

ANSWERING REVIEWERS



Dear Editor,

Please find enclosed the edited manuscript in word format (file name: 16540-Review.doc).

Title: Dedifferentiated fat cells: A cell source for regenerative medicine

Author: Medet Jumabay, Kristina I Boström

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 16540

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

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer (new text in the manuscript is in red font):

Reviewer 1

This review collected and discussed about a type of multipotent cells called DFAT. They are derived from adipose tissue. It is an interesting topic, but for me as a reader it is not clear how they are harvested from adipose tissue, whether it needs to a special technique or they are a fraction of this tissue and normally found in tissue. This part of manuscript needs a little revision. In addition, references are not uniform and according to journal guidelines.

We have added a detailed description of the method for DFAT cell preparation, with the inclusion of the appropriate references. Please see part of text in the section for Isolation and Dedifferentiation of Mature Adipocytes.

Reviewer 2

Jamabay and Bostrom summarize the recent advances in dedifferentiated fat (DFAT) cells as a potential source for regenerative medicine. The content is, in general, interesting and would be suitable for a wide readership. However, I have following reservations about the superiority of DFAT cells as a source for implementing regenerative medicine. (1) Although the authors discussed the potential problem of iPS cells in terms of tumorigenicity, they did not mention about the novel technologies such as the use of proteins or Sendai virus to induce iPS cells. Since these techniques allow obtaining virtually genome-modified free iPS cells, the superiority of DFAT cells to these iPS cells should be discussed such that a wide range of readers could understand the superiority. (2) Given that DFAT cells possess a potential to transdifferentiate into ectodermal cells besides mesodermal ones, it is imperative to keep the cell identity once the DFAT cell-derived cells get reached a desired phenotype (for example cardiomyocytes from DFAT cells). Since overexpression of a series of transcription factors to keep the desired lineage from DFAT cells is not an ideal solution, more discussions are required to justify the use of DFAT cells in the implementation of regenerative medicine. Minor concerns There are several typographic and grammatical errors.

We have discussed and cited the application of Sendai virus to generate iPS cells. We have added information in Section III on the methods so far used for tracking of DFAT cells. We have also added

that the potential need to maintain a specific cell identity once the DFAT cells have achieved a desired phenotype, or the methodology to do so, has not been assessed thus far for DFAT cells.

We have revised and corrected the English used in the text, and hope to have caught most of the errors.

Reviewer 3

In his review article the authors discuss properties of so called dedifferentiated (DFAT) cells, which can be isolated from adipose tissue. The paper is based on the literature data and on the own work of the authors. The authors call the cells isolated from adipose tissue as DFAT. However, there is a large body of publications which describe the cells isolated from adipose tissue as adipose tissue-derived MSCs. Are DFAT cells the same as adipose tissue-derived MSCs? The authors should show clearly the phenotypic and functional differences between DFAT cells and adipose tissue-derived MSCs. Otherwise, they speak about well described MSCs. Are DFAT really other cell lineage or they are MSCs cultured in different way than? classical" MSCs? Minor point: References must be checked by the authors and prepared more carefully, for example -The 1st reference contains both the first name and surname of authors, -Ref. 4. has not the name of journal, -Some references show all pages, some abbreviated form of the last page, -Some references have the year after the authors' names, other after the journal, -Ref. 33, has all authors (a total 17), but other references have only 3 authors and et al. -Etc, etc.

We have added text and discussion about MSCs and DFAT cells. We underlined the homogeneity and stem cell properties of DFAT cells as compared to ASCs.

3. The references have been corrected and put into the correct format.

Thank you for your time and effort in reviewing this manuscript. We have done our best to address the reviewers' concerns and constructive critiques. Please do not hesitate to contact me for any additional questions and concerns.

Thank you again for publishing our manuscript in the *World Journal of Stem Cells*.

Sincerely,

A handwritten signature in black ink, appearing to read 'm/jumabay', with a small blue circular stamp or mark to the right.

Medet Jumabay, MD, PhD