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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells
ESPS manuscript NO: 20353
Title: Migration of bone marrow progenitor cells in the adult brain of rats and rabbits
Reviewer's code: 02446204
Reviewer's country: Japan
Science editor: Xue-Mei Gong
Date sent for review: 2015-06-07 19:59
Date reviewed: 2015-06-08 14:34

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

The paper is very well written, presenting a unique approach to the treatment of brain diseases by combining the technique of an effective gene transfer using rSV40 vectors and that of stem cell therapy using bone marrow cells. Authors also showed that, even under physiological conditions without brain injuries, the rSV40 vector-transduced bone marrow-derived cells migrated to the brain, suggesting the steady-state supplementation of brain progenitor cells from bone marrow in healthy animals. An additional great point of this paper is that it is based on the observations of particularly long terms (i.e. ~ 16 months). Thus, the results obtained from their experiments are exceptionally valuable, even providing a solution to the controversy regarding the fate of bone marrow cells in the brain. Thus, the paper has provided valuable information for the technical development of regenerative medicine and also for an advanced understanding of brain homeostasis. I have only two minor suggestions. One is that it would be better if authors would write additional comments regarding the characters of the bone marrow cells that produced brain progenitor cells. Although authors properly mentioned hematopoietic stem cells and bone marrow stromal cells, there are still other types of cells showing multipotency including MUSE cells (Wakao S et al., Proc Natl Acad Sci U

S A. 2011;108:9875-9880) and mesenchymal stem cells (MSC) (Houlihan DD et al, Nat Protoc. 2012; 7:2103-2111, Niibe K et al., PLoS One. 2011;6:e17610). Because this paper will be read by researchers of broad fields including the experts in MUSE cells and MSCs, a brief comment from these standpoints will help readers to more easily understand the contents of the paper. The other suggestion is that it would be better if authors would add brief descriptions regarding the effect of CCR5 knockdown in Abstract. This finding is very interesting. Moreover, it has provided powerful information for an advancement of their unique system for in vivo gene delivery. In any event, I believe that this paper is worth-publishing in World Journal of Stem Cells. A grammatical error: 1) In page 22, line 10, the sentence "However the ultimate proof that …" should be corrected as "However, the ultimate proof that …".

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells
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Title: Migration of bone marrow progenitor cells in the adult brain of rats and rabbits
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Reviewer's country: United States
Science editor: Xue-Mei Gong
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] 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
[Y] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This manuscript reviews the potential for use of bone marrow-derived cells in transplantation toward the goal of neuronal augmentation. The authors review their work in which they use intrafemoral gene delivery for introduction of bone marrow-derived cells that may contribute to neuronal augmentation in the brain. The paper presents some interesting data, and re-poses some well-established questions, but may not yet be ripe for a review. Some aspects of the review are not particularly timely. In fact, most of the references are seven or more years old. Has the field not progressed during that time? It is already established that neurogenesis occurs in adults, and a review of this area may be superfluous. There also is evidence that an uncharacterized bone marrow-derived population of cells can contribute to appearance of neuronal precursors. The authors present the viewpoint that negative results reported elsewhere in transplantation experiments may relate to the time interval involved between introduction of the cells and analysis of the results. A critical question not addressed is if full maturity of the cells takes place and what type of neurons these might be. As the authors point out, the trans-differentiation mechanisms are not known in any detail. Expansion of information or speculation in this area would contribute significantly to the

paper. Homing mechanisms might be further examined at a molecular level, as could the differentiation process itself. There is little information presented on these issues. Also, as the authors point out, the experiments they review from their work does not address the characterization of the population(s) of cells that lead to the phenomena described occurring in the brain. The potential information that exists in this area should be addressed. A major portion of the paper is devoted to CCR5 effects or related ones, and this subject is presented as a major issue in the concluding remarks. However, this issue is not even mentioned in the abstract, and it is not completely clear if effects are direct or indirect. That the authors "confirm here that BM progenitor cells participate in neurogenesis in the adult brain, and migrate towards the DG and SVZ" is not entirely novel, and I am unsure if a review of the established data in this area is necessary. Regarding figures: Fig 9 adds little to the paper and Fig 2 deserves additional explanation in the legend ("LV," "C cells").

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells
ESPS manuscript NO: 20353
Title: Migration of bone marrow progenitor cells in the adult brain of rats and rabbits
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Reviewer's country: United States
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] 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	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is a very interesting and well-written review of a relatively novel use of in vivo gene delivery of the rSV40 vectors to increase availability of bone marrow (BM) derived progenitor cells for long-term transgene expression for potential treatment of neurological insults or disorders. The authors provide a fairly comprehensive overview of this line of inquiry and provide a strong case of the importance of CCR5 in migration and differentiation of the BM cells to the brain. The information provided is current, but the use of several undeciphered acronyms makes the reading somewhat difficult at times. Providing a list of abbreviations would help, or at least make sure that all acronyms are properly deciphered. There are a few minor editorial suggestions provided below: P2, L3: remove capitalization on Central Nervous System P2, L6 (from bottom): change "Kaicic" to "kainic" P4 L4 (from bottom): insert comma after "challenges" P6, last 3 last sentence is awkward. Put comma after "primates", "neurons", "zone", and "granular neurons"; change "Humans Neurons" to "human neurons". P9, L7: change "felt" to "thought" P15, L5: change "of our group" to "by our group" P16, L9: change "rare" to "few" P16, L17: change "resident" to "reside" P16, last line: change "4 months" to "at four months" P18, L11: change "16 month" to "16-month" P18, L13: put comma after "kidney)" and

change "that" to "which" P21, L11: change "criticalo" to "critical" P21 L2 (from bottom): change "This experimental design" to "Such experimental designs" P26, L1: change "Humans" to "humans" P27, L2 & 3: decipher or describe "RANTES. MIP-1, and CCR5 P31, L5: decipher "PBMC" (progenitor bone marrow cells?) P32, L4 and 7: decipher BBB and tPA P34, L3 (from bottom): insert "at" between "DG" and "4"

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ESPS PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[Y] High priority for publication
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[ ] Grade E: Poor		[Y] No	[ ] Major revision
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Comment: BM-derived progenitor cells migrating in the CNS express markers of neuronal precursors or immature neurons have been explored, showing inconsistent efficacy in repair of injury. Further studies show that only a fraction (less than 5% BM-derived progenitor cells) are induced to express markers of neuronal precursors or immature neurons. The manuscript addresses their approach that injection of SV(RevM10.AU1) into the rabbit bone marrow (BM), transgene- positive cells were seen in the dentate gyrus (DG) (Fig. 6). That is of great interst as it offers a new perspective. Of particular, I appreciated the authors cited 136 references with Adding bonus includes 9 figures, 3 Tables, making the manuscript much easier to read and understand. However, editing is needed to enhance the clarity, cohensiveness, and logic flow. Some examples are as follows. Specific comments: 1) An introductive paragraph governing the content should be placed before the first sub-headline. 2) Rephrase the subheading: Current "Gene delivery to bone marrow progenitor cells" doesn't reflect its content. 3) The manuscript addresses their approach that injection of SV(RevM10.AU1) into the rabbit bone marrow (BM), transgene- positive cells were seen in the dentate gyrus (DG) (Fig. 6). Some places state rats: Clarification is needed for different species.. 4) Table title should be placed on the

top of a table, not below the table as shown now. Try to revise the table titles as much summarized and descriptive as possible. 5) Restructure the abstract to cover all contents, to be concise. 6) Rephrase the title to point out it's about rat brain only, not human. 7) Page 2, Abstract: "Permanent" should be referred to "long-term." 8) Elaborate more on "an increase of BM progenitor cells migrating towards the brain following experimental seizure" for its possible mechanism of migration and engraftment. E.g., what's cytokine/chemokine profile upon experimental seizure. CCR5 ligand production? 9) Fig. 2: What is LV? It needs fully describing all 4 types cell in figure legend, not in text. 10) Fig. 4: legend "Bone marrow derived cells can migrate to the rat hippocampus" -- "Is it injured hippocampus" or normal one? It's well know stem cells (MSC) attracted to injury, not normal tissue. 11) Given redundancy of cytokines and chemokines, cell membrane chemokine receptor, CCR5, is just one aspect. 12) Cite more literature for the past 5 years. 13) Page 22: "We reported above that permanent BM-directed gene transfer using recombinant SV40-derived vectors led to expression of the genes delivered to the BM in mature neurons, and thus without CNS lesion." That's not logical. "delivered to the BM in mature neurons"????? 14) Overall, only structural analysis (location of cells, markers) is shown, how about the function?