ANSWERS TO REVIEWERS' COMMENTS:

Reviewer 1

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 reprograming efficiency.

We are grateful to the Reviewer for this remark. The precise characterization of drNPCs has been done in the previous work of J-E Ahlfors et al. [Ahlfors et al. Stem Cell Research & Therapy (2019) 10:166 https://doi.org/10.1186/s13287-019-1255-4]. Kindly see below a fragment of Fig.2 from this article describing CD44 and CD90 expression.

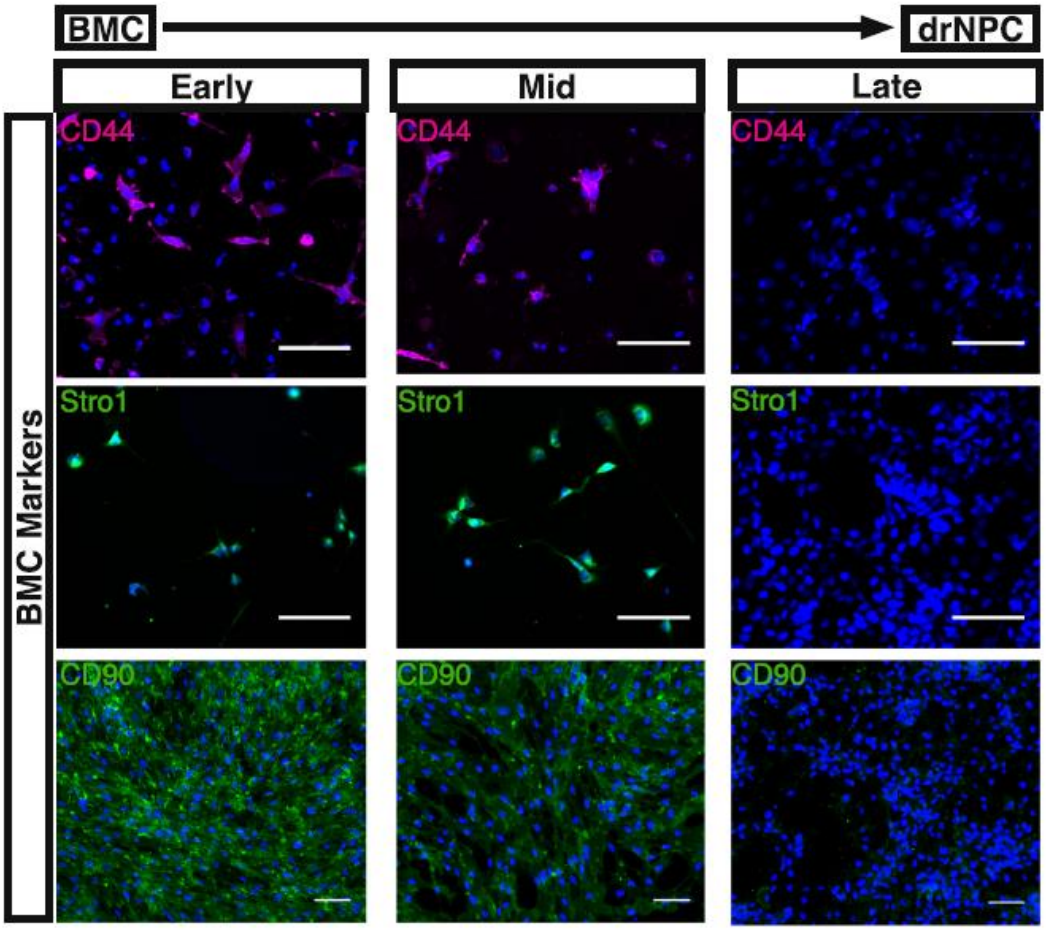


Fig. 2 BMC to drNPC reprogramming. In vitro cultures of bone marrow cells (BMCs) during reprogramming to drNPCs. At early time-points (days 1–3 in vitro), BMC-specific markers CD44, Stro1, and CD90 are expressed and no NPC-specific markers Nestin, Pax6, or Sox2 are observed. By the mid time-points (days 6–7 in vitro), downregulation of BMC-specific markers occurs. At late time-points (days 14–16 in vitro), no BMC-specific
markers are observed (https://doi.org/10.1186/s13287-019-1255-4)

2. What is the rationale for the dose of 5 × 106 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?

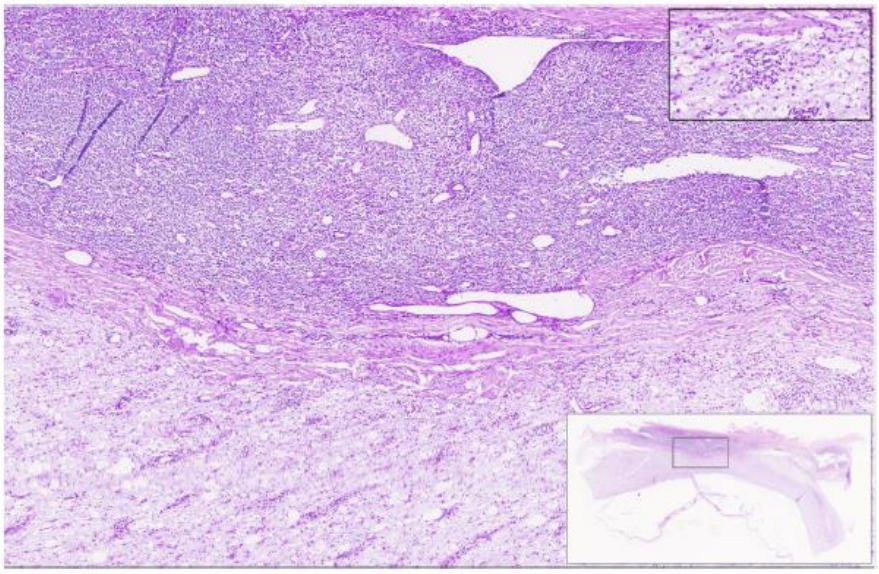
The number of 5×10^6 drNPCs is the maximum number of cells which might be suspended in a volume of 100 ul. The volume of 100 ul was chosen based on the optimal injection rate (5 ul/min) and the maximal time of drNPCs 95% survival rate in the syringe at room temperature (20 mins). Hanks' solution was chosen because the cell viability in it within 20 mins practically did not differ from the growth medium.

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.

The assessment of the sex difference influence in the treatment outcome was not a goal of this work. We can only assume that autologous cell transplantation should be more effective than allogeneic one.

4. When it comes to lesion volume analysis, it would be more intuitive to show the image of histological section.

We used histological sections to assess the lesion in the experimental and control groups, as well as for the analysis of inflammatory infiltration, glial response and fibrosis. We have added some Nissl and H&E stained sections in the Supplement (Suppl.Figs 7 – 10, kindly see an example below). However, we believe that for quantitative assessment of the lesion volume, MRI sections of native non-fixed spinal cord are much better.



Supplementary Fig. 8. Example of the H&E staining of the sagittal spinal cord section through the center of the injury (LC3 monkey).

Reviewer #2:

We are very grateful to the Reviewer for the high assessment of our work.

Please correct the sentence 1 of conclusion by delete (no)

We have double checked the first sentence of conclusion and still think that "no" should be there: "**There was no evidence of safety concerns regarding drNPCs transplantation into the spinal cord for at least 12 weeks post transplantation**…"

Reviewer #3:

We would like to thank the Reviewer for the work and for the high assessment of our study.

The Core tip is too short, only one sentence, and should be extended.

The Core tip in the previous version had been generated automatically during submission. We have corrected it.

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 all.

Corrected on page 3:

Briefly, direct reprogramming was made by means of transient transfection of a cocktail of three transcription factors: Musashi-1 (Msi1), Neurogenin-2 (Ngn2), and methyl-CpG binding domain protein 2 (MBD2).

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?

For flow cytometry, directly labelled primary antibodies were used. For ICC/IHC we used different nonlabelled antibodies except antibodies against SOX2, and macroH2A.1. In the last two cases PE labelled primary antibodies were used both for FC and ICC/IHC. However, in these cases we used secondary Alexa labelled antibodies to amplify a signal.

We have added the description of cell preparation on page 4:

Immunophenotyping of drNPCs

Cells were cultured for 14 days in complete growth medium followed by fixation with ice-cold buffered 4% paraformaldehyde for 30 min. For flow cytometry cells were detached with StemPro Accutase followed by fixation with buffered 4% paraformaldehyde for 10 min.

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?

We are grateful to the Reviewer for this remark. We hypothesize that in this non-immunosuppressed allogeneic model, only the undifferentiated human drNPC were able to evaded the host immune response adequately for there to be surviving Sox2+ drNPCs at the end of the study.

We tried to describe this hypothesis in the Discussion on page 18:

“In the current study we used allogeneic rather than autologous drNPC cells <…> This likely resulted in a lower number of surviving cells at 12 weeks post-transplant, and likely did not allow for the survival of any differentiated cells. The surviving Sox2+ donor cells nevertheless allowed for significant functional recovery by

supporting neurogenesis and synaptogenesis of the host neurons despite the absence of immunosuppression."

Conclusion. The last point of conclusion "Directed drNPC migration .....may 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.

We have corrected the Conclusion.

In conclusion, the authors would like to once again thank all Reviewers for their valuable comments, which undoubtedly contributed to the improvement of the quality of the article.