Response to the Reviewer's Queries

Date: March 05, 2022

Manuscript Title: Current progress and emerging technologies for generating extra-pancreatic functional insulin producing cells

Manuscript No: 74949

To,

Dr. Xiao-Long Liu, PhD, Professor
Editors-in-Chief
World Journal of Translational Medicine

Respected Sir,

We have incorporated the changes as suggested by Reviewers. Changes in the revised manuscript have been highlighted in **track version** throughout the manuscript (Please see below after point wise clarification).

Please find point-wise clarification of each comment:

Reviewer 1 (03673990):

The manuscript titled "Current progress and emerging technologies for generating extra-pancreatic functional insulin producing cells" sent to the World Journal of Translational Medicine is view of therapeutic strategies being performed to obtain insulin producing cells from extra-pancreatic sources. The authors take up a very interesting topic, which, due to the rapid development of various technologies in medicine, may soon result in real and effective ways of becoming independent from pancreatic or beta cell transplantation. The strong advantage of the paper study is independent presentation of extra-pancreatic sources of beta-cells, emerging technologies for cell transplantation in diabetes and transplantation sites. The authors in a clear way in the form of tables show the advantages and disadvantages of different transplantation sites as well the degree of beta-cell similarity in relation to target cells.

1. **However only in relation to one of the methods they describe in detail the viability of the transplanted cells and the effect on the maintenance of normoglycemia, it would be worth to show these effects for all studies.**

We have included all the available details for additional studies as suggested by the reviewer.

2. **There is also no more up-to-date literature or a description that there have not been many publications on the subject recently.**

   We have added additional more up-to-date literature with relevant description as suggested by the reviewer.

Reviewer 2 (05639036):

1. **The style of a scientific manuscript is not considered in this manuscript. For example, authors used an original figure on gene-expression analysis as figure 1. It is not suitable for review manuscript. Also, other figures had not suitable quality. Why you used figure 4?**

   As per the suggestion, we have removed original figures from the manuscript and revised all the figures with more appropriate details in high resolution. Figure 4 has been deleted.

2. **Induced pluripotent stem cells are a promising approach on cell-based therapy to avoiding immune rejection. There is no section about this cell, while it is most important cell! Also, authors mentioned iPS cells in figure 1. WHY?**

   We agree with the reviewer's point of view and accordingly added additional section for the potential of induced pluripotent stem cells in diabetes management. Figure 1 has been revised and iPS has been replaced with InPCs which refers to insulin producing cells.

3. **The number of headlines and sub-headlines and confusing. There are various grammatical and or thographical errors regarding English. References are too old. There is a major advance in this technology in recent years. Last recent cited article is related to 2016.**

   As per the suggestion, we have revised numbering of all the headlines and sub-headlines throughout the manuscript. Further the manuscript language and grammatical errors have been corrected by professional English writer. New references have been added and recent technologies have been described with more updated information.

Reviewer 3 (05426937): No Comments

Reviewer 4 (02728252):

This is a narrative review exploring the current progress and emerging technologies for generating extra-pancreatic functional insulin producing cells. The review summarizes extra-pancreatic sources to produce insulin secreting cells with reference to emerging technologies to fulfill the future clinical need.

1. **The review needs to be updated with a more recent references and English editing is mandatory. Could you please refer to table 2 in the text of the manuscript.**

   As per the suggestion, language and grammatical errors have been corrected by professional English writer and new up to date references have been added with more updated information. Further, Table 2 has been referred in the updated text of the manuscript.

Reviewer 5 (02446101):

In this manuscript, the authors discussed the current progress and emerging technologies for generating extra-pancreatic functional insulin producing cells. It's an interesting manuscript and provides some new ideas to the readers. In this paper, the main research advances in this field are systematically discussed and described.

1. **There's only one issue which should be addressed. In the section of "Extra-pancreatic sources of β–cells", hepatic stem/progenitor cells are the most promising cell source and should be discussed at first. So, acceptance after minor revision should be recommended for this manuscript.**

   As per the suggestion, we have shifted "**Hepatic stem/progenitor cells**" section first followed by other sources.

Best Regards,

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