

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46196

Title: Effects of various antimicrobial agents on the multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells

Reviewer's code: 03197771

Reviewer's country: Spain

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-02-13 11:52

Reviewer performed review: 2019-02-13 21:55

Review time: 10 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 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

The review article by Li and Yue, entitled: "Effects of various antimicrobial agents on the multi-directional differentiation potential of bone marrow-derived MSCs" consists of an update on the effects that antibiotics and other common therapeutic agents have on the

differentiation potential of BMSCs. The structure of the paper seems appropriate as the authors classify the effects according to the 3 main differentiation cell types potential and the type of compound, which may facilitate the readers the access to a particular section of interest. To improve this point it is recommended that section 3 is restructured accordingly. Also Table 2 needs to be redone including a similar format to Tables 1 and 3, indicating if Agents are antibiotic..etc. The abstract seems truncated in the last sentence. It seems that the purpose of the review is missing. The addition of a short sentence explaining the aim of the review will clarify to readers the main message of the manuscript. It will be of interest that the authors include the usual physiologic concentrations of antibiotics used in therapy and how the in vitro study-based evidence relates with them as a means of estimating the clinical relevance of the in vitro data on treated individuals. For example, references 14 and 15 are reporting conc. of rifampicin above 32 ug/mL to have a negative effect on MSCs. What is the conc. range in individuals treated with rifampicin? It is important that the authors add drug bioavailability information and how does this fit with in vitro information for each compound included, as long as there is information available. In this line, it is not clear what is the meaning of "blood concentration" in Table 1. It is also recommended that authors review the meaning of "significant inhibition", "severely inhibited" etc. As they are arbitrary terms, it would be more appropriate to set numeric values (above 30% etc). Also "differentiation" and "viability" are two different terms. They should not go together (page 10). Also, the whole manuscript has to be reviewed to avoid vague and subjective meaningless terms such as "good" when referring to antibacterial properties...etc; it should just read "antibacterial properties". Repetitive terms should also be avoided. The meaning of the following sentences is not clear in their present form. Please review: Section 2.1 "...and inhibit the effects of intracellular bacteria secreted in cells a" "Since, penicillin cannot tolerate the enzymes produced by a variety of



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bacteria, the results are more likely for it to be destroyed, increasing the probability” The sentence “azithromycin does not produce cytotoxicity in the concentration range of 0-200 µg/mL; however, it inhibits the differentiation potential of osteoblasts at very low concentrations” seems controversial. The cell line C2C12 does not undergo osteogenic differentiation. Please review the following sentence: “A similar inhibition was also reported in the C2C12 cell line [18].” Section 2.2 “induce pathogenic bacteria to cleave” A peptide cannot proliferate. Please review: “LL-37 has also been shown to be capable of proliferating,...” -Reference 11 it is not appropriate on its first appearance. To describe common differentiation criteria for MSCs, it is recommended that the authors use the following reference: Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315-7. -References 9, 10 and other contain over 6 co-authors. Generally only the 6 first are cited followed by et al., Please review specific journal (WJSC) format for cites. -Check italics for: Pseudomonas, in vitro etc -Abbreviations have to be fully described in its first appearance i.e. ATDC5 cells Please correct section after 4.3, cannot be labeled 2.4 Rephrase last sentence in the Conclusion section for clarity. Please review punctuation and other minor English grammar throughout the manuscript.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- [] The same title
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- [] Plagiarism
- [Y] No



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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46196

Title: Effects of various antimicrobial agents on the multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells

Reviewer's code: 02495033

Reviewer's country: South Korea

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-02-11 08:02

Reviewer performed review: 2019-02-15 05:03

Review time: 3 Days and 21 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" 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 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

WJSC-46196 In the present review, the authors reviewed the inhibitory and promoting effects many anti-microbials on the differentiation of MSCs into bone, chondrocyte, and adipocyte. The review is very extensive and sound, so may provide readers and



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investigators with good information. It is believed that antibiotics added to the culture medium also may affect the proliferation of MSCs. So, it is recommended that the authors should emphasize the significance of antibiotics in the medium.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46196

Title: Effects of various antimicrobial agents on the multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells

Reviewer's code: 03712811

Reviewer's country: Italy

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-02-11 21:09

Reviewer performed review: 2019-02-15 14:03

Review time: 3 Days and 16 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept	Peer-Review:
<input checked="" 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 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

In this study, the Authors aim at providing a review analysis of the effects elicited by a number of antimicrobial agents on three types of differentiation patterns, osteogenic, chondrogenic, and adipogenic, forming the multilineage repertoire of bone



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marrow-derived mesenchymal stem cells (BM-hMSCs). This is an interesting, and exhaustive review tracing an important background for a comprehensive dissection of the ability of both natural and synthetic antimicrobial agents to preserve, or conversely hamper, the differentiating potential of BM-hMSCs. This is also a remarkable area of inquiry, since the pharmacological treatment of bone infections is placed within the context of understanding to what extent this treatment may impair or favor joint tissue recovery based upon the drug effect on local tissue resident stem cells (or stem cells transplanted as a tool for local cell therapy).

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46196

Title: Effects of various antimicrobial agents on the multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells

Reviewer's code: 00567975

Reviewer's country: Austria

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-02-11 19:19

Reviewer performed review: 2019-02-18 19:58

Review time: 7 Days

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 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

In the present manuscript, the effect of different antimicrobial drugs on the multi lineage differentiation potential of bone marrow MSCs is reviewed. Review is good structured and see to cover all aspects of this topic. Several issues may be further considered by

Authors: Chapter Introduction. Natural penicillin is produced by fungi, not by pathogenic microorganism. Moreover, modern antibiotics are mostly synthetic ones, this should be clearly stated in the introduction. Chapter 2.1 Subheading in this chapter are somewhat confusing: why did Author use sometime groups of antibiotics (e.g. beta-lactam) and sometimes their therapeutic effects (e.g. anti-tuberculosis drug)? Author described in details the effect of different antibiotics on osteogenic differentiation and sometimes there are contradiction in the effect of antibiotics of the same group (e.g. cephalosporins) on the osteogenic differentiation. It would be interesting how these contradictory finding can be explained? Whole Review It would be important to emphasize on the clinical importance of the effect of antimicrobial drug. For example, how the concentration used in in vitro experiment are related to the clinical situation, serum concentration, minimal inhibitory concentration? Are there any studies showing the effect of antimicrobial drugs described by Author on MSC differentiation in vivo?

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46196

Title: Effects of various antimicrobial agents on the multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells

Reviewer's code: 02446229

Reviewer's country: Japan

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-02-13 10:27

Reviewer performed review: 2019-02-23 04:23

Review time: 9 Days and 17 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

The author summarize various knowledge about antimicrobial agents on the multi-directional differentiation of bone marrow-derived mesenchymal stem cells (MSCs). The collective information for osteogenic, adipogenic and chondrogenic

differentiation of MSCs in Table 1, 2 and 3, respectively in this review are important to think about therapeutic strategy and are worth to publish. I have some questions as described below. Please answer the question and possibly add your opinion in the manuscript. Q1: I suppose that antimicrobial agents can be administrated either locally or systemically in various orthopedic therapies. Local concentration of the antimicrobial agents in the bone marrow where many MSCs exist should be regulated by the controlled-release technology. Please mention about this problem and show author's opinion? Q2: In case of therapy based on the tissue engineering of bone and cartilage, MSCs can be cultured to be differentiate into osteoblast or chondrocyte with some adequate 3D scaffold in vitro. Which antimicrobial agents are preferable for such purpose, considering about the large scale of culture, antimicrobial spectra (species of microorganisms), risk of emerging drug-resistant microorganisms, etc.? Please mention about this point. Q3: Recently, MSCs are used for cell transplantation therapies not only for bone regeneration and cartilage regeneration in orthopedics, but also for recovery of stroke in brain, spinal cord injury, nerve repair, reduction of graft-versus host disease (GVHD) various diseases, etc. Growth factors and cytokines produced by MSCs can accelerate repair and regeneration in those cases. Collective knowledge about antimicrobial agents on MSCs are also useful for such clinical application of MSCs. How does the author think about those issues?

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46196

Title: Effects of various antimicrobial agents on the multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells

Reviewer's code: 02446191

Reviewer's country: India

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-02-12 07:39

Reviewer performed review: 2019-03-03 15:34

Review time: 19 Days and 7 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

Authors briefly describe about various antimicrobial drugs/ agents and their potential role in osteogenic, cartilage, and adipogenic differentiation of bone marrow-derived mesenchymal stem cells. Molecular mechanisms of antimicrobial agents towards



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regulation of multiple differentiation potentials of MSCs must be described in detail.

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BPG Search:

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