

Dear Editor and Reviewers,

I am glad to receive your letter. Thank you very much for your hard work and kind suggestions. I have read the comments carefully and revised the manuscript according to your suggestions. Thanks again for your excellent work.

The main corrections in the paper and the responds to the reviewer's comments are as following:

**Reviewer(s)' Comments to Author:**

**Response to Reviewer #1:**

Thanks for your valuable comments and suggestions which have led to significant improvement on the presentation and quality of this paper. The following are point-by-point responses to your concerns. And we shall detail the changes we have made on the paper.

***1. Perhaps the use of the term “scholar” is not the most appropriate in this context, and it is continuously repeated. Other terms such as experts, clinicians, researchers, etc. could be used.***

**Reply:** Many thanks for your kind comments. We have replaced the term “scholar” with other terms following your suggestion.

***2. Section (1): I have found the claim of rodents as promising source of commercial xenogeneic stem cells somewhat surprising. I have therefore looked through the available bibliography, as well as checked the references provided in the article. I have, however, failed to find evidence to support the claim of rodent cells being considered possible cell sources for their clinical use in transplantation protocols. Would the authors please care to provide some evidence to support this claim?***

**Reply:** Thanks for your kind comments. The opinion is extremely important to us. We are very sorry for the ambiguity caused by our misleading expression. We tried to express that rodents could be one possible source of xenogeneic stem cell in the future according to Kasraeian and Jia's researches. Kasraeian's research showed that mice BMSCs were capable to remain functional probably as hepatocyte-like cells in liver of infant rats after in utero xenotransplantation. Jia's researche showed that rat ADSCs can protect themselves from human xenoantibody and complement-mediated lysis. We have modified this part in the revised manuscript following your suggestion.

***3. In section (1): please clarify the expression “extensive cell origins”, regarding MSCs.***

**Reply:** Thanks for your valuable comments. We are very sorry for the ambiguity caused by our misleading expression. We have modified “extensive cell origins” to “extensive cell sources” in the revised manuscript.

**4. Section (2), 2nd paragraph: When referring to Ding's transplantation work, clarify "The results showed that human stem cells...." as "this type of human cells" (i.e. umbilical cord stroma-derived stem cells)**

**Reply:** Thanks for your comments. We are very sorry for our misleading expression. We have modified "human stem cells" to "this type of human cells" in the revised manuscript following your suggestion.

**5. Section (2.1): Please explain cellular desensitization, what it conveys.**

**Reply:** Thanks for your advice. We are very sorry for our unclear expression. In the cited reference, cell desensitization refers to the desensitization achieved by repeat injection of xenogeneic stem cells into a neonatal host, so that the stem cells can survive long-term transplantation in the xenograft environment of adult host. Although the desensitization mechanism and success rate need to be discussed, Heuer's research have demonstrated that hEPCs desensitization could surpass the survival time of conventional pharmacological immune-suppressive treatments. Thus, cellular desensitization may be used as a method to suppress the immune rejection of xenogeneic stem cell transplantation. We have modified this part in the revised manuscript following your suggestion.

**6. Section (2.2.): Please clarify the referral to cell chip in "Qiao et al. developed single-cell derived spheres of UCMSCs by combining a 3D culture with 2D arrayed patterns of single or multiple cells on one patch in the cell chip..."**

**Reply:** Thanks for your advice. We are very sorry for our unclear expression. In the cited reference, cell chip is a device to restrict cells to specific spatial locations by forming a region which promotes cell adhesion and another region which inhibits cell adhesion. We have attached the schematic diagram of cell chips fabrication here from the cited reference.

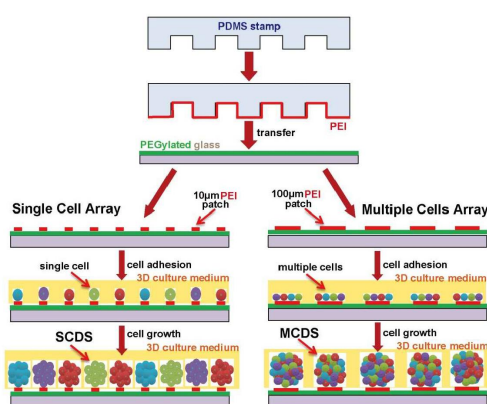


Figure 1. The scheme of cell chip fabrication and SCDS formation in 3D culture.

**7. Raynald et al.... Please correct reference, as it does not correspond to the list of references**

**Reply:** Thanks for your valuable advice. We are very sorry for this mistake. The correct reference is cited in the revised manuscript.

**8. Section (3.1): Please correct “Matsunari created pancreatic pig embryos...” to “... apancreatic pig embryos...”**

**Reply:** Thanks for your valuable advice. We are very sorry for this spelling mistake. We have corrected “pancreatic pig embryos” to “apancreatic pig embryos” in the revised manuscript.\_

**Editor Comments to Author (if any):**

Thanks for your valuable comments and suggestions which have led to significant improvement on the presentation and quality of this paper. The following are point-by-point responses to your concerns. And we shall detail the changes we have made on the paper.

**Science editor’s comment to author:**

**Response to Science editor:**

**1. The authors should add some figures or tables in the manuscript.**

**Reply:** Thanks for your advice. We have added one table and one figure following your suggestion.

**2. The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).**

**Reply:** Thanks for your advice. We have uploaded the approved grant application form(s) or funding agency copy of any approval document(s) following your suggestion.

**3. The column should be minireviews.**

**Reply:** Thanks for your advice. We have changed the column following your suggestion.

If you have any question, please don’t hesitate to contact me.

With best regards,

Yours Sincerely

Lei Liu

Prof., Dr.

State Key Laboratory of Oral Diseases & National Clinical Research Center for  
Oral Diseases & Dept. of Oral and Maxillofacial Surgery,

West China Hospital of Stomatology, Sichuan University,

Chengdu 610041, P.R. China

Ph: +86 28 85501456

Fax: +86 28 85582167

E-mail address: drliulei@163.com