

## ANSWERING REVIEWERS



Dear Editor,

The authors thank the academic editor and reviewers for their critical comments on the revised paper entitled: "Brain mesenchymal stem cell: the other stem cell of the brain?", submitted for publication in the "Frontier" section of WJSC. Please find attached the revised version of our manuscript (ESPS Manuscript NO: 7303).

We revised our manuscript according to the reviewers' suggestions: we include a table with marker profiles of the MSCs and the debate in Bianco's paper is now cited. Note that this paper received several comments like it is "biased and in some regards unfairly critical (Phinney et al., Nat Med, 2013 19: 812; see also Pittenger, Nat Med 2013 19:811).

We think this new version is a balanced paper dealing with representative achievements, comments on the state of current research, and proposes directions for future research, as expected for a "Frontier" paper.

Please, accept my best wishes for 2014.

Looking forward to your response,

Sincerely yours

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### **Response to Reviewer's 1 comment.**

As suggested by the reviewer, a table indicating the marker profile of MSC, HSPC, NSPC and pericytes is now included.

### **Response to Reviewer's 2 comments.**

We fully agree with the reviewer's comment that the concept of "Mesenchymal Stem cell", as it is currently developed, is object of debate (note, that the manuscript is intended for the "Frontier" section of WJSC). According to the reviewer comment the Bianco's paper is now

cited (ref [9]) and some of its issues are presented. For example, the following sentences have been added

**In the abstract:**

*“However, some controversies about the physiological role of the perivascular MSCs residing outside the bone marrow, and on their therapeutic potential in regenerative medicine exist”.*

*“The demonstration of the neuronal potential of MSCs requires stringent criteria like: morphological changes, the demonstration of neural biomarkers expression, electrophysiological recordings, and the absence of cell fusion”.*

**In the Introduction:**

*“However, the question remains if these ubiquitous cells behave in vivo as genuine stem cells or if their stem cell potential is a cell culture artifact<sup>[9]</sup>. The existence of these MSCs in virtually all postnatal organs does not necessarily mean that these behave as stem cells during development. For example, their physiological function could be limited to postnatal regenerative processes. Hence, the concept of MSC, initially well-defined and restricted to a multipotent progenitor for skeletal tissues and residing within the bone marrow has progressively evolved towards an all-encompassing concept including perivascular cells of almost any tissue [9]”.*

and

*“At the moment the potential of MSCs to regenerate human tissues in vivo is not yet clearly defined. Current research is ongoing to resolve this critical issue by improving MSC culture engineering and cell transplantation technology. A better characterization of the therapeutic potential of MSCs according to their tissue of origin is also a critical issue”.*

**In the “When MSCs transdifferentiate into neural cells: facts and artifacts” section.**

We fully agree that morphological differentiation is not sufficient and clearly indicate which experiments need to be included to validate the transdifferentiation.

*“For example, reporting neuronal differentiation of MSCs now requires observation of morphological changes, the demonstration of neural biomarkers expression, neurotransmitter responsiveness or electrophysiological recording, and absence of cell fusion[28][33][49][52][53]”.*

And

*“Accordingly, recent experiments using brain derived MSCs instead of bone marrow MSCs, provide additional evidence for a brain MSCs transdifferentiation into neuronal cells at the clonal level and on the basis of stringent criteria[54]”.*

Note that the concluding comments are related to the debate on the MSCs potential and on the perspective opened by this debate. By doing this we hope to provide an accurate and balanced paper dealing with “representative achievements, comment on the state of current research, and propose directions for future research” according to the scope of the “Frontier” section of WJSC.

