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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 47129

Title: Regenerative Therapy of Platelet Rich Fibrin Combined with Allogenic Bone Marrow-Derived Stem Cells on Rats' Critical Sized Mandibular Defects

Reviewer's code: 02446319

Reviewer's country: South Korea

Science editor: Jin-Lei Wang

Reviewer accepted review: 2019-03-08 04:25

Reviewer performed review: 2019-03-10 08:02

Review time: 2 Days and 3 Hours

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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced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

SPECIFIC COMMENTS TO AUTHORS

Thank you for great manuscript about Regenerative Therapy of Platelet Rich Fibrin Combined with Allogenic Bone Marrow-Derived Stem Cells on Rats' Critical Sized Mandibular Defects. Your results is almost histological data. if possible, I think it's more

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valuable manuscript if there are some Radiologic data (CT) .

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Name of journal: World Journal of Stem Cells

Manuscript NO: 47129

Title: Regenerative Therapy of Platelet Rich Fibrin Combined with Allogenic Bone Marrow-Derived Stem Cells on Rats' Critical Sized Mandibular Defects

Reviewer's code: 02567328

Reviewer's country: Italy

Science editor: Jin-Lei Wang

Reviewer accepted review: 2019-03-08 08:11

Reviewer performed review: 2019-03-12 13:39

Review time: 4 Days and 5 Hours

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

SPECIFIC COMMENTS TO AUTHORS

In this manuscript the authors report data regarding the use of Platelet rich fibrin (PRF) combined with mesenchymal stem cells (MSCs) for mandibular defects. The use of PRF alone or in association with different type of MSCs for bone defects and regeneration

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are already reported in literature. The results described in the manuscript are interesting but does not add anything new. It would be interesting if the authors identified how the presence of the MSCs makes it more effective bone regeneration in the presence of PRP. In the text the authors state" PRF membranes released autologous growth factors gradually expressed a stronger and more durable effect on proliferation and differentiation of rat osteoblasts". MSCs improve release of these growth factors or they themselves produce other factors that in sinergic way promote bone regeneration? The article must be improved by adding new data, so there are only preliminar data and a deepening is required . Moreover: - To which passage were the MSCs used? -For complete MSC characterization, it is necessary demonstrated also their ability to differentiate in mesengenic lineages - Why the authors did not use alizarin red as a dye to demonstrate bone formation? Alizarin Red is used to determine (qualitatively and quantitatively) the presence of calcific deposition by cells of an osteogenic lineage also at early stage.

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[Y] No

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Name of journal: World Journal of Stem Cells

Manuscript NO: 47129

Title: Regenerative Therapy of Platelet Rich Fibrin Combined with Allogenic Bone Marrow-Derived Stem Cells on Rats' Critical Sized Mandibular Defects

Reviewer's code: 00504800

Reviewer's country: United States

Science editor: Jin-Lei Wang

Reviewer accepted review: 2019-03-08 20:01

Reviewer performed review: 2019-03-17 22:59

Review time: 9 Days and 2 Hours

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

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Awadeen et al. demonstrates that platelet rich fibrin (PRF) membranes seeded with MSC has the potential to heal critical-sized bony defects, using a rat mandibular model. Overall the manuscript is easy for the reader to follow. The

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study is statistically well powered and the description of the analysis is good (with one question, noted below). I think the manuscript is worthy of publication once several issues are addressed. 1. For the most part, the differences between treatment groups appear to be distinct, and the statistics well done. I am not a statistician, but I question the use of the LSD post-hoc test. The LSD is most liberal post-hoc ANOVA test, meaning that it will find the most comparisons between groups to be significant. A good example of this is in Table 2, Week 1, LSD comparing groups II and III in which a difference between 0.9 +/- 0.03 and 0.88 +/- 0.02 was found to be significant, which is hard to believe. Is there another post-hoc test (such as Tukey's) which is more stringent that could be applicable here? 2. Is it known which passage the BMSC were at the time of thawing, and at the time of the in vitro experiments? It is not clearly stated in the Methods how long, or for how many passages, BMSC were cultured after thawing. 3. The characterization of MSC surface markers (page 9) is not well written, and the analysis does not clearly demonstrate consistent MSC marking. At first it sounds as if all antibodies are FITC conjugated, but then some PE conjugates are noted. For the histograms in Figure 2, CD34 and CD45 are usually <5%, CD90 and CD105 are usually >95%; see Alge DL et al., J Tissue Eng Regen Med 2010, among many others, for examples. In Figure 2D, a vast majority of the cells shown in the scatter plot are positive for CD34, CD45 or both, and I don't understand how the authors can state that only 6.8% of the cells are negative for these markers. The histograms for CD105 and CD90 are very poorly positive compared to other studies (for example, Alge DL et al. 2010). The results shown are not consistent with what others have reported for rat BMSC. Adding isotype control curves to the histograms would also be helpful. 4. Figures 3-5: While in some cases it is clear to the reader where the bony defect is located, if the authors could draw a circle to delineate the defect areas from the neighboring normal bone, particularly for group III where new bone growth is apparent, it would be

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helpful. 5. Four weeks is a relatively short period for bony defect healing. Is there a reason (other than cost and expediency) that the authors sacrificed the animals at 1, 2 and 4 weeks instead of, say 2, 4 and 8 weeks, to see more complete bone healing? Minor comments/corrections: Line 192: "Fluorescein" should be "fluorescence" Lines 288-301: This would be easier for the reader to follow if the authors consistently called the groups I, II, and III, and gave more specific figure information - for example, at end of line 291 say (Fig. 4A-C); say (Fig. 4D-F) at the end of the sentence on line 297. Line 342: …when they ARE used as a… Line 347: …growth factors , WHICH gradually… Line 355: Please revise the sentence beginning "A progressive polymerization…", it is confusing as written Line 368: …membrane IS superior… Line 369: …proliferation , and IS suitable… Line 387: performed is not the right word; detected would be better Line 397: The statement that macrophages decreased after the 4th week of the study is not correct, since the study only went for 4 weeks – please revise. Line 399: Delete "Glynne"

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