

OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-23-01414

Title: HiPSC-differentiated NPC derived small extracellular vesicles mitigate RGC degeneration in a mouse model of optic nerve injury

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COMMENTS TO AUTHORS

The article reveals that intravitreal injection of hiPSC-NPC-sEVs protects retinal ganglion cell against degeneration and allows progress towards obtaining effective therapies against diseases as prevalent as glaucoma.

The work is technically correct and presented in a clear and concise manner. The main uncertainty is that in the final part, authors identify a series of miRNAs enriched in the most efficient sEVs and assume that the observed effects are due to these miRNAs, but to make that statement it would have to be demonstrated experimentally by injecting those miRNAs alone and observing the same effect. In the present form it can not be ruled out that unidentified proteins or nucleic acids in sEVs could play an important role as well. Therefore, the conclusions should adhere to what is described in the results.

There are minor aspects that could improve the presentation of the results:

- In the summary it is confusing to talk about NPCs transplantation and then jump without any connection to the sEVs.
- In order to better interpret the relevance of the work, it is necessary to indicate the prevalence of diseases that lead to RGC degeneration or at least that glaucoma is the main cause of blindness.
- The orientation of the retinas in all photos should be the same (figure 2D vs figure 4A)
- the number of mice treated and retinas analyzed should be clearly indicated in the material and methods and in the figure legends.
- The nature and form of action of the PKH67 compound would have to be indicated.
- With respect to this and other similar studies with intravitreal injection of sEVs, could authors infer sEVs kinetics? Do the RGCs assimilate them within 48 hours? And if the RGCs were already damaged, would there be any effect? It would be interesting to discuss this topic to understand what a potential treatment should be like.