

Dear Reviewers,

Please find below our answers related to the manuscript 49591. 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:** 02446191

“Typological errors need to be corrected”

**Reply:** Typological errors were corrected.

**Reviewer's code:** 02702057

“Please add the aim of your study in the abstract and in the introduction section”.

**Reply:** The aim of study was added in the abstract (please, see lines 70 – 73) and in the introduction (please, see lines 112 – 115).

“In the introduction section please talk about cartilage regeneration thought engineered tissue engineering and mechanobiology to improve your editorial scope”.

**Reply:** I would like to thank you for the suggestion; however, I believe that the proposal of the current editorial is to discuss the multipotentiality of adipose stromal/stem cells analyzed under different aspects (e.g. different donors or different types of culture) without focusing in differentiation pathways.

“Some illustrations are needed to help better readers understanding”.

**Reply:** I totally agree. Please, see line 210 and page 16. A scheme was added to the manuscript showing the main stages of spheroid formation, highlighting its impact on stemness and multipotentiality of adipose stromal/stem cells.

“A reference missing, please quote the following paper: Biosynthesis of collagen I, II, RUNX2 and lubricin at different time points of chondrogenic differentiation in a 3D in vitro model of human mesenchymal stem cells derived from adipose tissue. *Acta Histochem.* 2014 Oct;116(8):1407-17”.

**Reply:** The suggested reference was added to the manuscript together with the following reference: Achilli TM, Meyer J, Morgan JR. *Expert Opin Biol Ther.* 2012 Oct;12(10):1347-60. doi: 10.1517/14712598.2012.707181. Please, see line 117.

“In the conclusion section please specify better the clinical relevance of your work”.

**Reply:** The clinical relevance was specified in the conclusion. Please, see lines 253 – 255.

**Reviewer's code:** 02860871

“This article is well written with few typos inside”.

**Reply:** Typological errors were corrected.

“Because the entire manuscript discuss about the stem and progenitors cells from subcutaneous adipose tissue (ASC), briefly comparing them with their bone marrow counterparts (MSCs), please presents in a table the difference between ASCs and bone marrow MSCs in order to be more clear”.

**Reply:** The suggested table was inserted in the manuscript. Please, see line 476 and page 16.

“The author mentioned the scaffold-free approaches to tissue engineering ‘spheroids’ have emerged optimizing the multilineage differentiation capacity of ASCs and MSCs. However, the limitation of this approach has not been discussed”.

**Reply:** The limitations of scaffold-free approach were described. Please, see lines 217 – 220.