

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 58180

**Title:** Vascularization and osteogenesis in ectopically implanted bone tissue-engineered constructs with endothelial and osteogenic differentiated adipose-derived stem cells

**Reviewer's code:** 03811591

**Position:** Peer Reviewer

**Academic degree:** BSc, PhD

**Professional title:** Research Associate

**Reviewer's Country/Territory:** Canada

**Author's Country/Territory:** Serbia

**Manuscript submission date:** 2020-07-12

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-09-03 17:17

**Reviewer performed review:** 2020-09-07 23:48

**Review time:** 4 Days and 6 Hours

<b>Scientific quality</b>	<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 Grade E: Do not publish
<b>Language quality</b>	<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
<b>Conclusion</b>	<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
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	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**

This research manuscript describes the effects of combining endothelial and osteogenic differentiated adipose-derived mesenchymal stem cells (ADSCs) with platelet rich plasma (PRP) on vascularization and osteogenesis in ectopically implanted bone tissue engineering (BTE) constructs. The authors have prepared 3 types of ectopic BTE constructs: I - BTE constructs containing endothelial and osteogenic differentiated ADSCs, combined with PRP and seeded onto bone mineral matrix (BMM) carrier - BPEO constructs, II - BTE constructs containing uninduced ADSCs, combined with PRP and seeded onto BMM carrier - BPUI constructs, and III - BTE constructs that contained only BMM carrier - BC constructs (control). These constructs were implanted ectopically into interscapular subcutaneous tissues of mice for up to 8 weeks. Percentage of vascularization was higher in BPEO implants compared to BPUI implants. Expression levels of endothelial-related genes in BPUI implants were generally higher than those in BPEO implants. Additionally, the authors state that BPEO implants had strong osteocalcin (a late osteogenic marker) immunoexpression. There are many comments that the authors need to address. 1. In introduction, the authors should cite and discuss the previous studies on BTE constructs containing endothelial cells and osteoblasts, and discuss the novelty of this study. 2. The authors should provide data for expression of endothelial-related genes in ADSCs after 12 days of in vitro endothelial differentiation induction. 3. Page 20: "Relative expression levels of endothelial-related genes in implants were generally higher in BPUI compared to BC and BPEO implants. One of the reasons for such expression pattern in BPUI implants was probably the presence of biological factors released upon PRP activation since these factors accelerate and improve ADSCs in vivo differentiation." Do the authors mean that these endothelial-related genes are highly expressed in ADSCs undergoing endothelial differentiation, but slightly

expressed in mature endothelial cells and ADSCs after 12 days of in vitro endothelial differentiation induction? 4. Page 25: “In spite of all favorable features if BPEO implants, these implants had strong regression of the tissue between BMM granules...” Which figure shows this sign? 5. Figure 2a: Why expression level of Vwf gene in all the implants was consistently lower than that in the calibrator sample from week 1 to week 8? 6. Figures 6-8: I don’t find any obvious differences between the groups in terms of immunoexpression levels of VEGFR-2, CD31 and osteocalcin based on the figures given. The authors should also provide the quantitative data and perform statistical analysis. 7. There are a few typo errors. For example, “B implants” (page 21) and “B group” (pages 22 and 24).

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**Title:** Vascularization and osteogenesis in ectopically implanted bone tissue-engineered constructs with endothelial and osteogenic differentiated adipose-derived stem cells

**Reviewer's code:** 04650978

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Full Professor, Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Serbia

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**Reviewer chosen by:** Ya-Juan Ma

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**Review time:** 9 Days and 3 Hours

<b>Scientific quality</b>	<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
<b>Language quality</b>	<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
<b>Conclusion</b>	<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
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	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 authors found BPEO constructs have favorable impact on vascularization and osteogenesis. It is very interesting and important. the results will help for bone regenerative medicine.