



PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46612

Title: Cell source as a major challenge in tissue engineering: aging as a limiting factor

Reviewer’s code: 02931898

Reviewer’s country: France

Science editor: Fang-Fang Ji (Quit in 2019)

Reviewer accepted review: 2019-03-08 14:50

Reviewer performed review: 2019-03-12 11:11

Review time: 3 Days and 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I have two major critics on this manuscript: 1- I think that this paper is too long, particularly since it is centered on the limiting effect of age. The three first chapters should be reduced. This part has been written more like a book (chapter 1 is even entitled “preface”!). The reader expects a more direct introduction. 2- I’m surprised by



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the paragraph entitled “genetically-modified stem cells”. This chapter should re-written by including the CRISPR-Cas9 technology, which is major a major breakthrough in the field. Particularly since the recent controversial application to human in vitro fecundation (see Nature, December 6th, 2018, volume 564). Furthermore, the ethical point of view should be underlined. Minor point: In the second sentence of the chapter “embryonic stem cells”, the authors say “ESCs are formed from 4 days blastocysts up to the ninth week”, which I don’t understand. Right after the blastula stage, at the gastrula stage (therefore long before the ninth week) it’s impossible to get ESCs!

Indeed I reviewed this paper, In the revised version the authors answered correctly to my remarks.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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BPG Search:

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- Plagiarism
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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46612

Title: Cell source as a major challenge in tissue engineering: aging as a limiting factor

Reviewer’s code: 02524648

Reviewer’s country: Spain

Science editor: Fang-Fang Ji (Quit in 2019)

Reviewer accepted review: 2019-03-09 09:08

Reviewer performed review: 2019-03-13 00:40

Review time: 3 Days and 15 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In their manuscript “Cell source as a major challenge in tissue engineering: aging as a limiting factor”, Khorraminejad-Shirazi and colleagues offer a very extensive account of some of the considerations that must be taken into account regarding cell sources and types for tissue engineering. The number of references is vast, which reflects a very



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commendable effort by the authors to cover the many aspects related to this topic. However, there is a series of important shortcomings in this review: - The English language should be thoroughly and extensively edited for the text to be easily read and understood. - Surprisingly, despite the very extensive bibliography, there is a general lack of references through many of the sections in the Ms; this is especially apparent in the first 3 sections. On the other hand, there are other parts (e.g. 4.1) where many references are indicated. In addition, many of the references presented have to do with very specific comments in the text, rather than with the general information the section deals with. Therefore, the reader is left with the feeling that the sentences are not well supported by bibliographical evidence. - Overall, a lot of information is indicated throughout the Ms, but a large part of this information is only briefly mentioned and not substantiated nor the topic adequately introduced or presented in sufficient depth (e.g. sirtuins). On the other hand, the second half of the Ms is full of specific, individual examples (e.g. a lot of information is given on specific properties of MSC and HSC in particular study cases) and the references for these examples. - There is a lot of repetition all throughout the various sections, indicative of an excessive partitioning of the text into small sections that should perhaps have been grouped together, e.g. iPSC appear in two different sections, autophagy is discussed and the information repeated in several parts of the Ms, mitochondria, autophagy, “rejuvenation” avenues should have been brought together or, at least, the information should have been distributed without repetitions, etc. (e.g. the information in section 4.6 is clearly duplicated in section 4.7) - In section 4.6 (last paragraph) the authors seem to identify the inhibition of tumour growth and lymph metastasis with increased cell viability and there also seems to be some crossing between cell survival and the survival of individuals. - When reading the manuscript, there is perhaps the feeling that genetic modification of stem cells or the use of stem cells/iPSC is considered as a viable avenue towards tissue engineering and



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transplantation, as well as the idea, especially after reading the conclusion, that aging can in fact be reverted and employed to build transplantable tissues, when this is not really the case and there are instead important hurdles to be overcome. - There is not a consensus in the way the subheadings are indicated (e.g. under section 2, the authors use I., II., III...., under section 3, a., b., ..., under section 4, 4.1, 4.2, ... In summary, although a commendable effort has been made by the authors and many interesting points have been addressed in their Ms: (a) these points need to be re-organised differently to avoid unnecessary duplications of the same pieces of information; (b) the general ideas must be clearly supported by a sufficient number of references, while a good number of the specific examples that are discussed in detail should be instead briefly mentioned so that the main messages of the Ms are not lost; (c) the problems that are currently faced by tissue engineering and transplantation, although indeed brought into the Ms, must be more clearly defined, so that there is no subtle message to the reader that the way towards tissue engineering has already been paved by the advent of genetic modifications (e.g. telomerase manipulation), the use of embryonic stem cell / iPSC, and the reversal of aging as a process that does not raise any serious concerns. I would recommend extensive re-writing of the Ms following these guidelines.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46612

Title: Cell source as a major challenge in tissue engineering: aging as a limiting factor

Reviewer's code: 02398061

Reviewer's country: United States

Science editor: Fang-Fang Ji (Quit in 2019)

Reviewer accepted review: 2019-03-13 14:52

Reviewer performed review: 2019-03-15 14:19

Review time: 1 Day and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is a comprehensive article on cell sources for tissue engineering and replacement therapy, as well as aging as a factor in stem cell senescence and functional decline. In most parts, the article is well written and covers a broad range of literature. It touches on the most important issues attached to stem cells in context of cell therapy and aging.



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There is a discrepancy between the first part on tissue engineering and stem cell sources, including abstract and sections 1-3, and the second part discussing in depth the molecular and cellular aspects of cell aging. While the second part reads well and is comprehensive, the first part requires some editing: - It is advised to having at least the first part and the abstract reviewed by a native English-speaking person. Again, both the abstract and the first part are a bit “bumpy.” Throughout the manuscript, there are many mistakes, some odd sentences, including choice of words and syntax. - It is not clear why the discussion of iPSC is done twice in sections IV and 3. It should be in section 3 alone. - The literature selection could be improved in sections 1-3. Some of the citations are outdated and should be replaced with more recent publications (e.g., macular degeneration and Parkinson’s disease, current standing of ASCs, latest updates on clinical successes, e.g., on gene-engineering SCs, such as sickle cell anemia, ...). Altogether, while the principles have been discussed, the text is lacking examples and literature on the most updated standings of SC use both in basic and preclinical research and in clinical application. A much more thorough screening of the updated literature is necessary. - There are no citations in section 4. (Cellular aging is a limiting factor). - There should be a better distinction between the different usages of cells for therapeutic application. For example, transplanting cells is fundamentally different than transplanting organs. This also includes the usage of stem cell sources, either as a direct source for transplantation, or as source to produce organs. This should be made clearer in the text. Sections 4.1. - 4.6. should include more discussion on pluripotent stem cells - there is a larger literature on “aging” of these cells, both during propagation and differentiation, which has not been touched on. On a general note, the article heavily cites review articles - there could be a better balance between reviews and original articles. The title is a bit misleading. I would remove “challenge” and find a better way to reflect the broader nature of the article.



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Below are the comments. Thank you. Kai The manuscript has been improved taken into account the comments of the reviewers. It now reads a lot better and provides a comprehensive overview on cell sources for tissue engineering and replacement therapy, aging as a factor in stem cell senescence and functional decline, and some discussion on “geroprotection”. There are still several aspects that could be improved. One major issue is the reference list that needs to be carefully checked again. Many references don’ t match the text, in particular starting at page 15 in section miRNAs, ... There are also some statements and sentences that are not entirely correct. For example, Page 11, last sentence on iPSC bias: “iPSCs were found to have a different story; while iPSC cell lines have a slightly skewed differentiation capacity, it has no correlation with the cell source they are originated from [88, 89].” The statement is incorrect. There is also a literature claiming that the differentiation capacity of iPSC is biased to their originated cell source, probably an effect of retained epigenetic profiles. Page 15: “... a somatic cell can either be fused with the cytoplasm of an enucleated oocyte...” - this is incorrect, the nucleus of a somatic cell is fused. Page 17, the new text on ROS.” For instance, they showed that while all three of the piperlongumin (PL), beta-phenylethyl isothiocyanate (PEITC), and Lactic acid (LA) increased ROS in the cultured cells, only PL and PEITC, two ROS-based chemotherapeutic agents, killed the cells and LA “spared them.” Additionally, although chemical depletion of glutathione increased ROS much higher than PL and PEITC, it did not affect the cell growth in cultured samples [162].” - These statements refer to cancer cells and it is unclear if similar mechanisms also occur in stem cells.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46612

Title: Cell source as a major challenge in tissue engineering: aging as a limiting factor

Reviewer's code: 03372822

Reviewer's country: Portugal

Science editor: Fang-Fang Ji (Quit in 2019)

Reviewer accepted review: 2019-03-12 10:17

Reviewer performed review: 2019-03-17 20:04

Review time: 5 Days and 9 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors address very relevant issues in their manuscript. However, the overall manuscript is organized as a list of topics with no real link between them. There are even 2 "iPSC" sections that could be blended in a unique section. Hematopoietic stem cells and Mesenchymal stem cells are probably the cells used "routinely" nowadays which



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present the safest use. These cells are merely described in the section presenting aging-related issues. The conclusion is largely biased towards aging and do not summarize the full content of the manuscript. Minor comments: 1 - a few typos were detected in the text, but activated English WORD corrector should easily pick them up, 2 - 4th line of the first iPSCs section, the authors indicate "These factors have been shown to contribute to maintenance of pluripotency in adult cells and are sufficient to generate ...". In this sentence, "adult stem cells" should be substituted by "EMBRYONIC stem cells".

In my opinion the authors have addressed the concerns raised by the reviewers and substantially improved the manuscript. Some minor English mistakes and inconsistencies (such as usage of both denomination s iPSC and iPS cells) persist. Overall, the manuscript can be accepted for publication.

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