Name of Journal: *World Journal of Stem Cells*

Manuscript NO: 58129

Manuscript Type: REVIEW

Title: Adipose-derived stem cells: pathophysiologic implications *versus* therapeutic potential in systemic sclerosis

Dear Editors,

Thank you very much for allowing us to revise our **Invited Manuscript NO: 58129** entitled "**Adipose-derived stem cells: pathophysiologic implications versus therapeutic potential in systemic sclerosis**" by Irene Rosa, Eloisa Romano, Bianca Saveria Fioretto, Marco Matucci-Cerinic and Mirko Manetti.

The manuscript has been revised according to the Reviewer's and the Editorial Office's comments and suggestions.

The point-by-point responses to the Reviewer's and Editorial Office's specific comments are as follows:

Reviewer #1:

Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)
Specific Comments to Authors: Systemic sclerosis (SSc) is a complex multiorgan disease characterized by vascular damage, perivascular inflammation, presence of specific autoantibodies and progressive fibrosis of the skin and internal organs. The initial vascular damage seems to precede and provoke the organ inflammation, followed by accumulation of fibrotic collagen and other extracellular matrix components in vessel walls and interstitial tissue. SSc shows substantial heterogeneity in its clinical symptoms, patterns of organ involvement, and natural history. Skin involvement is a nearly universal feature of SSc. It is characterized by variable extent and severity of skin thickening and hardening. Progressive skin fibrosis has been associated with worsening lung function in patients with dcSSc. The key issue in taking therapeutic decisions in SSc is assessment of inflammatory process activity, and intensity of fibrotic reaction. Generally, patients with SSc are treated with organ-based symptomatic treatment. However, patients with diffuse skin involvement and/or severe inflammatory organ involvement are usually treated more aggressively with systemic immunosuppressive therapy because of the increased risk of complications and organ failure. Unfortunately, current pharmacotherapies are often ineffective, poorly tolerated and associated with many side effects. A number of preclinical and relatively small clinical studies have investigated the efficacy and safety of novel therapy - fat grafting and adipose-derived SVF/ADSC-based treatments in SSc, generally reporting promising

therapeutic effects regardless of the type of fat and fat-derived cell preparation and/or purification. For that reason, the importance of the issue researched by the authors is, in my opinion, significant. This manuscript concerns analyses on pathophysiologic implication versus therapeutic potential of adipose-derived stem cells in SSc. This manuscript takes into account many literature reports, therefore data provided in the manuscript are valuable and may have an impact on the existing literature. Authors critically describe potential significant differences between ADSCs from SSc patients and healthy donors, which could be significant in the future clinical trials. They thoroughly describe clinical data and implications of white adipose tissue and related ADSCs and mature adipocytes in SSc pathogenesis. Therefore, understanding of the putative role of the adipocytic cell lineage in the development of SSc-related tissue fibrosis may pave the way for the discovery of novel therapeutic targets to prevent or reverse fibrosis by reducing disease progression (which certainly should be confirmed in larger studies). According the reviewer opinion the presented data are worth publishing, as can increase awareness that fat grafting and adipose-derived SVF/ADSC-based treatments in SSc can be a safe and effective therapeutic method.

Response: We thank the reviewer for his/her careful reading of our Review article, acknowledging the significance of our manuscript and classifying both Scientific/Language Quality as Grade A (Excellent/Priority publishing).

EDITORIAL OFFICE'S COMMENTS

(1) Science Editor: 1 Scientific quality: The manuscript describes a minireviews of the adipose-derived stem cells: pathophysiologic implications versus therapeutic potential in systemic sclerosis. The topic is within the scope of the WJSC. (1) Classification: Grade A; (2) Summary of the Peer-Review Report: This manuscript concerns analyses on pathophysiologic implication versus therapeutic potential of adipose-derived stem cells in SSc. This manuscript takes into account many literature reports, therefore data provided in the manuscript are valuable and may have an impact on the existing literature; and (3) Format: There are 2 tables and 2 figures. A total of 130 references are cited, including 29 references published in the last 3 years. There are 3 self-citations. 2 Language evaluation: Classification: Grade A. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJSC. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) The column should be review. 6 Re-Review: Not required. 7 Recommendation: Conditional acceptance.

Response: We thank the Science Editor for acknowledging the significance of our manuscript, confirming the Scientific Quality and Language Quality classification as Grade A, and recommending conditional acceptance. As requested, we have arranged the figures using PowerPoint to allow reprocessing by the editor. The column/article type has been changed to "Review" in the 58129_Auto_Edited file that we uploaded as *Manuscript File in the Step 6 of the F6Publishing system. Please, note that the system did not allow us to

change the column/article type in the Step 2 (Manuscript Information) of the F6Publishing system.

(2) Editorial Office Director: I have checked the comments written by the science editor. The manuscript type can be changed to "Review".

Response: The column/article type has been changed to "Review" in the 58129_Auto_Edited file that we uploaded as *Manuscript File in the Step 6 of the F6Publishing system. Please, note that the system did not allow us to change the column/article type in the Step 2 (Manuscript Information) of the F6Publishing system.

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements, and the manuscript is conditionally accepted with major revisions. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. Before final acceptance, authors need to correct the issues raised by the editor to meet the publishing requirements.

Response: We thank the Company Editor-in-Chief for judging that our manuscript met the basic publishing requirements and recommending conditional acceptance. We confirm that we revised the manuscript according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. We also confirm that we corrected the issues raised by the editor to meet the publishing requirements.

We hope that in the present form our manuscript can be accepted for publication in the *World Journal of Stem Cells*. We look forward to hearing from you as soon as a new decision has been reached by the Editorial Board.

Kind regards,

Mirko Manetti

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