

Dear Reviewers,

Please find below our answers related to the manuscript 49231. We would like to thank for all constructive criticisms and valuable comments, which contributed for an overall improvement of the manuscript. We hope that you will now find the revised version acceptable for publication.

Looking forward to a favorable final review process.

**Reviewer's code: 03811054**

Comment#1 in abstract section: The sentence: "in this review, we explore the use of spheroids from adult mesenchymal stem/stromal cells in the developmental engineering of cartilage and bone" is incomplete.

REPLY: We modified the sentence. Please, see lines 88-89 in abstract section.

**Reviewer's code: 02524648**

"The one dimension that does not appear to have been properly addressed is the limitations that using scaffold-based approaches pose and in what manner these are overcome by the use of spheroids".

REPLY: We addressed the limitations of scaffold-based approaches, as suggested. Please, see lines 119-127 of the reviewed manuscript.

In the absence of line numbering throughout the MS, some comments have been directly introduced into the text (e.g. in both figures, the scale bar measurement must be indicated as  $\mu\text{m}$ , and not as  $\mu\text{M}$ ).

REPLY: We attended all these comments.

Comment #1 in abstract section: "Developmental tissue engineering". Please clarify its meaning.

REPLY: We clarified the meaning of the expression "developmental tissue engineering" throughout the text. Please, see lines 84 and 88-89 in abstract section; lines 440-442 in conclusion section of the reviewed manuscript.

Comment #3 in core tip section: "Scaffold-base approach". IMPORTANT: Please explain in further detail the limitations of scaffold-based strategies, and insert references that support this claim of scaffold-based strategies being more limited.

REPLY: The core tip section must have a maximum of 100 words, as described in "Guidelines for manuscript preparation and submission minireviews", impairing a more detailed description. The limitations of scaffold-based strategies were described in introduction section together with new references. Please, see lines 119-127 of the reviewed paper.

Comment #5 in "SPHEROID FUSION" topic: In the sentence: "one advantage of spheroid fusion is that the kinetics and morphological changes can be easily quantified using high-throughput

technology, mainly by time-lapse brightfield images and fluorescence microscopy”, please add reference(s).

REPLY: We added the suggested reference (104). Please, see line 966 of the reviewed manuscript.

**Reviewer’s code 03810998:**

Please add 1-2 tables to summarize the use of adipose stem cells-derived spheroids for bone and cartilage regeneration *in vitro* and especially *in vivo*.

REPLY: We added 1 table. Table 1 summarizes the *in vitro* and *in vivo* studies with adipose stem cells-derived spheroids for bone and cartilage engineering. Please, see pages 34-36 of the reviewed manuscript

Please use 1-2 schematic figures to summarize the fabrication of spheroids and their interaction with the local microenvironment and tissues.

REPLY: We added 2 schematic figures. Figure 1 summarizes the main methods of spheroids fabrication (page 29). Figure 2 summarizes the interaction of spheroids with local microenvironment to form bone and cartilage tissues (page 30).

Please add more recent original article to provide the readers with the most advanced techniques of adipose stem cells-derived spheroids for tissue regeneration, especially in the field of additive manufacturing.

REPLY: We added one more recent original article by Rumiński et al., 2019, using adipose stem cells-derived spheroids for improving osteogenesis. Please, see lines 232-240. However, in the field of additive manufacturing using adipose stem cells-derived spheroids, we didn’t find studies in PubMed database (search date: September 19, 23:22pm, key words used in the search: “adipose stem cells-derived spheroids additive manufacturing”).

Minor language editing is necessary.

REPLY: Our manuscript was already revised. Please, see the official editing certificate for non-native speakers of English attached in submission process.