**Reviews for** “Prospects for Stem cell-based Regenerative Therapies in India”

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**Decision: Accepted pending minor revisions**

**Reviewer 1** has selected to remain anonymous.

Originality, novelty and significance of results: Adequate

Technical Quality of Work:

Comprehensibility and Presentation of Paper: Adequate

What is the overall impression: Adequate

**Reviewer Recommendation Term:** Accepted pending minor revisions

**Narrative (as sent to corresponding author):**

The author provides an interesting expose of Indias stem cell therapy landscape. The review would benefit from less focus on describing various stem cell types in the introduction but with more focus on the topic of stem cells in India. Although I understand that MSCs are the predominant cell type in most clinical trial, it would be interesting to get more info, both historic an current on work with cell and stem cell-based therapies of they eye which I believe India has a long history of. This perspective should be expanded. It would also be important to describe the efforts using pluripotent stem cells in India as I'm sure there are more efforts on this topic than described. Is there no current effort to bank iPSCs in India?
Minor comment, Luxturna is not a stem cell therapy, but a gene therapy.

**Reviewer 2** has selected to remain anonymous.

Originality, novelty and significance of results: Adequate

Technical Quality of Work: Good

Comprehensibility and Presentation of Paper: Excellent

What is the overall impression: Good

**Reviewer Recommendation Term:** Accepted pending minor revisions

**Narrative (as sent to corresponding author):**

The review by Boopalan et al., provides a thorough overview of ongoing clinical trial activities with stem cells in India. The manuscript introduces the field with a balanced description of different types of stem cells and their potential applications for treatments as well as provides a useful summary of the cell therapies which have been granted market approval so far. The review provides a highly useful and impressively comprehensive overview of ongoing trial activities in India in Fig. 2 and Table 1 - such compiled resources are highly valuable to researchers in the field, since clinical trial information is otherwise scattered over many separate sites. The manuscript further describes also relevant problem with stem cell therapies in India, such as trial results which are not published and the availability of unproven and illegal treatments with cell therapies at private clinics. Overall, I think the manuscript is well-written, balanced and thorough in its overview, and only have a few minor comments:

1) Please insert relevant references to support the statement on page 2: "Stem cell therapy has shown promising results in preclinical and clinical trials for several diseases including, Parkinson's disease, Diabetes mellitus, Crohn's disease and various haematological disorders."

2) The authors write on page 4: "Multipotent stem cells are also found in other tissues like the brain, the retina, the liver and the gut [4,6]." However, this statement is not entirely correct, since the liver does not contain stem cell, but rather regenerates through expansion of differentiated hepatocytes. Similarly, the retina cannot regenerate and is not believed to contain any stem cells. It should also be mentioned that although the brain contains stem cells, these are very limited in both number and differentiation potential.

3) The authors write on page 4: "In general, stem cells reside in a "stem cell niche", which is a micro-environment that favours self-renewal of such stem cells. Notably, these stem cells remain dormant under normal conditions and are only activated by signals generated by damaged tissue or injury." Again, this statement is not correct, since stem cells in the skin, intestine and blood and constantly active in tissue regeneration, also under normal homeostatic conditions.

4) On page 6, when listing approved MSC-based therapies (Prochyman, Temcell, Cartistem, Cellgram and Stemirac, please mention which diseases they are indicated for.

5) On page 9, it is stated about trial results from MSCs "Multiple reasons are attributed to such moderate outcomes and they include potential immune rejection by monocytes within 24 hrs after injection resulting in poor graft survival." It should be mentioned here that poor trial outcome from MSC trials can also in many cases be attributed to inadequate efficacy data from animal models and unclear hypotheses about the mechanism of action.

6) In the description of limbal stem cells, it should be mentioned that Holoclar was the first stem cell product to be approved by the EMA, in 2014.

7) For Fig. 2C, please specify what is on the Y-axis (i.e. "number of clinical trials")

8) For Fig. 2D, it wold be more intuitive to order the columns on the y-axis according to Phases, i.e. Phase 1 to 4 from left to right. Also, please increase font size on the labels.

**Author’s reply to reviewers:**

List of figures modified in the revised manuscript
Figure 1: We have converted the image to greyscale for better contrast and to avoid unnecessary use of color images
Figure 2: We have redone the graphs for better resolution and clarity. We have modified graphs as suggested by the reviewer (Rev#2, question 7 and 8). All panels are in greyscale.

Response to Reviewer comments
General Comment
Please attend to the reviewer comments below and resubmit your manuscript accordingly, within 30 days. While we would like for you to keep an introduction about various stem cell types, please expand, where relevant, with comments on how each of these cell types are being developed also in India.
Response: We have included relevant information on the establishment and availability of human Embryonic Stem Cells (hESCs) and induced Pluripotent Cells (iPSCs) generated in India and the details about their availability in various repositories (pages 3-4). Also see response to Rev#1.
Reviewer#1
The author provide an interesting expose of Indias stem cell therapy landscape. The review would benefit from less focus on describing various stem cell types in the introduction but with more focus on the topic of stem cells in India. Although I understand that MSCs are the predominant cell type in most clinical trial, it would be interesting to get more info, both historic an current on work with cell and stem cell-based therapies of they eye which I believe India has a long history of. This perspective should be expanded. It would also be important to describe the efforts using pluripotent stem cells in India as I'm sure there are more efforts on this topic than described. Is there no current effort to bank iPSCs in India?
Minor comment, Luxturna is not a stem cell therapy, but a gene therapy.

Response: We have included relevant information on the establishment and availability of human Embryonic Stem Cells (hESCs) and induced Pluripotent Cells (iPSCs) generated in India and the details about their availability in various repositories (pages 3-4).
We have included a detail account on the status of stem cell therapies in treating corneal diseases along with relevant references and information on clinical trials (page 9).
As the reviewer pointed out, Luxturna is a gene-therapy product and not a stem cell therapy product, and therefore, we have removed the sentence (deleted on page 16).

Reviewer#2
1) Please insert relevant references to support the statement on page 2: "Stem cell therapy has shown promising results in preclinical and clinical trials for several diseases including, Parkinson's disease, Diabetes mellitus, Crohn's disease and various haematological disorders."

Response: We have included the relevant references (Ref: 3-6), (pages 2, 19).

2) The authors write on page 4: "Multipotent stem cells are also found in other tissues like the brain, the retina, the liver and the gut [4,6]." However, this statement is not entirely correct, since the liver does not contain stem cell, but rather regenerates through expansion of differentiated hepatocytes. Similarly, the retina cannot regenerate and is not believed to contain any stem cells. It should also be mentioned that although the brain contains stem cells, these are very limited in both number and differentiation potential.

Response: We thank the reviewer for pointing out the error; we have corrected it (page 4-5)

3) The authors write on page 4: "In general, stem cells reside in a "stem cell niche", which is a micro-environment that favours self-renewal of such stem cells. Notably, these stem cells remain dormant under normal conditions and are only activated by signals generated by damaged tissue or injury." Again, this statement is not correct, since stem cells in the skin, intestine and blood and constantly active in tissue regeneration, also under normal homeostatic conditions.

Response: We thank the reviewer for pointing out the error; we have corrected it (page 5)

4) On page 6, when listing approved MSC-based therapies (Prochyman, Temcell, Cartistem, Cellgram and Stemirac, please mention which diseases they are indicated for.

Response: We have included disease names targeted by MSC-based therapies (page7).

5) On page 9, it is stated about trial results from MSCs "Multiple reasons are attributed to such moderate outcomes and they include potential immune rejection by monocytes within 24 hrs after injection resulting in poor graft survival." It should be mentioned here that poor trial outcome from MSC trials can also in many cases be attributed to inadequate efficacy data from animal models and unclear hypotheses about the mechanism of action.

Response: We have included the additional points as suggested by the reviewer (page 11).

6) In the description of limbal stem cells, it should be mentioned that Holoclar was the first stem cell product to be approved by the EMA, in 2014.

Response: We have included Holoclar, the 1st EMA approved stem cell product (page 10).

7) For Fig. 2C, please specify what is on the Y-axis (i.e. "number of clinical trials")

Response: We have included labels on the Y-axis (Fig. 2C)

8) For Fig. 2D, it wold be more intuitive to order the columns on the y-axis according to Phases, i.e. Phase 1 to 4 from left to right. Also, please increase font size on the labels.

Response: We have modified the graph as suggested by the reviewer (Fig. 2D)

**AFTER THE REVISIONS THE ASSOCIATE EDITOR DECIDED TO ACCEPT.**