

Dear editors and reviewers,

Thanks very much for your comments. We resolved all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report, please check. We expect our revised manuscript to meet the requirements for final acceptance and publication, and look forward being published in your journal.

1 MANUSCRIPT REVISION DEADLINE

We request that you submit your revision in no more than **14 days**. **Please note that you have only two chances for revising the manuscript.**

Thanks for your reminding. We extended our revision deadline until to 17th, May through email.

2 PLEASE SELECT TO REVISE THIS MANUSCRIPT OR NOT

Please login to the F6Publishing system at <https://www.f6publishing.com> by entering your registered E-mail and password. After clicking on the “Author Login” button, please click on “Manuscripts Needing Revision” under the “Revisions” heading to find your manuscript that needs revision. Clicking on the “Handle” button allows you to choose to revise this manuscript or not. If you choose not to revise your manuscript, please click on the “Decline” button, and the manuscript will be WITHDRAWN.

We get it.

3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Comments: Over all a very nice effort to address the research question. The title and background is accordingly mentioned. Methodology is described in detail and this is appropriate to address the research objectives. Results have been nicely presented and discussion is well written, however a few sentences need to be added for the future directions • Plz confirm if conventional RT-PCR was done for iPSCs characterization or qRT-PCR and also Gapdh is mentioned in the table

of primers, but it says in the text that the data was normalized by using B-actin only, clarify. Also mention the qPCR platform used • If a cell line for iPSCs (MiPS.5) was commercially purchased, wasn't it already characterized and what's the rationale for doing so many experiments for its characterization in the study? • As mentioned in conclusion Sinomenine was used for the first time with iPSCs and the treated imDCs can be used in the field of transplantation immune tolerance, plz elaborate on how they can be used in a clinical setting and how much these results will correlate with human iPSCs derived imDCs.

Dear reviewer,

Thanks very much for your comments. We resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. **Firstly**, thanks for your reminding about PCR. qRT-PCR was used for iPSCs characterization, and β -actin expression was used to normalize the data, and Gapdh was removed from Table 1. **Secondly**, the iPSCs lines MiPS.5 were purchased from Shanghai Sisansai Biological Technology Co Ltd, But the Co Ltd did not provide a certificate of identification, so we did so many experiments for its characterization in our study to ensure its authenticity for the following study. **Thirdly**, as mentioned in conclusion Sinomenine was used for the first time with iPSCs and the treated imDCs can be used in the field of transplantation immune tolerance. Our study will lay the foundation for the application of human iPSCs in a clinical setting. We are currently conducting further studies on the induction of immune tolerance by SN enhancing the differentiation of human iPSCs into imDCs, and also exploring the optimal dose and injection time for its use in a clinical setting. **Lastly**, Professor Hongkui Deng of Peking University has successfully obtained iPSCs by chemical reprogramming of humansomatic cells, and the research were published in 《Nature》. The iPSCs are not obtained by virus transfection, which avoid side effects such as teratoma formation. We believe that the iPSCs clinical application prospects are very attractive. Plz refer to the following article[\[a\]](#).

[a] **Guan J**, Wang G, Wang J, Zhang Z, Fu Y, Cheng L, Meng G, Lyu Y, Zhu J, Li Y, Wang Y, Liu Y, Liu B, Yang Z, He H, Zhong X, Chen Q, Zhang X, Sun S, Lai W, Shi Y, Liu L, Wang L, Li C, Lu S, Deng H. Chemical reprogramming of human somatic cells to pluripotent stem cells. Nature, 2022:undefined(undefined), undefined.[PMID: 35418683 DOI:10.1038/s41586-022-04593-5]

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: 1. The topic of the article is novel, the previous literature has paid more attention to the therapeutic effect of penicilline on potentially inducing immune tolerance, while this article focuses on describing that chycholinergic can maintain the immature state of dendritic cells derived from iPSC,

which helps to solve the problem of immature dendritic cell sources, there are few relevant reports. 2. The overall logic of the article is clear, but most of it is limited to apparent observation: (1) the endocytotic capacity of iPSCs-imDCs has not been detected; (2) the specific dose of sinomenine is best for maintaining the immature state of iPSCs-imDCs, and it is recommended to set up a sinomenine dose gradient test; (3) cell density is also an important factor determining cell fate, and it is recommended to try different cell densities on different effects of immune tolerance in organ transplantation to obtain the optimal protocol. 3. Some references in the article are not time-sensitive, and when consulting the literature, it is found that the related articles on sinomenine and immunity have shown an upward trend year by year in recent years, and it is recommended to update the literature; follow-up can continue to excavate the specific mechanism of sinomenine in maintaining the immature state of iPSCs-imDCs.

Dear reviewer,

Thanks very much for your comments. We have performed language editing of this manuscript at the recommended non-native English language editing company and provided proof. (1) The endocytotic capacity of fluorescein isothiocyanate (FITC)-Dextran of SN-iPSCs-imDCs and SN-iPSCs-DCs were detected by flow cytometry, plz see Figure 5 in results. (2) That's ture. We set up a sinomenine dose gradient test (0, 50, 100 or 200 μ M) to treated iPSCs, and found the optimal concentration of SN was 100 μ M, refered to the definition: The optimal concentration of the drug was defined as the maximum administered concentration at which cell viability was > 95%. Because differentiation from iPSCs to imDCs requires three stages and takes up to 25 days. It is difficult to complete to the specific dose of sinomenine is best for maintaining the immature state of iPSCs-imDCs in limited time. In the next step, we will set up a precise gradients to confirm the specific dose of sinomenine is best for maintaining the immature state of human iPSCs-imDCs. Moreover, the procedure for inducing the differentiation of iPSCs into DCs comprised three stages. Further research is required to establish at which stage intervention with SN improves induction. We have added these in the discussion part.(3) This comment is very reasonable. The cell density is also an important factor determining cell fate, we set up two cell densities (10^5 cells and 10^6 cells) on different effects of immune tolerance in organ transplantation to obtain the optimal protocol. Our results showed 10^6 SN-iPSCs-imDCs is optimal protocol. Because 10^5 SN-iPSCs-imDCs induce immunotolerance in animal model just did once in limited revised period. We can't publish and show the results in [attachment](#). Please see [attachment in Supplementary Material and 75984-Image-File-revision_1902](#). In the future, we will study more different cell densities to obtain the optimal protocol, and explore the optimal dose and injection time to maintain the balance between SN-iPSCs-imDCs and Treg in vivo.(4) We have updated the references as proposed. We will continue to excavate the specific mechanism of sinomenine in maintaining the immature state of iPSCs-imDCs. For example, we will extract SN-iPSCs-imDCs supernatant exosomes

to sequence miRNAs to confirm whether miRNAs play an important role in the induction of immunotolerance.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

We perform further language polishing at the professional English language editing companies we recommend, and we will provide a new language certificate along with the manuscript.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

(1) **Title:** Abbreviations are not permitted. Please spell out any abbreviation in the title.

We did it.

(2) **Running title:** Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.

We revised it.

(3) **Abstract:** Abbreviations must be defined upon first appearance in the Abstract. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).

We revised it.

(4) **Key Words:** Abbreviations must be defined upon first appearance in the Key Words.

We did it.

(5) **Core Tip:** Abbreviations must be defined upon first appearance in the Core Tip. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)

We did it.

(6) **Main Text:** Abbreviations must be defined upon first appearance in the Main Text. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)

We did it.

(7) **Article Highlights:** Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).

Example 2: Helicobacter pylori (H. pylori)

We did it.

(8) **Figures:** Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text. Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

We revised it.

(9) **Tables:** Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

Abbreviations are not showed in the our Table title.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The theme of this paper is novel and the overall logic of the paper is clear, but most of it is limited to observational results and lacks exploration of potential mechanisms.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Dear Science editor,

Thanks for your comments. We perform further language polishing at the professional English language editing companies you recommend, and we provide a new language certificate along with the manuscript. We will study exploration of potential mechanisms in our next paper. Thanks for your understanding.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the 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. Before its final acceptance, the author(s) must provide the Chinese version of the ethical approval document. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. 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.

Dear editor-in-chief,

Thanks very much for your comments. We resolve all issues in the manuscript according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision, and make a point-by-point response to each of the issues raised in the peer review report. In addition, we provide the Chinese version of the ethical approval document. Moreover, We use uniform presentation for figures. Lastly, we provide decomposable Figures (in which all components are movable and editable), and organize them into a single PowerPoint file, add the copyright information to the bottom right-hand side of the picture in PowerPoint: Copyright ©The Author(s) 2022.

7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

Step 1: Author Information

Please click and download the [Format for authorship, institution, and corresponding author guidelines](#), and further check if the authors names and institutions meet the requirements of the journal.

Step 2: Manuscript Information

Please check if the manuscript information is correct.

Step 3: Abstract, Main Text, and Acknowledgements

(1) Guidelines for revising the content: Please download the guidelines for Original articles, Review articles, or Case Report articles for your specific manuscript type (Basic Study) at: <https://www.wjgnet.com/bpg/GerInfo/291>. Please further revise the content your manuscript according to the Guidelines and Requirements for Manuscript Revision.

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(3) Requirements for Article Highlights: If your manuscript is an Original Study (Basic Study or Clinical Study), Meta-Analysis, or Systemic Review, the “Article Highlights” section is required. Detailed writing requirements for the “Article Highlights” can be found in the Guidelines and Requirements for Manuscript Revision.

(4) Common issues in revised manuscript. Please click and download the [List of common issues in revised manuscripts by authors and comments](#) (PDF), and revise the manuscript accordingly.

Step 4: References

Please revise the references according to the [Format for References Guidelines](#), and be sure to edit the reference using the reference auto-analyser.

Reminder: It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Step 5: Footnotes and Figure Legends

(1) Requirements for Figures: Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file, and submit as “**75984-Figures.pptx**” on the system. The figures should be uploaded to the file destination of “Image File”. 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. Please click to download the sample document: [Download](#).

(2) Requirements for Tables: Please provide decomposable Tables (in which all components are movable and editable), organize them into a single Word file, and submit as “**75984-Tables.docx**” on the system. The tables should be uploaded to the file destination of “Table File”.

Reminder: Please click and download the [Guidelines for preparation of bitmaps, vector graphics, and tables in revised manuscripts](#) (PDF), and prepare the figures and tables of your manuscript accordingly.

Step 6: Automatically Generate Full-Text Files

Authors cannot replace and upload the “Manuscript File” separately. Since we only accept a manuscript file that is automatically generated, please download the “Full Text File” or click “Preview” to ensure all the contents of the manuscript automatically generated by the system are correct and meet the requirements of the journal. If you find that there is content that needs to be modified in the Full-Text File, please return to the corresponding step(s), modify and update the content, and save. At this point, you then have to click the "Save & Continue" button in Step 5 and the F6Publishing system will automatically regenerate the Full-Text File, and it will be automatically stored.

Step 7: Upload the Revision Files

For all required accompanying documents (listed below), you can begin the uploading process via the F6Publishing system. Then, please download all the uploaded documents to ensure all of them are correct.

- (1) 75984-Answering Reviewers
- (2) 75984-Audio Core Tip
- (3) 75984-Biostatistics Review Certificate
- (4) 75984-Conflict-of-Interest Disclosure Form
- (5) 75984-Copyright License Agreement

[We did it. Thanks for all your help.](#)