

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60418

Title: Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End?

Reviewer's code: 00609419

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: Canada

Manuscript submission date: 2020-10-30

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2020-11-16 10:44

Reviewer performed review: 2020-11-19 15:41

Review time: 3 Days and 4 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This manuscript authored by Mathieu Rheault-Henry et al. is a comprehensive and well-constructed review, focusing on the stem cell therapy for heart failure. I fully recommend it for publication, with little changes/proofreading as listed below: There is a lack of the keywords. Pg7: at the lower part of the 2nd paragraph, '...Cell and Science[19,20],' change to 'and'. Pg11: guess the word PSCs meant 'iPSCs' in a few places, and also in the 6th line from the bottom in pg25. Pg15: in the middle of the page '... LV function,' finishes with full stop. Pg17: the 8th line in the first paragraph 'mesenchymal precursor cells' should be MPC? Pg21: the last 5th line in the first paragraph, 'The Centers for Disease Control and Prevention (CDC)' Is it CDCP? Pg28: the 8th from the bottom, 'Cardiac progenitor cells ...' meant CPC? It would be better to provide a list of abbreviations at the end of the manuscript.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60418

Title: Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End?

Reviewer's code: 02595715

Position: Peer Reviewer

Academic degree: DSc

Professional title: Professor

Reviewer's Country/Territory: Russia

Author's Country/Territory: Canada

Manuscript submission date: 2020-10-30

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2020-11-16 09:14

Reviewer performed review: 2020-11-20 09:15

Review time: 4 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled “Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End?” by Rheault-Henry et al rises an important question of modern translational research. Stem cells draw a lot of public attention during last two decades however no significant practical achievements have been done so far and are not seen in the nearest future. The reason for this is the lack of solid scientific basement for the cell therapy of myocardium. The manuscript is interesting and well written however I would advise to introduce some corrections and changes. P.6 section STEM CELLS AND THEIR APPLICATIONS. “Cells derived from the zygote have the ability to differentiate into any embryonic or extraembryonic cell type in the body and are termed totipotent.” It is impossible to derive cells from the zygote because it is just one cell. Upon its division two-cell, 4-cell, etc blastomere is formed. On blastomere stage cells are totipotent because they have ability to differentiate into the embryo and the trophoctoderm. Later on blactocyst stage cells of the ICM are able to differentiate into embryonic and extraembryonic cell types. Extraembryonic cells and trophoctoderm form placenta. “Human ESCs can differentiate into all three germ layers but lack the potential to create extra-embryonic tissues like the placenta..”- it is incorrect for both human and mouse ESCs, they can form extra-embryonic tissue, however mouse ESCs do not form trophoctoderm, although human ESCs do. “The successful creation of iPSCs was first documented by Shinya Yamanaka and James Thomson in 2007, and George Q. Daley in 2009[11].” It is incorrect, the creation of iPSCs was first documented by Takahashi&Yamanaks in 2006, later independently Yamanaka and Thomson established human iPSCs in 2007. “...although it is apparent that some degree of epigenetic memory is retained with iPSCs making it challenging to reprogram them to a fully pluripotent state[13].” It is incorrect. Recent studies demonstrated that there are no any specific epigenetic memory (see Shutova et al 2016 etc). Section Results, ADULT STEM CELLS



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Cardiac stem cells. “ it is now well established that CSCs express markers of cardiogenesis and can differentiate into cardiomyocytes and vascular endothelial cells[38].” These data are from P.Anversa paper. P.Anversa was blamed for scientific misconduct and majority of his papers about CSCs were retracted <https://academic.oup.com/eurheartj/article/40/13/1036/5423360>. I am sure that it will be better to avoid the citation of the accused author. Authors also cite another paper by Anversa and mention that it was retracted. There were retracted almost 20 papers and I do not even think that the concept of CSCs is correct and alive. The field was significantly compromised by Anversa misconduct. Section Discussion. The majority of section is devoted to the ethical issues and unproved therapies. Indeed, the all field and particularly of the adult stem cells is highly compromised and demonstrated no clinical benefits for patients. However, I would recommend to put more attention to scientific basis of therapies rather on the momentary ethical concerns of the nonexistent treatments.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60418

Title: Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End?

Reviewer's code: 03195661

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

Manuscript submission date: 2020-10-30

Reviewer chosen by: Jia-Ru Fan

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Reviewer performed review: 2020-12-03 03:44

Review time: 18 Days and 19 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This review focused on the pros and cons of the different types of the stem cells used in clinical trials and discussed the limitations of the stem cell therapy and its promising future, which presented an overview of the history of the stem cell therapy in heart failure. The language has high quality and rigorous logic. Overall, this review is interesting and impressive, and acceptable for publication. There are some suggestions to be addressed. 1: The clinical trials with different stem cell therapies can be summarized in a table, so the readers can easily track the clinical trials and profoundly understand these. 2: in the part of the “microvesicles and exosomes”, as also mentioned in the discussion, the exosomes have been involved as a vital branch of this field, thus a vivid picture of microvesicles and exosomes for therapy in heart may be suitable.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60418

Title: Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End?

Reviewer's code: 02446098

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

Manuscript submission date: 2020-10-30

Reviewer chosen by: Jia-Ru Fan

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Reviewer performed review: 2020-12-03 04:09

Review time: 18 Days and 14 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript, entitled “Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End”, discussed past, present, and future clinical trials, factors that influence stem cell therapy outcomes as well as ethical and safety considerations. Indeed, this review was not well organized and several issues should be addressed before the manuscript can be accepted. E.g., several subtitle of Result. The pathophysiology of heart failure and the target of stem cell therapy for HF should be well summarized, such as direct differentiation, paracrine effects, parameter changes of HF after therapy, et al. For endogenous cardiac regeneration, such as YAP signal pathway, plays important roles, the topic on how stem cell increases the turnover rate of myocytes should be covered; Past, present clinical trials should be summarized in a Table for better understanding. Table 1: Safety parameters of various stem cell types, please list the citations in table.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60418

Title: Stem Cell Therapy for Heart Failure: Medical Breakthrough, or Dead End?

Reviewer's code: 02595715

Position: Peer Reviewer

Academic degree: DSc

Professional title: Professor

Reviewer's Country/Territory: Russia

Author's Country/Territory: Canada

Manuscript submission date: 2020-10-30

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-12-23 09:20

Reviewer performed review: 2020-12-23 10:36

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Authors significantly improved the manuscript and I is my pleasure to recommend it for



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