

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60359

Title: Disease modifying treatment of spinal cord injury with directly reprogrammed neural precursor cells in non-human primates

Reviewer's code: 05191122

Position: Peer Reviewer

Academic degree: DSc, PhD

Professional title: Full Professor

Reviewer's Country/Territory: Poland

Author's Country/Territory: Russia

Manuscript submission date: 2020-10-27

Reviewer chosen by: Xi-Fang Chen (Quit in 2021)

Reviewer accepted review: 2020-11-13 10:57

Reviewer performed review: 2020-11-18 22:17

Review time: 5 Days and 11 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" 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 Grade E: Do not publish
Language quality	<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
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	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

Manuscript NO: 60359 Spinal cord injury (SCI) is a serious damage, and lack of effective treatment for patients is leading to permanent disability. Cellular therapies with neural stem/progenitor cells are currently on focus in regenerative medicine to restore spinal cord function, however, there is an ethical problem for NSC/NPC acquisition. Generation of autologous or allogeneic human NSCs/NPCs by direct reprogramming of somatic cells is a solution to overcome the ethical issue. In this manuscript the Authors introduced the study of the safety and efficacy of intraspinal transplantation of allogeneic directly reprogrammed NPCs (drNPCs), created from the bone marrow mononuclear cells, in NHP model of complete subacute SCI. The study are well documented, however, some issues need to be addressed before final acceptance for publication. The Core tip is too short, only one sentence, and should be extended. Methods. The methodology of preparation of Directly Reprogrammed Neural Precursor Cells should be briefly described in the current manuscript not only refer to the reference no 11 by Ahlfors JE et al. There is no clear if flow cytometry was performed by using the same antibodies as for ICC and how the cells were prepared for analysis? Discussion. In the Discussion section there is missing an explanation/hypothesis why multipotent Sox2+ drNPCs do not differentiate into neuronal or glial cells if they are tissue-specific neural precursor cells? Conclusion. The last point of conclusion "Directed drNPC migrationmay provide exosome and paracrine trophic" is speculative and should be removed or rephrased because the Authors did not studied the effect of exosomes or trophic factors on drNPC migration.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60359

Title: Disease modifying treatment of spinal cord injury with directly reprogrammed neural precursor cells in non-human primates

Reviewer's code: 02945510

Position: Peer Reviewer

Academic degree: PhD

Professional title: Full Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Russia

Manuscript submission date: 2020-10-27

Reviewer chosen by: Xi-Fang Chen (Quit in 2021)

Reviewer accepted review: 2020-11-12 01:24

Reviewer performed review: 2020-11-21 05:32

Review time: 9 Days and 4 Hours

Scientific quality	[<input checked="" type="radio"/>] Grade A: Excellent [<input type="radio"/>] Grade B: Very good [<input type="radio"/>] Grade C: Good [<input type="radio"/>] Grade D: Fair [<input type="radio"/>] Grade E: Do not publish
Language quality	[<input checked="" type="radio"/>] Grade A: Priority publishing [<input type="radio"/>] Grade B: Minor language polishing [<input type="radio"/>] Grade C: A great deal of language polishing [<input type="radio"/>] Grade D: Rejection
Conclusion	[<input checked="" type="radio"/>] Accept (High priority) [<input type="radio"/>] Accept (General priority) [<input type="radio"/>] Minor revision [<input type="radio"/>] Major revision [<input type="radio"/>] Rejection
Re-review	[<input checked="" type="radio"/>] Yes [<input type="radio"/>] No
Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No

SPECIFIC COMMENTS TO AUTHORS

The study carried out in this manuscript is excellent and potted spot lights in treatment of spinal cord injury. The authors done complete thoracic SCI in mature *Macaca mulatta* and then injected intraspinal transplantation of 5 million of programmed neural precursor cells (obtained from bone marrow of a female of the same species) in rostral and caudal to the lesion site two weeks post injury by 28G needle attached to a Hamilton 500 microsyringe, The treated animals were follow up after 12 weeks by hind limb examination, MRI and monitoring of transcranial myogenic electrical potentials, MEPs and SSEPs for m. abductor hallucis(AH), m. tibialis anterior, (TA) and m. quadriceps femoris. Besides immunohistochemical assessments of β -tubulin III, Nestin , SOX2 ,MAP2 , NF200 , GFAP , BDNF and macroH2A.1. The done work is of high quality. The different parts of the manuscripts are well constructed and tables and figures are excellent and highly illustrated the degree of improvements. The authors attributed spinal improvements to the presence of multipotent Sox2+drNPCs. Please correct the sentence 1 of conclusion by delete (no) I accept and strongly recommended publication as it is for the valuable information in the manuscript.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60359

Title: Disease modifying treatment of spinal cord injury with directly reprogrammed neural precursor cells in non-human primates

Reviewer's code: 05384690

Position: Editorial Board

Academic degree: DDS, MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Russia

Manuscript submission date: 2020-10-27

Reviewer chosen by: Xi-Fang Chen (Quit in 2021)

Reviewer accepted review: 2020-11-11 08:43

Reviewer performed review: 2020-12-09 11:32

Review time: 28 Days and 2 Hours

Scientific quality	<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
Language quality	<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
Conclusion	<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
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	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 evaluated the safety and neurological recovery of the transplantation of directly reprogrammed neural precursor cells (drNPCs) in the non-human primate (NHP) model of spinal cord injury. The functional improvement after the treatment of drNPCs was significant and the involvement of NHP might offer stronger evidence for the clinical translation of drNPCs treatment. However, there are some flaws in this article that should be taken into consideration. Major concerns: 1. In this research, drNPCs were generated from BMSCs and used in the subsequent transplantation. Therefore, the characterization of drNPCs was important. It is better to detect the markers of BMSCs, such as CD44 and CD90, to verify the reprogramming efficiency. 2. What is the rationale for the dose of 5×10^6 drNPCs in this research? There are many kinds of vehicle for the sustentation of cells such as artificial cerebrospinal fluid or PBS. What is your rationale for using Hanks' solution in this study and would the transplant vehicle affect cell viability? 3. All the recipient NHP were male and the donor NHP were female. It would be better to elicit the influence of sex difference in the treatment outcome. 4. When it comes to lesion volume analysis, it would be more intuitive to show the image of histological section.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Manuscript NO: 60359

Title: Disease modifying treatment of spinal cord injury with directly reprogrammed neural precursor cells in non-human primates

Reviewer's code: 05191122

Position: Peer Reviewer

Academic degree: DSc, PhD

Professional title: Full Professor

Reviewer's Country/Territory: Poland

Author's Country/Territory: Russia

Manuscript submission date: 2020-10-27

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2021-01-25 08:21

Reviewer performed review: 2021-01-26 09:16

Review time: 1 Day

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" 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
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<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
Peer-reviewer statements	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



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

The Authors address to most of my comments sufficiently. I accept the manuscript in the present form.