Revisiones solicitadas por revistas internacionales

Dr. José Juan Antonio Ibarra Arias

1. **PONE-D-11-09776**
   BIOCOMPATIBLE AGAR-BASED BRIDGES AS CANDIDATES TO PROVIDE GUIDE CUES IN SPINAL CORD INJURY REPAIR
   Dear Dr Ibarra,
   I invite you to review a manuscript for PLoS ONE.
   Specifically, I would be grateful if you would review a paper entitled "BIOCOMPATIBLE AGAR-BASED BRIDGES AS CANDIDATES TO PROVIDE GUIDE CUES IN SPINAL CORD INJURY REPAIR" for this journal.
   Authors:
   Eduardo Martín-López, Ph.D.; Margarita Darder; Eduardo Ruiz-Hitzky; Manuel Nieto-Sampedro
   Please find more detailed information about PLoS ONE and the review process, and a copy of the abstract appended below.
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   If possible, I would appreciate receiving your review within 10 calendar days of your acceptance. You may submit your comments online at the above URL. There you will find text fields for confidential comments to the editor and comments for the author.
   With kind regards,
   Prof. Cesario V Borlongan
   Academic Editor
   REVISIÓN:

The manuscript entitled “Biocompatible Agar-based bridges as candidates to provide guide cues in spinal cord injury repair “ by Martín-Lopez *et al* attempted to test the biological response of several agar-based biopolymers as structural matrix scaffolds. They mixed agar with κ-carrageenan, gelatin and gum. Polysulfone tubules were placed into the biopolymers before gelling, and removed after gelling to form empty linear nerve-guiding channels. Gel degradation was determined by weight loss in two different culture media. The central regions of all gels were visualized using environmental scanning electron microscopy. After a T8 spinal cord (SC) transection (4-5 mm of length) the biopolymers were implanted into the SC gap, ensuring contact of the bridges and the spinal stumps. In order to evaluate the biological response and the usefulness of biopolymers, the authors performed anterograde tracing of the corticospinal tract, behavioral testing as well as histological and immunohistochemical studies. They found that almost all gels were stable to degradation and all of them formed porous structures. Towards the end of the study (1

month after implant), a low host reaction to all bridge materials was observed. In the same way, the authors claim to have found cell ingrowths through the empty channels; however, the channels lost linearity and there wasn't any axonal regeneration from the spinal tissue crossing through the bridges.

There is no doubt about the relevance of this kind of studies; however, in the case of the present manuscript, there are some major and minor issues that must be clarified or carried out before it can be considered for publication.

Major issues:

1.The number of animals used for almost all the experiments is quite low (2-3) as to make any substantial conclusions. Due to: 1) the relevance of findings, 2) the bias that a low number of animals could originate in the final results. It is imperative that the authors sustain their findings on experiments with at least 5 animals. The latter will avoid possible bias derived from a low number of samples. Although the study appears to be merely descriptive, I invite the authors to make an effort to use a larger sample size. In its present form, the work seems to be just a pilot study.

2. There isn't any kind of analysis. As mentioned above, the authors just described findings and neglected several interesting data that could be quantitatively analyzed. For instance, it should be desirable for this reviewer to know the number of macrophages, lymphocytes or even Schwann cells around or in the implants. In the same way, it would be attractive to know if the inflammatory response is statistically different among the different implants or if there is any difference in relation to the number of neural cells growing into the biopolymers.

3. I suggest improving the quality of figures; especially figure 5 appears to be more of an edited image than a real one. Furthermore, in figure 5c, the authors claim to show (results section) cell invasion at the beginning of the tubules; however, the quality of the image impedes the ability to see any cell.

Minor issues:

1. Pages are not numbered.

2. Authors evaluated motor outcome, they did not find any significant recovery. Once again, in this case 2 or 3 animals are not suitable for BBB analysis. Aside from this, it is imperative to evaluate not only motor but also sensory recovery.

COMMENTS TO THE EDITOR

The present manuscript is not conclusive; it requires more experimental work and editing. I suggest that the authors make more efforts as to analyze a higher number of animals and present figures of better quality. This will provide better support for their results. I recommend rejecting the manuscript.