

Name of Journal: *World Journal of Stem Cells*

Manuscript NO: 76421

Manuscript Type: MINIREVIEWS

Title: "Stem cell therapy for insulin-dependent diabetes: are we still on the road?"

Correspondence Author: Wei Wang

Dear Editor,

Thank you very much for your attention and referees' evaluation and comments on this review. We have revised the manuscript according to your kind advices and referees' detailed suggestions. Enclosed please find the responses to the referees. We sincerely hope this manuscript will be finally acceptable to be published on the World Journal of Stem Cells. Thank you for all your help and looking forward to hearing from you soon.

Best regards

Sincerely yours

Lu Yang

Please find the following response to the comments of referees:

Response to the referees' comments

Referee A

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors demonstrated about cell therapy by inducing beta cell differentiation from various stem cell types. In manuscript, the authors explained development of embryonic stem cells and differentiation of stem cells into beta cells to improve diabetes. It is considered to be a paper that well classifies the advantages and disadvantages of stem cell types and uses. However, the data analysis between of the papers related to embryonic cell development (page 3-4) and stem cell

differentiation techniques (page 5-8) seems very weak. In addition, it is considered that the following direct/indirect issues need to be resolved. 1. The purpose of the author's statement is unclear. Is the author explaining the stem cell differentiation method for the treatment of diabetes? Or does it explain the outcomes of treatment? The authors should clearly set goals of review paper. 2. In introduction, cited data from IDF Diabetes Atlas by the authors is ambiguous. On the basis of Atlas, the exact timing and number of patients with diabetes onset should be presented. 3. In page 3, the sentence "The limitations of human donor-derived β cells alternatives, availability of insulin-secreting β cells from pluripotent stem cells (PSCs)" is not complete, and the meaning does not fit the context of the paragraph related to insulin-secreting beta cell differentiated from stem cells. 4. In fact, after the chapter discussing pancreas development, research examples using development factors should explain in induction of pancreas differentiation using various stem cells. However, the relationship of chapters between the pancreas development and the differentiation of PSCs into insulin-secreting beta cells has not been clearly described. 5. The full names of the first abbreviations used in the sentence, such as FGF, MPP, and PTF1A, were not mentioned. And, what is 6-7 'wpc'? Is this 'weeks post conception'? 6. Name of this paper is stem cell therapy for insulin-'dependent' diabetes. But, the author focused on independent diabetes treatment in the chapter. The subject and content are contradictory. 7. In addition, it does not clearly distinguish diabetes treatment by cell source of ESC, iPSC, and MSC, so the readability is poor.

Response: Thanks for the referee's kind suggestions. My explanations are as follows:

1. This review focuses on the current status of research using stem cells to treat patients with diabetes. In this manuscript, we introduce the development of islets and compare some differences in the development of islets between mice and humans. Three different stem cell types are also described, which can induce differentiation of islet beta cells, but each has advantages and disadvantages in treatment. 2. I have added specific IDF data in the introduction section of this manuscript. 3. Thanks for correcting! I have modified the corresponding statement. 4. In the corresponding

paragraphs of the article, I have added relevant content to specifically express the relationship between transcription factors and pluripotent stem cells. 5. I have added abbreviations and full names in the corresponding parts of the manuscript and given specific explanations for the time words. 6. The manuscript focuses on advances in stem cell therapy for diabetes. Stem cell therapy is one of the treatments for diabetes. The advantages and disadvantages of different types of stem cell therapy are presented in this review. 7. I have added the cell source of ESC, iPSC, and MSC in the corresponding part of the manuscript.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Excellent and complete manuscript on the state of art of stem cell treatment for patients with diabetes mellitus due to insulin shortage. the references are complete and the discussion is also wide and complete. In my opinion the authors should more mention on pancreas transplantation that is still not the best option for such patients.

Response: Thanks for your review. As the title suggests, the manuscript focuses on the current state of research into stem cell treatments for diabetes. The process of islet development and the advantages and disadvantages of three different stem cells in treatment are introduced in the manuscript. Thank you for your advice! I have added some information about islet transplantation to the prospectus section of the manuscript.

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: The manuscript titled “Stem cell therapy – dependent diabetes: are we still on the road?” sent to the World Journal of Stem Cells is a review of the current state of the use of stem cells as a replacement therapy in patients with insulin depletion, especially type 1 diabetics. The authors take up a very interesting topic, which, due to the rapid development of various therapeutic technologies in diabetes type 1, may result in real and effective way of its treatment soon. The strong advantage of the paper is presentation of stem cell therapy from different perspectives. The authors first widely describe the embryonic development of endocrine cells starting from its progenitors showing the differences of human and mouse models in this process, what could counteract the simple translation into the human being. The authors describe different sources of stem cells being studied in the described indication, starting from embryonic, via induced pluripotent stem cells, ending in adult stem cells. Then they show the advantages and disadvantages of different type of stem cells for diabetes documenting their effectiveness and safety on the newest studies. Taken into consideration that the present progress of stem cell therapy in different indications is being not only studied, but also applicated, its usage in diabetes seems to be very close for reality. The FDA approved in 2021 for clinical trial the new drug with stem cells has been a proof of such a concept. The authors indicate the present state of authorization and legacy of stem cell therapy and other limitations enabling its official presence in the clinical practice. The authors in a clear way in the form of figures and tables show the application of induced pluripotent stem cells, the differences between human and mouse pancreatic embryogenesis, advantages and disadvantages of different types of stem cell therapy for diabetes. The authors could present the embryonic development of endocrine cells in the form of a table and show the critical points for the use of stem cells in this process. There is also no more up-to-date literature or a description on the subject recently. Finally the paper is extremely worth to be published in the World Journal of Stem Cells.

Response: Thank you for your approval of this manuscript! I am so glad to receive your positive comments!

Reviewer #4:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: I very much likes the manuscript, the English language is adequate, the information is brief and up-to-date.

Response: Thank you very much for your review!

Referee B

(1) *Science editor:*

Manuscripts focus on stem cell therapy for diabetes. The authors describe the different stem cell sources studied in the indications and demonstrate the advantages and disadvantages of different types of stem cells in the treatment of diabetes. The manuscript is well, concisely and coherently organized and presented and the style. Abbreviations that appear for the first time should be explained.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade B (Very good)

Response: Thanks for your review! I have added abbreviations and full names in the corresponding parts of the manuscript.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report,

Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: <https://www.referencecitationanalysis.com/>. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list.

Response: Thanks for your review! I will provide the editable figures in PPT format.