

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 22478

Title: Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy?

Reviewer's code: 02398400

Reviewer's country: United States

Science editor: Fang-Fang Ji

Date sent for review: 2015-09-06 15:47

Date reviewed: 2015-10-19 20:46

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The manuscript by De Becker and Van Riet reviews the current literature describing the mechanisms that regulate homing of mesenchymal stem cells (MSCs) to target tissues in vivo. The authors emphasize the role of the SDF-1/CXCR4 signaling axis and provide a fairly comprehensive overview of the literature related to this topic. Emphasis on engineering MSCs to enhance homing is well written and the authors do a good job describing the different published approaches. The review requires further editing for English grammar. Comments 1. In the introduction the authors state that MSCs "can escape immune recognition". This is a highly subjective statement that requires further clarification. Indeed, there is a wealth of published data showing that MSCs stimulate allo-graft responses in rodent, swine, and non-human primate models. Therefore, the authors should elaborate on this statement by adding further context. 2. The reference list given in Table 1 does not appear to be exhaustive as one citation is provided for many different molecules. The authors should state whether the list reflects initial works and/or is meant to be exhaustive. If the latter is true then a more complete list of citations should be provided.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 22478

Title: Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy?

Reviewer's code: 00289357

Reviewer's country: France

Science editor: Fang-Fang Ji

Date sent for review: 2015-09-06 15:47

Date reviewed: 2015-10-21 19:38

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[] Grade B: Very good	[] Grade B: Minor language polishing	[] The same title	[] High priority for publication
[] Grade C: Good	[] Grade C: A great deal of language polishing	[] Duplicate publication	[] Rejection
[] Grade D: Fair	[] Grade D: Rejected	[] Plagiarism	[] Minor revision
[] Grade E: Poor		[Y] No	[] Major revision
		BPG Search:	
		[] The same title	
		[] Duplicate publication	
		[] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is an interesting well-described review. The work is technically well conducted and well written. It addresses an interesting clinical area in an application. Minor revisions Introduction Sentence This interest arises from the following MSC characteristics: they can escape immune recognition, they have immunomodulatory capacities. Add the following references: Immunosuppressive effects of mesenchymal stem cells: involvement of HLA-G. Nasef A et al. Transplantation. 2007 Jul 27;84(2):231-7 Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells. Nasef A et al Gene Expr. 2007;13(4-5):217-26. Selected Stro-1-enriched bone marrow stromal cells display a major suppressive effect on lymphocyte proliferation. Nasef A et al. Int J Lab Hematol. 2009 Feb;31(1):9-19 Sentence Clinical applications have been studied most extensively in Orthopaedics where MSC are used for repair of large bone defects and in Haematology for the treatment of graft-versus-host disease and support of engraftment [4,6] Add the following reference: Infusion of allogeneic-related HLA mismatched mesenchymal stem cells for the treatment of incomplete engraftment following

autologous haematopoietic stem cell transplantation. Fouillard L, et al. Leukemia. 2007 Mar;21(3):568-70 Sentence In this setting homing and persistence of MSC in the target tissue is desirable [9-12]. Add the following reference: Long-Term Quantitative Biodistribution and Side Effects of Human Mesenchymal Stem Cells (hMSCs) Engraftment in NOD/SCID Mice following Irradiation. Francois S, et al. Stem Cells Int. 2014;2014:939275. Sentence In haematology MSC are currently mainly tested to control graft versus host disease and to support haematopoiesis after haematopoietic stem cell transplantation. Add the following reference: Innovative cell therapy in the treatment of serious adverse events related to both chemo-radiotherapy protocol and acute myeloid leukemia syndrome: the infusion of mesenchymal stem cells post-treatment reduces hematopoietic toxicity and promotes hematopoietic reconstitution. Fouillard L, et al. Curr Pharm Biotechnol. 2013;14(9):842-8. Sentence Devine et al. performed MSC transplantations in baboons and found MSC in a variety of tissues with highest signal in the gastro-intestinal tract, the percentage of MSC in the different tissues was estimated between 0.1 and 2.7% [13]. Modified : Devine et al. and Chapel et al. performed MSC transplantations in Non-Human primate and.....(Chapel A et al. 2003) Sentence: Several other groups have also shown that MSC homing is improved after irradiation [13, 31-35] Change reference Reference 32 (Br J Radiol 2007; 80 Spec No 1: S49-55) by Local irradiation not only induces homing of human mesenchymal stem cells at exposed sites but promotes their widespread engraftment to multiple organs: a study of their quantitative distribution after irradiation damage. Francois S, et al. Stem Cells. 2006 Apr;24(4):1020-9. Reference 34 (J Gene Med 2003; 5:1028-1038) by New emerging concepts in the medical management of local radiation injury. Benderitter M et al. JJ. Health Phys. 2010 Jun;98(6):851-7

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 22478

Title: Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy?

Reviewer's code: 02902002

Reviewer's country: China

Science editor: Fang-Fang Ji

Date sent for review: 2015-09-06 15:47

Date reviewed: 2015-10-23 16:40

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This review aimed to review the mechanisms of MSC homing and strategies to enhance the homing efficiency. This is a hot topic in the translational research of stem cells. It would be better if the authors can state clearly the sources of MSCs, the route of administration and the target tissue in the studies quoted in the manuscript. The authors may consider focusing only on stem cell homing to bone marrow. The future research directions should be discussed to increase the impact of this review. The English of the manuscript needs to be polished. There are many grammatical mistakes and the meanings of some sentences are not clear. My specific comments about the manuscript are listed below. 1. The review mainly focuses on homing mechanisms and strategies to improve homing efficiency. This should be stated clearly in the title. If the authors consider to focusing only on stem cell homing to bone marrow, the title also needs to be revised to indicate this intention. 2. The sources of MSCs, the route of administration and the target tissue in the studies quoted in the manuscript should be stated. Please check throughout the manuscript. 3. P.3, Line 4, be consistent in using the term "MSC" or "MSCs" to refer to mesenchymal stem cell"s". 4. P.3, line 14-18, please add

references. 5. P.3, line 18, clarify what “in this setting” means. 6. P.3, line 19-20, rewrite this sentence. 7. P.3, line 20-22, please add references. 8. P.3, line 29-32, rewrite this sentence. 9. P.3, line 34, this reviewer thinks that there may be some differences in the strategies used to improve homing efficiency depending on the target tissues. Hence, it would be better to state clearly if the authors are interested in bone marrow homing. 10. The section heading “Homing and migration of MSC” should be revised to more specifically reflect the content in that section. 11. Are there any differences in migration or homing efficiency of MSCs isolated from different sources? Please discuss. 12. The association between outcomes and route of MSC administration should be discussed. The advantages and limitations of different routes of MSC administration should be discussed. 13. P.4, line 10, what does “at 35 years” mean? 14. P.5, line 1, it should be G-protein coupled receptors 15. P.5, line 1-3, add reference. 16. P.5, line 3, clarify what “both” means. 17. P.6, line 14, should be “Much effort focuses...” 18. P.6, line 28, should be “Treatment of MMPs in MSCs...” 19. P.7, line 29-31, was it a pre-treatment? 20. P.7, line 38-37, should state the source of MSC and indicate that it is an effect of hypoxia. 21. P.7, line 4-7, this statement is not clear. Please rewrite. 22. P.7, line 9, should be “... MSC cultured and maintained at completed confluence...” 23. P.7, line 11, should be “... MMPs that decreases the migration capacity when compared to MSC cultured at low confluence” What was the seeding density in that study? 24. P.7, line 15-16, what was the route of MSC administration in that study? 25. P.7, line 22-23, what was the route of MSC administration in that study? 26. P.8, line 2-4, this statement is not clear. Please rewrite. 27. P.8, line 6-7, This statement is not clear. Please rewrite and add a reference. 28. P.8, line 13-14, clarify what “in this study” refers to. Please add a reference. 29. Figure 2 should be referred to in the manuscript. 30. P. 9 line 11-12. More explanations are needed for this statement. Why is the use the US, magnetic or electric field to enhance MSC homing regarded as not very practical? 31. Suggest adding a section on “future research directions” to increase the impact of the review article. 32. The English of the manuscript should be improved. 33. Table 1: the source of MSC and the target tissue should be mentioned. 34. Add a short description to both figure 1 and figure 2. Add an abbreviation list in figure 2.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 22478

Title: Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy?

Reviewer's code: 02446158

Reviewer's country: Belgium

Science editor: Fang-Fang Ji

Date sent for review: 2015-09-06 15:47

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The current submitted review highlights the topic of MSC homing and migration. The subject is quite interesting for the readers in light of all developments and accumulated information related to cell therapy/regenerative medicine fields. The authors further discussed the approaches that have been used to improve both processes. The review remains quite very descriptive and significantly lacks deep interpretations and discussions. The quality and consistency of the review should be elevated before publication. Here some points that I addressed and could be discussed in view of the improvement of the manuscript: 1- The proposed table is roughly descriptive. Some parts are not discussed in the main text like the growth factors receptors 2 - The potential pro-coagulant activity of MSC that could hamper both processes should be discussed 3- A simple comparison between all studied MSC should be discussed 4- Homing could be critical for allowing the transplanted MSC to reach the target organ but, according to what is published both in preclinical and clinical studies, it seems not related to engraftment regulation. Modifying parameters that may improve homing could modulate positively/negatively the plasticity and/or engraftment of the cells. The authors should



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discuss such issue 5- The nature of the substrate on which the MSC proliferate in vitro/ the passaging number (different depending on the MSC used) may also significantly impact their homing. The authors should also provide a brief update on what could alter the membrane expression profile of the MSC in vitro 6- The CXCR4/CXCL12 axis strategy (major discussed point) is not yet conclusive. Hence, the authors should provide at least of the more attractive current other investigated issues.