

2 September 2021

Dear Editor and Reviewers,

Please find enclosed the revised version of our manuscript entitled “Application of Dental Stem Cells in Three-Dimensional Tissue Regeneration”.

Thank you for reviewing our manuscript. We feel that all the comments are very helpful in improving the legibility, objectivity and scientific evaluation of the manuscript.

In the revised manuscript, in accordance with the valuable suggestions of the reviewers, we have made various modifications. The statistics and confounders in the original version and concerns of the reviewer were modified accordingly. Furthermore, the entire manuscript was carefully revised by following the instructions as directed by reviewers. The answers made are detailed, point-by-point, in a separate letter to the reviewers. All the changes are highlighted.

We hope that the revised manuscript will retain your attention, and you will judge the revised manuscript to be suitable for publication in *WJSC*.

Thank you

Yours truly,  
Tzung-Hai Yen

**Reviewer #1:** Authors have extracted data from 88 PubMed studies and included only one third related to five different types of stem cells from dental sources such as DPSCs, SHEDs, PDLSCs, SCAPs, and DFPCs. Although authors have comprehensively reviewed 3D-culture of these cells in different studies, yet several crucial strategies mimicking with clinical applications were lacking due to limited keywords focusing mainly on stem cells. Furthermore, authors failed to provide clear road map for applying such strategies in clinical settings. These were scarcity of data for the use of decellularized biological membranes for preparing 3D-dental regenerative constructs which is a crucial approach for regenerative dentistry. Further, dental sources can't be the most suitable choice for harvesting stem cells due to increased contamination issues and less number. Authors could have also discussed alternative choices of stem cells for generating 3D-biological constructs for application in regenerative dentistry. The mechanism of action of futuristic technologies of 3D-engineered dental constructs could have been discussed in detail to provide more authentic application of dental cells and different types of scaffolds. Overall, several crucial points remained to discuss for the presented topic of interest. Authors could have shown schematic representations and important figures to exploit more of dental stem cells knowledge gaps with better clarity. In the end several formatting errors could be seen throughout the texts.

**Response:** Thank you for the comments.

As stated in the title, “Application of Dental Stem Cells in Three-Dimensional Tissue Regeneration”, this review is a very selective report describing the application of dental stem cells particularly on the 3D tissue reconstruction. Therefore, we apologize that other sources of stem cells for generating 3D-biological constructs for application in regenerative dentistry are not covered in this article.

We understand that there is a scarcity of data for the use of decellularized biological membranes for preparing 3D-dental regenerative constructs, which is a crucial approach for regenerative dentistry. Compare to other type of stem cells, dental sources of stem cells indeed are not the most suitable choice for harvesting stem cells. However, the regenerative potentials of dental stem cells have been supported by many research publications. The limitations of the dental stem cell application on basic research and clinical practice are added in the clinical application of dental stem cell section to provide different point of view on the current status of dental stem cells application.



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Thank you again for the suggestion, the 3D-engineered dental construct technology is outside the scope of this review. Finally, the article has been checked for formatting errors, and the spotted errors have been corrected.

**Reviewer #2:** The manuscript is well written and gives an overall view on the application of Dental Stem Cells in Three-Dimensional Tissue Regeneration. The flow of information and citations are noteworthy. Just few minor corrections on the right use of terminologies are indicated. And also minor correction on the title.

**Response:** Thank you for the comments. The corrections have been corrected according to reviewer's suggestion.

**Reviewer #3:** Review Many thanks for the opportunity to review the manuscript submitted by Hsiao et al. Overall the article is quite in-depth and thoroughly referenced throughout with up-to-date, highly relevant articles. The process and reasoning behind the choice of articles reviewed in the paper is logical and well explained. Table 1 is an excellent summary of dental SCs used in 3D studies. All citations are present in the reference list. However, there a few issue that need to be addressed if the article is to be published. •

Abstract: SC do not regenerate into other types of cells, they differentiate. Please change this.

**Response:** Thank you for the comments. The sentence has been revised into “Dental stem cells can differentiate into different types of cells”.

• Page 5: The statement ‘DPSCs cocultured with apical bud cells (ABCs) exhibited more active odontogenic differentiation ability than DPSCs cocultured with BMSCs and ABCs [12]’ is incorrect or at least badly phrased – the comparison was between DPSC/ABC co-culture & BMSC/ABC (see ref 11 Yu et al. 2007) not DPSC/ABC versus DPSC/BMSC co-cultured. Please address this issues.

**Response:** Thank you for the comments. We rephrased the sentence as “DPSCs cocultured with apical bud cells (ABCs) exhibited more active odontogenic differentiation ability than BMSCs cocultured with ABCs”.

• Page 9: The statement ‘DPSCs were designed to be printed with...’ is surely incorrect or at least confused – the DPSC were not designed to do anything, they were printed along with growth factors such as VEGF & BMP-2. Please address this.

**Response:** Thank you for the comments. The sentence has been revised as “Park, et al designed to print DSPCs along with vascular endothelial growth factor (VEGF) in the central zone and with bone morphogenetic protein-2 (BMP-2) in the peripheral area of the 3D-printed construct to fabricate vascularized bone structures”

• Page 12: please state that the SHEDs were used in a rat model as this is not clear from the text.

Response: Thank you for the comments. We provide more information regarding the application of SHED in rat model. “ The rat static nerve defects in the mid-thigh level were covered with silicon conduit containing SHED-conditioned medium and resulted in the increase of Schwann cells, axon density and the number of regenerated myelinated fibers.”

• Please improve or remove figure 1 – as it stands it is not particularly useful or informative.

Response: Thank you for the comments. The figure is served as a graphic abstract to illustrate the concept of dental stem cells in 3D tissue regeneration. Many reviewer articles provide similar figures to present the overview concept of the review [1-3]. We also rephased the sentence to present clearer concept on figure 1. “ In this review, we aim to give a clear point of view on each type of dental stem cell used in combination with 3D tissue scaffolds, such as microsphere, hydrogel, or 3D printed scaffolds to regenerate into tooth, neuron, bone, blood vessel and cartilage.” (in the introduction section)

1. Tatullo, M., et al., *Strategic Tools in Regenerative and Translational Dentistry*. Int J Mol Sci, 2019. **20**(8).
2. Ude, C.C., et al., *Application of stem cells in tissue engineering for defense medicine*. Mil Med Res, 2018. **5**(1): p. 7.
3. Asadian, M., et al., *Fabrication and Plasma Modification of Nanofibrous Tissue Engineering Scaffolds*. Nanomaterials (Basel), 2020. **10**(1).

Minor issues to address:

- Abstract: it is ‘anatomical’ not ‘anatomic’

Response: Thank you for the comments. The word has been revised.

- Change ‘coculture’ for co-culture’ and ‘cotreated’ with ‘co-treated.’

Response: Thank you for the comments. The word” co-culture and co-treated” have been revised.

- Check and remove first initial from citations such as p. 14 ‘Cho, H et al. compared the effect...’ – there are a few instances of this niggling issue – please address this.

Response: Thank you for the comments. The first initial have been removed.



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**Reviewer #4:** The manuscript is a brief report well written.

**Response:** Thank you for your help

