

RESPONSE TO REVIEWERS,

Thank you to the reviewers and editors for reviewing our paper and offering very helpful suggestions for improvement. Please note our point by point responses in bold below.

Name of journal: World Journal of Stem Cells

Manuscript NO.: 35695

Column: Minireviews

Title: The Ying and Yang of Mesenchymal Stem Cells and Aplastic Anemia

Reviewer #1: This is an excellent summary of MSC biology as it pertains to AA, and clarifies the current state of this field. I only have a few minor comments for the authors to address prior to publication. Page 7, paragraph under "Impaired MSC function" heading: I am not aware of reports that MSC can differentiate into HSC or other hematopoietic cells. Unless I am mistaken, the Pittenger 1999 paper you cite (ref. 18) does not claim this, and in fact (to my reading) clearly states that no hematopoietic cells were obtained from expanded MSC cultures. Thus, I would recommend removal of "and hematopoietic cells" . I would also remove the reference to hematopoietic cell differentiation from Figure 1 and its legend. Page 8, bottom paragraph, 8 lines from bottom: I would recommend adding the phrase "from AA patients" after "...studies suggest MSCs" for clarity. Page 12, third line from bottom: rational, not rationale. I congratulate you again on writing a very nice review.

The comment that MSC differentiate into hematopoietic stem cells was an error and has been removed from the manuscript, figure, and figure legend. The additional grammatical suggestions have also been made

Reviewer #2: The manuscript entitled "The Ying and Yang of Mesenchymal Stem Cells and Aplastic Anemia" summarizes current knowledge on experimental approaches of mesenchymal stem cells use for aplastic anemia treatment. It is clear that immunological system is involved in AA manifestation however exact mechanisms remain unknown. To this end MSC transplantation maybe beneficial due to known immunosuppressive effect of MSC in vitro. Additionally MSC may provide cell niche for hematopoietic cells. The manuscript is clearly written and maybe recommended for publication. However I would like to admit that MSC were never differentiated into hematopoietic cells, on contrary in the cited ref 18 (page 7) inability of MCS differentiation into CD14, CD45 cells has been demonstrated.

The comment that MSC differentiate into hematopoietic stem cells was an error and has been removed from the manuscript, figure, and figure legend.

Reviewer #3: This is a short well written paper on the potential role of MSC in therapy for aplastic anemia.

Reviewer #4: In this manuscript Broglie et al discuss the etiology of Aplastic Aneamia (AA) and the potential of mesenchymal stem cells (MSC) for the treatment. While the manuscript is concisely written, the lack of epidemiology background in AA makes it difficult to follow, especially for those who are not in the field. Since AA comprises congenital (Fanconi, dyskeratosis congenita, and Shwachman-Diamond syndrome) and acquired forms, the authors should mention this, even though they focus on acquired form in this review. It will also be helpful for readers to have a comparison between MSC monotherapy and MSC as adjunct for hematopoietic stem cell transplantation as a therapy.

A section on epidemiology and presentation of acquired AA has been added to the manuscript. Additional information was added to differentiate acquired AA from congenital bone marrow

failure syndromes. Also, to help contrast the goals, interventions and outcomes of MSC therapy, either as an adjunct to HCT or as monotherapy, a table was added (Table II).

Reviewer #5: The review by Broglie et al. gives a fine and complete overview of the role of MSCs in AA and their possible use as therapy.