

Dear editors and reviewers:

Thank you for your letter.

We highly appreciate the comments concerning our manuscript entitled “Clinical trials using dental stem cells”. These comments are valuable and very helpful for revising and improving our paper, which will be of great significance to our research. We have analyzed the comments carefully and have made corrections in which we hope to meet with approval. The main corrections and the adjustments in the paper we have made under the reviewers’ comments are as follows:

## **Responses to the reviewer’s comments:**

### **Reviewer #1:**

#### **Specific Comments to Authors:**

Specific Comments to Authors: This is an interesting and comprehensive Review article, covering a relevant field of enquiry from both the translational side, and the clinical application of stem cells, particularly the dental pulp stem cells (DSCs). The article is well planned and articulated in its parts. I have some minor remarks, that in my opinion need to be addressed: - In the introduction section, the Authors state “Currently, MSCs are widely used in regenerative medicine and the treatment of many diseases, such as cardiovascular disease, neurodegenerative diseases, dental diseases, and metabolic diseases”. Although this phrase is associated with a reference, this is by far an over-statement, since it’s giving the impression that MSCs are on the clinical way for the treatment of a number of complex diseases in which they are only at the first levels of experimental application, mainly with a partial proof of concept of safety. These are not consolidated therapies yet! I suggest that these concepts are reported more cautiously. - Figure 1 is not cited within the text. It can be recalled on page 6, within the section “CHARACTERISTICS OF DSCs”. - Similarly, Table 2 doesn’t appear to be recalled within the main text. It should be cited within the section “DSC-BASED CLINICAL TRIALS FROM PUBLISHED ARTICLES” (pages 8, 9, and 10, in the section “Other conditions”). - At page 9, the sentence “The excellent performance of the scaffold might cover the contribution of PDLSCs insignificant”, should be better re-phrased. As an example: The excellent performance of the scaffold may have overshadowed the contribution by PDLSCs. - At page 15, “DSC-CM and its components (such as EVs) provide several key advantages over cell-based applications, including avoiding the risk of host immunogenic reactions and tumor formation, cost-effectiveness, long-term storage capacity, and simpler evaluation of safety and efficacy”. It should be noted that EVs are not devoid of

tumorigenic risks and therefore “tumor formation” should be omitted from this sentence. In fact, depending on their cargo, exosomes can suppress or promote tumor cell progression, and can enhance or reduce cancer cell response to radio- and chemo-therapies. In addition, exosomes have been reported to trigger chronic inflammation and lead to immune evasion and tumor progression through their ability to transfer non-coding RNAs between cells and modulate other molecular signaling pathways such as PTEN and PI3K/Akt in cancer.

### **Responses to Reviewer #1:**

We are quite delighted to receive your comments on our manuscript and very grateful for your time and help.

1. The sentence “Currently, MSCs are widely used in regenerative medicine and the treatment of many diseases, such as cardiovascular disease, neurodegenerative diseases, dental diseases, and metabolic diseases” has been revised to “Currently, MSCs are currently being explored for the treatment of many diseases, such as cardiovascular disease, neurodegenerative diseases, dental diseases, and metabolic diseases”.
2. Figure 1 has been cited with the text in the section “INTRODUCTION” and “CHARACTERISTICS OF DSCs”. Table 2 has also been cited with the text in the section “DSC-BASED CLINICAL TRIALS FROM PUBLISHED ARTICLES”.
3. The sentence “The excellent performance of the scaffold might cover the contribution of PDLSCs insignificant” has been revised to “The excellent performance of the scaffold may have overshadowed the contribution by PDLSCs”.
4. The word “tumor formation” has been deleted in the manuscript. Thank you very much for your comments and help with our article.

### **Reviewer #2:**

#### **Specific Comments to Authors:**

Dear authors, We have read with attention and interest your manuscript, which brings a wide survey of clinical trials using dental stem cells. The topic is well introduced, with the crucial elements of translating the fundamental research (already 20 years of Dental Stem Cells research) towards clinical applications. The title of the manuscript is very simple (and clear) and correspond to the investigations. The main interest of the study is that you bring together, in one manuscript, an exhaustive view of the topic (all clinical trials). The presented work is not to be debated, as it is a picture of the existing situation. Therefore, the title should include

this aspect of temporality: you present an exhaustive view of the clinical trials until 2022. (i.e 'Actual overview of Clinical trials using dental stem cells' The paragraphs "Safety issues regarding DSC-based therapy" and "Current limitations and perspectives" correspond to a discussion about the topic, and bring some interpretation and perspectives.

The main limitation of this submitted manuscript is that it looks a bit too much like a catalog, and we miss some rationals explaining / justifying the interest of cell therapy using dental stem cells. Indeed, for each disease/condition, stem cells can be used with various objective (immunomodulation / host cell recruitment / Proliferative effects...). I'd be of great interest for the reader to get some insights about the objectives of cell grafts, for each disease (i.e anti-inflammatory effect and immunomodulation for psoriasis; cell recruitment and proliferation for pulp regeneration...). An additional Figure illustrating the various applications (and the reasons why stem cells are applied there) would also help the reader to get a quick view of the current clinical use. An other remark would be on the concept of stemness: a definition of MSC have been stated in 2006, but might be under debate, especially when we are considering dental stem cells, recovered without strain. The term "Stem" is sometimes substituted by "Stromal". These 2 aspects (rationals explaining the objective of cell grafting, in each disease + few words about Stem or Stromal) could be included in the paragraph "Characteristics of DSC". We believe your manuscript is of high interest fo researchers and clinicians, but few modifications / additions would strengthen the overall interest.

### **Responses to Reviewer #2:**

We are quite delighted to receive your comments on our manuscript and very grateful for your time and help.

1. The title has been revised to "Clinical trials using dental stem cells: 2022 update".
  2. The effect of various DSC-based therapies on diseases and the explanation of "stromal" and "stem" was added in the paragraph "Characteristics of DSC".
  3. Figure 1 was recreated and added the details about the effect of DSCs on diseases.
- Thank you very much for your comments and help with our article.