

January 22, 2014

Dear Editor:

Please find enclosed the edited manuscript in Word format (file name: 8043-Review.docx).

Title: Adipose stem cell-based regenerative medicine for reversal of diabetic hyperglycemia

Author: Hyun Joon Paek, Courtney Kim, Stuart K. Williams

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 8043

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated in accordance to the journal's requirements.
2. A section describing each author's contributions has now been added to the cover page.
3. Revision has been made according to the suggestions of the reviewer:
 - a. "Please include in your table the study of Dave S.D et al (*Indian J Endocrinol Metab.* 2012 Mar;16 Suppl 1:S65-9. doi: 10.4103/2230-8210.94264. *Ex vivo generation of glucose sensitive insulin secreting mesenchymal stem cells derived from human adipose tissue. Dave SD, Vanikar AV, Trivedi HL.) that reported the generation of insulin-secreting human AD-MSC without using xenogenic material.*"

The medium composition used by Dave *et al* is same as the one used by Timpler *et al*. However, it is now referenced in the table as well.
 - b. Additional references suggested by the reviewers have been added.
 - i. "In introduction, paragraph 1 1. Mechanisms of PDL1-mediated regulation of autoimmune diabetes I Guleria et al. *Clinical Immunology* 2007 2. Role of ICOS pathway in autoimmune and alloimmune responses in NOD mice MJI Ansari et al. *Clinical Immunology* 2008."

The first reference by Guleria *et al.* was not relevant to the content of the first paragraph of the Introduction, so it was not cited in the revised manuscript. The second reference recommended by the reviewer, however, has now been cited and added to the bibliography.
 - ii. "In Introduction, paragraph 2 1. Early increase of retinal arterial and venous blood flow velocities at color Doppler imaging in brittle type 1 diabetes after islet transplant alone M Venturini et al. *Transplantation* 2006 2. Kidney Function After Islet Transplant Alone in Type 1 Diabetes Impact of immunosuppressive therapy on progression of diabetic nephropathy. P Maffi et al. *Diabetes Care* 2007 3. Determination of asymmetric and symmetric dimethylarginines in plasma of hyperhomocysteinemic subjects R Paroni et al. *Amino acids*

- 2005 4. *Left ventricular function in insulin-dependent and in non-insulin-dependent diabetic patients: radionuclide assessment* E Astorri et al. *Cardiology* 1997 5. *Proteomics reveals novel oxidative and glycolytic mechanisms in type 1 diabetic patients' skin which are normalized by kidney-pancreas transplantation* F Folli et al. , *PloS one* 2010."
- iii. "In introduction, paragraph 3 1. *A novel clinically relevant strategy to abrogate autoimmunity and regulate alloimmunity in NOD mice* A Vergani et al. *Diabetes* 2010."
- iv. "In introduction, paragraph 5 1. *Immunological applications of stem cells in type 1 diabetes* P Fiorina et al. *Endocrine reviews* 2011 2. *Immunological and regenerative properties of cord blood stem cells*. R Francese et al. *Clinical Immunology* 2010 3. *Congenetic mesenchymal stem cell therapy reverses hyperglycemia in experimental type 1 Diabetes* M Jurewicz, et al *Diabetes* 2010."

The third reference recommended by the review describes immunomodulatory effect of mesenchymal stem cells rather than direct differentiation into insulin-producing cells. Therefore, this particular reference was not cited in the revised manuscript.

- c. "Although the main potential capacity of insulin produced AD-MSC, two published trials conducted by Trivedi et al included co-transplantation of AD-MSC with hematopoietic stem cells admitting that the addition of HSC was designed to augment the effect of AD-MSC that I think is more convenient to discuss these studies in your last paragraph "challenges and opportunities for ASCs in diabetes"."

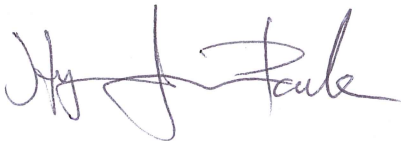
This paragraph has now been moved to the "Challenges and Opportunities for ASCs in Diabetes" section as recommended by the reviewer.

- d. "I would like to see as a physiologist some illustrations and tables comparing a normal islet cell with its receptor and molecular markers and a stem cell with the markers with regard to their differentiation."

A new table has now been added comparing molecular markers between undifferentiated adipose-derived stem cells and ADSC-derived, insulin-producing cells.

Thank you very much again for an opportunity to publish our manuscript in the *World Journal of Diabetes*.

Sincerely Yours,



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