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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Stem Cells
ESPS manuscript NO: 11414
Title: The ability of bone graft substitutes to support the osteoprogenitor cells: an in-vitro study
Reviewer code: 00609371
Science editor: Ling-Ling Wen
Date sent for review: 2014-05-20 21:15
Date reviewed: 2014-05-21 09:34

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

COMMENTS TO AUTHORS

The major concerns: 1) The unquantified, incomplete live/dead staining &SEM data. Fig 1 shows only unquantified data from 3 (out of 7) BGSs. These data are inconclusive. 2) The unacceptable interpretation of ALP data. The authors used ALP as the only osteogenic marker in this manuscript without mention any potential alternative interpretation the data. In fact, ALP is expressed by a variety of cells, including MSC. 3) Completely lack of in vivo data. In vitro data alone could be misleading.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Stem Cells
ESPS manuscript NO: 11414
Title: The ability of bone graft substitutes to support the osteoprogenitor cells: an in-vitro study
Reviewer code: 02446114
Science editor: Ling-Ling Wen
Date sent for review: 2014-05-20 21:15
Date reviewed: 2014-05-26 10:57

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

COMMENTS TO AUTHORS

This study should check the Alizarin Red S staining, bone-relative gene expression and in vivo assay to confirm their conclusion.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Stem Cells
ESPS manuscript NO: 11414
Title: The ability of bone graft substitutes to support the osteoprogenitor cells: an in-vitro study
Reviewer code: 00503929
Science editor: Ling-Ling Wen
Date sent for review: 2014-05-20 21:15
Date reviewed: 2014-06-04 10:21

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

COMMENTS TO AUTHORS

This manuscript describes, in a clearly written style, a series of experiments in vivo attempting to define which, out of a panel of commercially available materials used as bone graft substitutes, performs best with respect to colonization by osteogenic cells and expression of a differentiation marker (alkaline phosphatase). The study was carried out in a system which minimizes the relevance of mechanical factors on the outcome, and care was taken to normalize alkaline phosphatase activity relative to the number of cells in the same, as estimated from the DNA content. However, it seems that these materials were highly heterogeneous, not only in chemical composition, but in degree of porosity, consistency, stability in the medium for a period of weeks, and so on. Therefore, best performance in this study does not necessarily relate to an easily identifiable property, or even a combination of properties. One of the risks of this situation is that one product that performs much better than the rest in this assay may receive strong endorsement without any clear explanation, and without evidence that this best performance will be accompanied by better clinical results in the in vivo situation, where mechanical factors are decisive. There is no doubt about the practical relevance of the issues involved, and the authors are to be commended for careful design of the quantitative experiments with alkaline phosphatase. Other aspects, however, are very difficult to quantify, and this applies to the procedures used to “enhance” the homogeneity of contact of the seeded cells with the materials, which vary from granular powders to soft solids, and which are not necessarily mixed

with the cells to the same extent, no matter how much you stir the plates. I also find it difficult to see how volume of these very different preparations could be adjusted with the necessary precision, with the help of a beaker. Most importantly, much of the conclusions depend on images (Figure 1) which can be interpreted in different ways, and are certainly not quantitative. I am especially concerned about the disparity between cell staining (left) and scanning electron microscopy (right) for the same materials (see 1c and 1d, for instance). Cells are plentiful in the left panels, and undetectable in the right panels, at least in some cases. Also, totally different electron microscopy aspects are offered for the same material, when one compares the colonization by freshly harvested vs in vitro expanded cells (again, compare 1c to 1d, for instance). I find it hard to accept that the structure of the material to which no cell is attached becomes radically different as a consequence of different sources of the same cell type being present in the same culture. I think these issues need to be addressed in order to make their conclusions more solid. An additional issue (which may or may not be trivial) concerns the fact that the research is supported by an educational grant from an organization which has the same name as the manufacturer of most products tested. I understand only one product from that supplier performed exceptionally well, and others from the same source were not outstanding. This may simply reflect the objective findings of the authors, but it may raise doubts in the minds of commercial competitors, who did not have a comparable material for testing, especially if the funding is ultimately shown to come from the same source as the test material. I would recommend that the authors clarify whether this outstanding material is only available from this specific source, or can be obtained from more than one supplier, and if so, whether it also performs exceedingly well in their hands.