Responses to the Reviewer

Dear Reviewer,

Thank you very much for taking the time to review our work and provide your suggestions for improvements. We are pleased that you found the paper to be of interest. We believe that your comments have helped improve the manuscript considerably and we are very grateful for your input.

Comment 1. To make the section easier to read, the overall structure of the article needs to be reorganized.

The article's structure has now been reorganized. The discussion of the pathophysiology of osteoarthritis and how adipose-derived mesenchymal stromal cells (MSCs) are likely to modulate this process have been moved to follow the Introduction. Our review of the study by Wu *et al.* (2023) is now included under the section entitled, "Adipose-derived regenerative therapies for knee osteoarthritis: Important distinctions". We then highlight how the properties of different adipose-derived regenerative therapies may differ due to the nature of their preparation and components. Future challenges facing the use of these therapies for treating knee osteoarthritis are then discussed, in accordance with the Reviewer's advice, before the Conclusions.

Comment 2. Please provide the reference for the claim "regeneration is likely to be promoted by ASCs via immunomodulatory mechanisms and the secretion of chondroprotective biomolecules".

We have now included the following references to support this statement:

Reference Number 52: **Murphy MB**, Moncivais K, Caplan AI. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. *Exp Mol Med* 2013; **45**: e54 [PMID: 24232253 DOI: 10.1038/emm.2013.94]

Reference Number 54: **Maumus M**, Manferdini C, Toupet K, Peyrafitte JA, Ferreira R, Facchini A, Gabusi E, Bourin P, Jorgensen C, Lisignoli G, Noël D. Adipose mesenchymal stem cells protect chondrocytes from degeneration associated with osteoarthritis. *Stem Cell Res* 2013; **11**: 834-44 [PMID: 23811540 DOI: 10.1016/j.scr.2013.05.008]

Reference Number 55: **Ohashi H**, Nishida K, Yoshida A, Nasu Y, Nakahara R, Matsumoto Y, Takeshita A, Kaneda D, Saeki M, Ozaki T. Adipose-Derived Extract Suppresses IL-1β-Induced Inflammatory Signaling Pathways in Human Chondrocytes and Ameliorates the Cartilage Destruction of Experimental Osteoarthritis in Rats. *Int J Mol Sci* 2021; **22**: 9781 [PMID: 34575945 DOI: 10.3390/ijms22189781]

Comment 3. The pathological and physiological mechanisms of osteoarthritis do not mention the role of subchondral bone in OA. As far as I know, subchondral bone plays an important role in osteoarthritis. Is adipose derived regenerative therapies effective for subchondral bone regeneration?

We have now extended the section entitled, "Pathophysiology of osteoarthritis" to include a discussion of the role of subchondral bone in the disease process. An additional paragraph has been added to the section entitled, "Adipose-derived mesenchymal stromal cells: Mechanism of action", which explores current evidence regarding the ability of adipose-derived regenerative therapies to promote bone repair.

Comment 4: "Further elaborate on the challenges faced by adipose derived regenerative therapies for the treatment of knee osteoarthritis in future."

We have now included an additional section in the manuscript entitled, "Future challenges". This discusses the potential future obstacles to translation of adipose-derived regenerative therapies into clinical practice.