The aim of Figure 2 was to show the treatment strategies mentioned in the section of CSC approaching therapy that are being developed by several groups and we consider are important, so the figure was properly cited in the previously named section CSC approaching therapy, “**Despite the broad variety of CSC publications in the last years, the discovery of effective therapies has remained elusive, however, some advances have been made in the field that**

could be getting us closer to direct CSC elimination. A brief resume of some of these strategies is showed in Figure 2”.

In the last paragraph of the introduction we wrote **“Despite the well-documented role of CSCs in chemo and radio resistance (22–24), an increasing interest in implementing strategies against CSCs in patients, in order to improve their clinical outcome, has grown in recent years because conventional therapies are effective in controlling tumor growth at the beginning but, over time, relapsing is a main problem due to sparing of CSCs (22,25,26)”**. As you suggested, we reconsidered our words and the context so we changed the text as follows, **“Due to the reported participation of CSCs in chemo and radio resistance (22–24), an increasing interest in implementing strategies against CSCs in patients, in order to improve their clinical outcome, has grown in recent years because conventional therapies are effective in controlling tumor growth at the beginning but, over time, relapsing is a main problem due to sparing of CSCs (22,25,26)”**.

Finally, the word overexpressed was corrected, and revised in the whole manuscript.

Reviewer 04:

“In the manuscript, the author reviewed the phenotype of cancer stem cells and the therapeutic strategies to target cancer stem cells for cancer treatment. The manuscript focuses on the clinical relevance of cancer stem cell and is well-organized with up-to-date information. The abstract summarized the main points of the manuscript but could be more concise”

We appreciate your revision and considered your comments for the improvement of this manuscript.

Finally, we would like to thank the referees for their comments that help to improve this manuscript. We feel we have made the necessary changes so that it should be now suitable for publication in *World Journal of Stem Cells*. If you need additional information, please contact me.

A handwritten signature in black ink, appearing to read 'Elizabeth Ortiz Sánchez', written in a cursive style.

Dra. Elizabeth Ortiz Sánchez
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