OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00840
Title: A porous collagen scaffold with axially-aligned luminal conduits combined with neural stem cells promoting the recovery of spinal cord injury
Reviewer's Name: Itzhak Fischer
Reviewer's country: USA

COMMENTS TO AUTHORS

The study is focused on transplantation experiment in a model of SCI using a porous collagen scaffold with aligned channels seeded with NSC in order to promote migration of the transplanted cells and direct growth to achieve connectivity across a transection lesion and functional recovery. The authors report "motor functional recovery, neural generation, and axon growth, meanwhile without an additional introduction of adverse inflammatory response". Although this approach is not new careful documentation of efficacy analysis of the mechanisms of repair remains valuable.

Strengths:

The importance of treatment of SCI

The use of aligned and porous scaffolds that can be combined with cells transplants and allow directional axon growth

The combination of anatomical and functional analysis

Weaknesses:

Conceptual issues

* The use of aligned scaffolds is difficult to apply to the clinically relevant contusion injury, and while the use of a transection injury is appropriate to test the efficacy of this strategy, it is unlikely to be relevant for clinical application.
* It is not clear why the authors use embryonic hippocampal neurons for repair of SCI rather than spinal neural stem cells. Again, the use of primary cultures rather than stocks of NSC that can be characterized and banked for multiple transplants limits the relevance of this study.
* The authors state that they hope to induce migration of transplanted NSCs, promote the connection between distal and proximal axons and facilitate the infiltration of immune cells into the core of scaffold. However, it is a descriptive list of wishful results rather than a coherent strategy. How would the migration of NSCs (neurons and astrocytes) contribute to repair? Are neurons used for replacement or relay formation? what kind of neuronal phenotypes are desired or expected? would astrocytes form inhibitory scar? would attracting immune cells into the scaffold compromise the integrity of the axons?
* Similarly, the authors should be aware that the real challenge is not growing axons through a permissive scaffold (shown in many studies) but getting then to exit and connect with the non-permissive and inhibitory host and then directing them to make appropriate connections rather than maladaptive, which often result in pain and spasticity.

Results

* The authors report that "rats with NSCs/collagen scaffolds transplantation had a persistent recovery in locomotion during our observation periods, with a significantly higher BBB score than that in control and alone collagen scaffold groups ($p < 0.05$) (figure 3(c) and 3(d))". Strangely, they never report the value of the BBB score and the interpretation of the quality of this recovery. Extrapolating from the figure it seems to be about 8, which is remarkable for recovery after transection. Here is the improvement at BBB 6-8

6 Extensive movement of two joints and slight movement of the third joint.
7 Extensive movement of the three joints in the hindlimbs.
8 Sweeping without weight bearing or plantar support of the paw without weight bearing.

Here is what the authors need to do:

a. another motor test to confirm the remarkable recovery and to make sure it is of functional value rather than increased spasticity

b. Verify that the treatment does not promote maladaptive pain

* Although the authors show NF and 5HT it is not clear whether the exons transverse the scaffold and re-enter the host. A much better technique would be tracing of ascending sensory axons and descending brain stem or cortical tracts.

* Histological analysis should include scar formation and presence of microglia

* The legends need to be improved