Title: An in vitro study of the effect of 5-ALA-mediated photodynamic therapy on oral squamous cell carcinoma

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Author’s response to reviews:

Dear Editor,
Thank you for your helpful comments concerning our manuscript entitled “The effect and mechanism of 5-ALA-mediated photodynamic therapy on oral squamous cell carcinoma in vivo and in vitro” (ID: OHEA-D-20-00183). Those comments are all valuable and very helpful for revising and improving our manuscript, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. We have uploaded a clean revised text file and the file "Response letter to Reviewers". The main corrections in the paper and the responds to the reviewer’s comments are list below. Please let us know if there are additional inadequacies in our manuscript. Thank you for your endeavor to facilitate timely publication of our manuscript.
Sincerely,

Liangpeng Xu

We would like to express our sincere thanks to the reviewers for their constructive and positive comments.

Reviewer reports:
Reviewer 1: It is great honor for me to make review on this interesting paper.
I do appreciate to authors for their intent to make big investigation and research.
I have got few remarks so far.
The tables do not show all groups times and findings. So we could not compare all times and groups. The labels should be simplified, data should be more comprehensive. So statistics could not be evaluated. Could you please add more tables and data.
Responds: I am sorry for the inconveniences caused by the shortcomings in our research. We adopted different experimental times and groups for different research parts, so not all tables have
the same times and groups. However, the statistical results of the current grouping were statistically significant and sufficient to support our research conclusion. We will include more groups and statistical results in the follow-up study, hoping to get your understanding. Thank you for carefully reading and commenting on our manuscript, and your constructive suggestion helped us a lot.

In the section discussion on the line 15 * reference 8 does not match. Please check the reference number 8.

Responds: I am sorry for the inconveniences caused by our mistake, and we have checked and corrected the reference now.

It is not clear what is the OSCC degree of differentiation in your paper? Could you please give more explanation on cytology? Could we have the thickness of OSCC culture of your study?

Responds: Thank you for reading and commenting on our manuscript. In fact, we did not do in vivo experiments, and we have now deleted the description of in vivo experiments from the article. I am sorry for the inconveniences caused by our mistake.

The conclusion is so strong with regards to the data you provided. That is so pro PDT. However, the literature you must add and discuss in your paper should be Rosin, Flávia Cristina Perillo, et al. "Photodynamic Therapy Mediated by 5-aminolevulinic Acid Promotes the Upregulation and Modifies the Intracellular Expression of Surveillance Proteins in Oral Squamous Cell Carcinoma." Photochemistry and photobiology 95.2 (2019): 635-643. This novel study says that within 5-ALA-mediated PDT Bcl-2, p-Akt, p-mTOR and iNOS were up regulated in neoplastic cells of OSCC, suggesting an activation of anti-apoptosis and cell proliferation pathways. This fact must be considered in the establishment of PDT protocols for OSCC treatment.

thank you

Responds: Thank you very much for your constructive suggestion. We have carefully referred to the literature you mentioned and quoted it in our manuscript. We appreciate for your carefully reading and commenting on our manuscript, and your suggestions have made a great sense.

Reviewer 2: Interesting study. However

1. Language needs extensive revision

Responds: Thank you for reading and commenting on our manuscript. Because I am not a native English speaker, this manuscript has proofread by a language editing company to improve the article for language and style now.

2. Explain what the "in vivo" Component

Responds: I am sorry for the inconveniences caused by our mistake, and we have deleted the related description about “in vivo”, cause we did not in vivo experiments in the study.

3. Graphical representation of Data

Responds: Our present presentation is sufficient to express the results of our research data, so we do not add the data of pictures. Thank you for reading and commenting on our article and hope to get your understanding.

4. List the study groups clearly

Responds: I am sorry for the inconveniences caused by our half-baked description. We have now modified and rewritten the Method section according to your advice to make our manuscript clearer.

5. Discussion can be shorter and pertain to the study components
Responds: Thank you for your helpful suggestions, and we have now simplified and rewritten the Discussion section according to your advice. Thank you for reading and commenting on our manuscript again.

Reviewer 3: Thank you very much for presenting a study of contemporary interest. The experiment has been carefully designed and conducted. In my opinion, presentation of the study findings could be further improved.

Title: Does not accurately reflect the reported study. Reported research studies the effect of 5-ALA mediated photodynamic therapy in laboratory conditions using cell cultures. This is an in vitro study and results can only be extrapolated into in vivo

Responds: I am sorry for the inconveniences caused by our mistake, and we have deleted the related description about “in vivo”, cause we did not in vivo experiments in the study.

Background:
This is well written. However, the aim of the study as mentioned in the last sentence does not clearly define the research question.

Responds: I am sorry for the inconveniences caused by our half-baked description, and we have modified the last sentence to make the aim of the study defined clearly.

Methods and Results:
I think there is lack of clarity and cohesion in the way the experiment has been described. Strongly recommend using a figure/table to describe the different groups clearly to help reader to follow the results. Table 4 shows Groups I, II, III, IV but there is no definition of these in the Methods. Overall, the manuscript will improve significantly if the authors could be more explicit in their description of the experiment performed and present the steps in logical order.

Responds: I am sorry for the inconveniences caused by our half-baked description. We have now modified and rewritten the Method section according to your advice to make our manuscript clearer.

Discussion: Some statements need to be supported by references.

Responds: Thank you for your helpful suggestions, and we have now added some references from recognized peer-reviewed international journals in the Discussion section according to your advice. Thank you for reading and commenting on our manuscript again.

We appreciate for Editors and Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.