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June 29, 2018

Dear Editor Fang-Fang Ji,

We thank you and the reviewers for their time and efforts in considering our manuscript for publication in World Journal of Hepatology.

Please find enclosed the edited manuscript in Word format (file name: 39857_Revised Manuscript.docx).

The manuscript has been improved according to the suggestions of reviewers. A point-by-point response to the reviewer's comments could be find on the following pages. Revision has been made according to the suggestions of the reviewer #2.

We have also followed and fulfilled the managing editor´s requests. Specifically, regarding two of these requests, we have to say that: 1- we have deleted the "ARRIVE guidelines statement:" because this work does not involve *in vivo* animal experiments; and 2- in line 469, we have replaced "(Table 4)" by "(detoxification of 14.3 ± 3.6 μmol/g wet tissue after 120 min incubation, n=6)" to solve the table order conflict. We have deleted the supplementary Figures S1 and S2 from the manuscript file as now we have uploaded this material as 39857_Supplementary Material.pdf file.

Sincerely,

María Dolores Pizarro

María Eugenia Mamprin

Lucas Damián Daurelio

Joaquín Valentín Rodríguez

María Gabriela Mediavilla

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 39857

Title: Experimental Bio-Artificial Liver: importance of the architectural design on ammonia detoxification performance.

Reviewer's code: 03647881

Reviewer's country: Taiwan

Science editor: Fang-Fang Ji

Date sent for review: 2018-05-23

Date reviewed: 2018-05-31

Review time: 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

According to María Dolores Pizarro et al. "Experimental Bio-Artificial Liver: importance of the architectural design on ammonia detoxification performance.", which is excellent

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study to demonstrate the importance of adapting the BAL device to the biological component characteristics to obtain an adequate BAL performance in animal study. Thanks!

Answer: Thank you for acknowledging and enthusiastically support our work.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 39857

Title: Experimental Bio-Artificial Liver: importance of the architectural design on ammonia detoxification performance.

Reviewer's code: 03471188

Reviewer's country: China

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-01

Date reviewed: 2018-06-05

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

In the current study, Pizarro et al., presented a very interesting and useful protocol of using two BALs to alleviate liver failure. The novelty of the study is good. The entire experiments are well-designed and well-written.

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Answer: *We appreciate your recognition to our work.*

I have only several suggestions: 1. The ABSTRACT is quite long. Authors should consider to shorten the length.

Answer: *We have shortened the ABSTRACT section.*

2. It is necessary to compare and discuss the authors' BAL with other clinical-used BAL devices.

Answer: *At present. there is no BAL accepted for clinical use. Strictly speaking about cell-based extracorporeal liver support devices, several clinical trials have been conducted (HepatAssit®, Vitagen ELAD®, LSS, MELS, Excorp Medical BLSS and AMC-BAL). Some of them are already in phase III clinical trials and, overall, they have shown some success specially in bridging patients to liver transplantation. One of the drawbacks of these trials is the deteriorated condition of the patients enrolled. As a result of the observations of these trials, another issue pointed out by the researchers in the field is that it should be analysed what kind of patients are better treated by each device (i.e., chronic, acute or acute on chronic failure, primary graft nonfunction and even Etiology).*

Our prototype still needs to be scaled up and challenged against animal models of liver failure to meet clinical consideration. Then it seems to us that comparing this device with the ones already being tested in clinical trials may result premature. Nevertheless, we have included the following text under the DISCUSSION section assessing this question:

"At present no BAL is in use to clinically treat liver failure. Some clinical trials have been conducted (for an updated review consult the work of Sakiyama et al.[30] and references therein) with some success. All of these devices use isolated liver derived cells: four of them use porcine primary hepatocytes either fresh (named LSS, Excorp Medical BLSS and AMC-BAL) or cryopreserved and microcarrier attached (HepatAssit®); one uses human primary hepatocytes (MELS) and one uses HepG2/C3A cell line (Vitagen ELAD®). Among the reasons why they have not reached routine utilization in clinical settings yet, we can name the complexity of isolating

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hepatocytes and the difficulties for maintaining these cells viable for prolonged periods of time which limit the assembly and transport of the devices confining its use to the centres where they are developed. An exception to this could be ELAD® system that uses a cell line but for which the costs of producing the amount of cellular material required makes it expensive and again limited to places with the facilities and expertise to conduct cell culture at large scale. In this sense our BAL prototype, although it still has to successfully pass through the stages of scaling up and challenging against animal models of liver failure, proposes the use of hand cut LMOs obtained by a low-cost technique and for which hospital personal could be trained straightforwardly. Also, the required biological material could be obtained from donor livers not acceptable for transplantation but meeting the criteria to obtain adequate pieces to feed this kind of BAL and possibly to be used in multiple treatments. In this way, pre-assembled BALs could be filled with LMOs obtained in the same centre where they are immediately going to be applied. The prototype we are presenting in this work is constructed with standard laboratory and medical supplies so we envisage that they could be constructed at reasonable costs and, consequently, commercialized at reasonable prices."

3. Limitation of the current BAL should be discussed, as well as the commercial prospects.

Answer: The topic is addressed in the same paragraph introduced to ponder reviewer's comment number 2. under the DISCUSSION section (and copied above in our previous answer). We are aware that the process of scaling up a flat-bottomed device can present difficulties when trying to achieve the amount of surface necessary to house a large quantity of tissue as could be required to treat a patient. We have in mind that probably a system similar to the multilayered flasks available for large scale culture could be a solution but we really cannot make a prediction at this point of our research.

4. Many minor errors, for example, in the ABSTRACT, LMO should be expanded, and some other grammatical and formatting errors.

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Answer: We have expanded LMO in the ABSTRACT. We had carefully re-read the manuscript and errors were detected and corrected. We hope to have satisfactorily polished our grammar and format mistakes.

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