José Fábio Santos Duarte Lana, MD.
Institute of Bone and Cartilage
1386 Presidente Kennedy Avenue - Room 29, 2nd floor
Phone: +55 19 3017-4366 / +55 19 3392-6549
josefabiolana@gmail.com

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Dear Editors,

We have received your e-mail with the Reviewers' comments regarding our manuscript, entitled "Bone Marrow-Derived Products: A Classification Proposal - ACH" by Purita and colleagues submitted to World Journal of Stem Cells. We would like to thank the editors and the reviewer who spent precious time evaluating this manuscript. We have worked thoroughly to answer all queries raised by the reviewers in order to improve the quality of our manuscript and make it suitable to be published at World Journal of Stem Cells. We are presenting below all the queries stated by the reviewers as well as the way we have dealt with them to perform the requested changes. We present below a list that responds to the reviewers' comments.

SPECIFIC COMMENTS TO AUTHORS

REVIEWER: A well written manuscript aiming the role of a concept paper meant to classify bone marrow derived products for clinical use. Comments I would recommend not including abbreviations within the title (ACH is not explained in the abstract as well, its meaning might be notorious for the authors but the situation can be different for international readers.

AUTHOR RESPONSE & ACTION TAKEN: Thank you for your consideration, the correction was done as requested and the title has been changed to “Bone Marrow-Derived Products: A Classification Proposal - Bone Marrow Aspirate, Bone Marrow Aspirate Concentrate or Hybrid?”

REVIEWER: I would argue that VSELS remained controversial and their bone marrow born origin has not been actually proven while MUSE cells (written with caps as is an acronym which need to be explained as well) have been obtain from other tissues (such as adipose or skin) and is not characteristic for BM. It is good to cite the papers mentioning VSELS and MUSE.

AUTHOR RESPONSE & ACTION TAKEN: We thank the reviewer for the observation and we apologize for our equivocal statement. When we originally made the statement that BM contained VSELs we were basing our arguments on the work published by Kucia (2008), who described the attainment of VSELs from murine BM and human umbilical cord blood. However, we did not find any articles describing the presence of these cells in human bone marrow. Since our objective is to describe a biological product derived from human bone marrow, we chose to adjust the corresponding piece of information by eliminating the controversial statement suggesting the presence of VSELs in human BM. The same is true for MUSE cells since there is no consensus and BM would not be the most suitable site of extraction of these cells. Considering these observations, the information displayed on page 6, lines 19-21, was therefore adapted.

REVIEWER: The hematopoetic function of BM is supported by mesenchymal stroma which harbor MSCs

AUTHOR RESPONSE & ACTION TAKEN: We agree with the reviewer and some information was added to the original text (page 6, lines 137-138).

REVIEWER: Indeed MSCs can be driven to differentiate (rather than transdifferentiate) towards mesenchymal lineages in vitro and in vivo in animal models of various diseases. More contemporary evidence refer to scheletal stem cells as being the source for musculoskeletal tissue regeneration (Chan et all Cell 2018, Ambrosi et al Frotiers in Cell and Developmental Biology 2019)

AUTHOR RESPONSE & ACTION TAKEN: The reviewer raised an important observation. We added some information to the original text (page 6, line 138).

REVIEWER: The classification system proposed is scientifically correct however it might be not too much practical. Every classification system needs to introduce a motivation for patient clustering and for improving therapeutic selection. What is the authors opinion regarding the correlation between classification system they propose and specific patient outcome? Are there studies supporting this or they plan to perform such studies in order to assert the classification system?

AUTHOR RESPONSE & ACTION TAKEN: We agree with the observations raised by the reviewer. When we discuss biological products with therapeutic effects we have to consider the complexity of these products, the diversity of preparation methods and the individual differences. Since the topic revolves around autologous biomaterials, attempts to standardize or simplify the techniques would be somewhat challenging.

We noticed that when the literature does not show variation in nomenclature for the same type of biological product, there is inappropriate terminology instead.

On the other hand, discrepancy in clinical results diminishes the credibility of the biological products at hand, which may reflect the difficulty in standardizing nomenclature. As such, we believe that initially, the standardization of a biological product on a basic level regarding extraction method and composition may facilitate the reader’s comprehension and reinforce the correlation between product composition and clinical outcome. That being said, we added corresponding information to page 18, lines 450-451.