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Title: Establishing a Rabbit Model of Perianal Fistulizing Crohn's Disease

Lu S et al. Establishing A Rabbit Model of FAPLs.

Dear Editor and reviewers,

We are very grateful to the reviewers for their pertinent and detailed proposals of the manuscript. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to us researches. We have studied comments carefully and have made correction which we hope meet with approval.

Now we resubmit the manuscript to your journal 'World Journal of Gastroenterology' and hope it can match your editorial criteria. The summary of the changes and the responses to all recommendations have been presented in the subsequent pages.

Thank you very much!

Sincerely yours,

Shuangshuang Lu, Wenjia Liu, Qiuya Niu, Chunyan Huo, Yuqing Cheng, Enjing Wang, Rongnan Li, Fangfang Feng, Yiming Cheng, Rong Liu and Jin Huang.

Reviewer #1:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Lu S et al describe the creation of artificial perianal fistulas in a total of 17 New Zealand rabbits in whom TNBS proctitis was induced at two different approaches. The intention of this research is certainly worthwhile, however, major problems with this manuscript need to be addressed:

- ETHICAL issues of animal experiments cannot be judged, as the document of the local Animal Care and Use Committee and the Institutional Review Board approval submitted are written in Chinese and therefore cannot be evaluated by this reviewer.
- **Reply to the referee:** Thank you for your comments. We have uploaded the English version of ETHICAL issues of animal experiments again. Please check it.
- The body of the manuscript, starting with INTRODUCTION indicates 33 references, but the list of REFERENCES is not numbered, so the references cited in the text cannot be attributed to the cited papers.
- **Reply to the referee:** Thank you for your comments. We have renumbered the references and made sure that its order corresponds to the citation of the paper.
- The ABSTRACT refers several times to "pathological" analysis, when probably "histological" is meant. In INTRODUCTION the phrase "Modern medicine thinks..." should be changed, as "Medicine" does not think (Maybe..Modern medical concepts describe...) MATERIALS and METHODS refer to Supplemental Table 1,2 and 3 which have not been submitted to this reviewer and cannot be checked.
- **Reply to the referee:** Thank you for your comments. We made some changes according to the mistakes you pointed out about the use of words and grammatical content. And this paper has been improved, reorganized and edited again. We have uploaded the language editing certificate. And we have submitted supplementary Tables 1, 2 and 3. Thank you!

- Was the Circadian rhythm considered and the day/night light used accordingly?
- **Reply to the referee:** Thank you for your comments. Our experiment considered circadian rhythm and used day/night light accordingly. In the *MATERIALS AND METHODS; Animals and groups* section, we have supplemented the description of animal feeding conditions. The indoor temperature was controlled between 24-28 °C, and the relative humidity was maintained between 50% and 70%. 10-15 air changes per hour and 12 hours of light each day. Thank you!
- How were the animals restrained and/or anesthetized when the TNBS solution was "continuously infused into the intestine once a week until the completion of 3 weeks of continuous intestinal enema"? Did the animals really get continuous enemas through 3 weeks?
- **Reply to the referee:** Thank you for your comments. Based on your question, we have changed the description of the "method and times of administration" in this paper. Different doses of TNBS mixed solution (Table 1) were infused into the intestine once a week for three weeks, three times in total. If you need to see a detailed record of the TNBS Enema Process, we would be happy to provide it to you. Thank you!
- EUS Assessment, first line "...on the day of removing the fistula and hanging the thread..." Why and how was the fistula removed?
- **Reply to the referee:** Thank you for your comments. We apologize for the inaccuracies in our description that have caused you confusion. And we made changes to the error description in the "EUS Assessment" section. The time of inserting anal fistula operation thread was different in each group. After anal fistula formation, on the day of removing the thread inserted into the fistula, the perianal fistula of experimental rabbits in each group was examined by EUS for the first time. And the thread inserted into the fistula which is showed in FIGURE 1A. Thank you!
- RESULTS Endoscopy and Pathology: The statement in the text referring to Table 2 "...the scores in Group A were significantly higher than the scores in Group B (P<0.05) is not correct, as on Day 21 P for the difference is shown as p=0.810.

- **Reply to the referee:** Thank you for your comments. This is our mistake. We have made changes in the paper. According to the statistical analysis (Table 2), except for DAI score, the scores in Group A were significantly higher than the scores in Group B ($P < 0.05$). Thank you!

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Innovative and interesting article providing a model for the assessment of Crohn perianal' s disease fully deserving publication. Indeed, complex fistulas have several therapeutical approaches (fistulectomy, VAAFT, PRP, Stem cells) and a model to better evaluate, assess and develop new techniques is much required.

Reply to the referee: Thank you for your comments. This article has been improved, rearranged and re-edited to meet the publication requirements. Thank you!

EDITORIAL OFFICE' S COMMENTS

Authors must revise the manuscript according to the Editorial Office' s comments and suggestions, which are listed below:

(1) Science editor:

This study aims to improve the induction method of colitis and establish a reliable and reproducible perianal fistulizing Crohn' s disease animal model to evaluate new treatment strategies. And improved method of CD colitis induction successfully established a rabbit perianal fistula CD preclinical model, which was confirmed by endoscopy and pathology. This is an interesting study.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Reply to the referee: Thank you for your comments. This article has been improved, rearranged and re-edited to meet the publication requirements. Thank you!

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office' s comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...” . Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Reply to the referee: Thank you for your comments. We have re-edited all the figures and tables in this paper at your request. And we have uploaded the new file as requested. And this article has been improved, rearranged and re-edited to meet the publication requirements. Thank you!

Sincerely thanks for your concise and professional comments. We deeply appreciate the time and effort you've spent in reviewing our manuscript.

Finally, thank you very much for giving us so much precious advice which helps us to develop the revised manuscript.