

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7103-review.doc).

**Title:** The Evaluation of a Hybrid Bioartificial Liver Support System using CL-1 cells in Cynomolgus monkey models with D-galactosamine induced acute liver failure

**Author:** Zhi Zhang, Yi-chao Zhao, Yuan Cheng, Guo-deng Jian, Ming-xin Pan, Yi Gao

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 7103

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

**Responses to review comments were listed below:**

Reviewer 1:

This is an experimental study to evaluate the safety and efficacy of Hybrid Bioartificial Liver Support System (HBALSS) in cynomolgus monkey models with acute liver failure and its feasibility in clinical application. The authors conclude that cynomolgus monkey models with acute liver failure have been successfully established, the novel hybrid bioartificial liver can significantly reduce serum biochemical levels, and animal extend survival time, displaying its significant role in liver support. The authors address the challenge of treating acute liver failure. The methodology was applied properly. The results obtained are discussed and are suitable data for stimulating the development of experimental models for the study and treatment of acute liver failure. The references are in adequate number and are current. Figures and tables are appropriate in number, clear and the subtitles are well prepared. Table 4 seemed expendable.

**Response:** Thank you for your praise. We have included the P value in the Table 4, to demonstrate significance.

Reviewer 2:

Dear authors, Thank you for submitting your study to the WJG, I enjoyed very much reading your paper. However, it can be improved by some editing and language/grammar correction. While reviewing your paper I left few comments and suggestions, please check them out and consider revising.

**Response:** Thank you for your helpful comments. We have revised the manuscript accordingly.

Reviewer 3:

To authors This is a very interesting paper about the efficiency of Hybrid Bioartificial Liver Support system (HBALSS) for D-galactosamine induced acute liver failure. Authors conclude HBALSS could improve the animal's clinical, biochemical levels and

extend the survival time of animals. I ask some questions. 1. Prothrombin time is a typical parameter of acute liver failure. How about prothrombin time in this experimental study? 2. Authors say "NH3 and Fisher ratio are two key indicator for acute liver failure". I think that NH3 and Fisher ratio are indicator of hepatic encephalopathy. Therefore, authors had better comment prothrombin time before and after HBALSS support for D-galactosamine induced acute liver failure.

Response: As stated by the reviewer, prothrombin time is a typical parameter of acute liver failure. However, after the cynomolgus monkey model for liver failure was established, we routinely used heparin as an anticoagulant during the artificial liver treatment. Since it has been shown that heparin would affect prothrombin kinetics [1], it wasn't useful to compare the prothrombin time-course in animals treated with heparin. Therefore we didn't use prothrombin time as an indicator for change in liver function here.

[1] Schultz NJ, Slaker RA, Rosborough TK. The influence of heparin on the prothrombin time. *Pharmacotherapy*. 1991;11(4):312-6.

3. I think the picture of Fig4 is D-galactosamine induced liver failure without HBALSS support. Please show the histology of acute liver failure with HBALSS treatment.

Response: In our original experimental design, we used survival time of treated animals as the main indicator for evaluating the HBALSS. Anesthesia negatively impacts survival time of the cynomolgus monkey; thus, we chose to minimize the period that each animal was under general anesthesia during the HBALSS treatment, opting not to take a biopsy at that time.

#### **Changes to the manuscript have been marked in Blue**

Response to the comments in the manuscript:

[h1] This technique was used mostly as a bridging therapy until the organ becomes available!

Response: We have amended the description.

[h2] The introduction is too long, most of what is written here can be added in the discussion section of the paper.

Response: We have shortened the Introduction section.

[h3] Please number the pages!

Response: We have numbered the pages.

[h4] Sometimes you capitalized and sometimes you don't!

Response: We have capitalized them all.

[h5] Why the red highlight?

Response: It was a typing error. We have corrected it.

[h6] Something is missing, the sentence is incomplete!

Response: We have revised the sentence.

[h7] Why in red highlight?

Response: It was a typing error. We have corrected it.

[h8] What do you mean by this paragraph, please clarify!

Response: We have rewritten this paragraph.

[h9] You have to use the correct way of writing the units!

Response: Thank you for your comment; we have corrected the units.

[h10] This paragraph is hard to understand, please clarify!

Response: We have rewritten this paragraph.

[h11] The discussion section still requires some minor editing!

Response: We have edited the discussion section.

[h12] Can you add another column to present the P value and to demonstrate the significant changes!

Response: The P values have been added to the Table.

[h13] It would be better if you add another column to demonstrate the P value

Response: The P values have been added to the Table.

[h14] Are these changes significant? It is hard to appreciate the changes without the P values?

Response: The P values have been added to the Table.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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