

June 16, 2014



Dear Prof. Su-Xin Gou:

Thank you for giving us an opportunity to revise the manuscript.

Please find enclosed the revised manuscript in Word format (file name: 10940-revision.doc).

Title: Intestinal microbiota pathogenesis and fecal microbiota transplantation for inflammatory bowel disease

Author: Zi-Kai Wang, Yun-Sheng Yang, Ye Chen, Jing Yuan, Gang Sun, Li-Hua Peng

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10940

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

1 Format has been updated

The revised manuscript (file name: 10940-revision.doc), the copyright assignment and answering reviewers were all resubmitted.

A point-to-point response to reviewer comments is listed below, and the revised contents are highlighted in yellow.

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

(1) Comment 1: The manuscript: "Intestinal microbiota pathogenesis and therapeutics in Inflammatory bowel disease" by Zi-Kai Wang et al aimed to shed light on the potentialities of using fecal microbiota transplantation and the use of synthetic microbes for promising treatments of IBD. General comments It is always a tricky issue to comment or circumvent a review paper, as it depends on the author's choice and opinions. The article offers an interesting review/overview on both the key and lacking evidences for the role of microbial-mediated therapy in IBD. The information and the comments that are generated in this paper are highly consistent, up-to-date, consistent and interesting,

especially those dealing with the donor selection's criteria which is rarely reached. The MS is clear and concise and the discussion through all the text is well conducted and documented. According to the general value of this paper that strengthens the concept that (i) fecal microbial transplantation is a key point to control human diseases and (ii) recommendations are needed to ensure safety of using such therapeutics, while data are still lacking and required more and appropriate studies to substantiate; I consider it suitable for publication in World Journal of Gastroenterology and would recommend that it can be accepted in its present form. As a specific remark, the abstract could be slightly shortened.

Answer: Thanks a lots for your comments. We have revised the abstract following your suggestion.

(2) Comment 2: This is a nice to read complete review providing important information in the field. Before publication, I suggest only minor changes that can be carried out, in particular: Abstract: change microflora to microbiota. Introduction: what abnormal microbiome mean? What is normal?; What the Author mean for "disturbed metabolites"?; Point n. 7 is not clear, do the Author mean compositional microbiome differences between different populations? Disturbance of Intestinal Microbiome in IBD: in this paragraph the Authors should include and discuss this very recent publication: Tong, Maomeng, Xiaoxiao Li, Laura Wegener Parfrey, Bennett Roth, Andrew Ippoliti, Bo Wei, James Borneman, et al. "A Modular Organization of the Human Intestinal Mucosal Microbiota and Its Association with Inflammatory Bowel Disease." PLoS ONE 8, no. 11 (November 19, 2013): e80702. doi:10.1371/journal.pone.0080702. Disturbance of Intestinal Microbiome in IBD: there are some repetitions in the paragraph particularly for what regards the Bacteroidetes and Firmicutes changes in IBD. Disturbance of Intestinal Microbiome in IBD: the link between butyrate reduction and the correspondence reduction of key butyrate producers (Clostridium clusters IV and XIVa) should be highlighted. HOST-MICROBE IMMUNITY INTERACTIONS IN IBD: not only pathogens but also commensals possesses pathogens associated molecular patterns. When discussing faecal transplantation two additional papers should be included and commented: Angelberger, Sieglinde, Walter Reinisch, Athanasios Makristathis, Cornelia Lichtenberger, Clemens Dejaco, Pavol Papay, Gottfried Novacek, Michael Trauner, Alexander Loy, and David Berry. "Temporal

Bacterial Community Dynamics Vary Among Ulcerative Colitis Patients After Fecal Microbiota Transplantation.” *The American Journal of Gastroenterology* 108, no. 10 (October 2013): 1620–30. doi:10.1038/ajg.2013.257. Song, Yang, Shashank Garg, Mohit Girotra, Cynthia Maddox, Erik C. von Rosenvinge, Anand Dutta, Sudhir Dutta, and W. Florian Fricke. “Microbiota Dynamics in Patients Treated with Fecal Microbiota Transplantation for Recurrent *Clostridium Difficile* Infection.” Edited by Gabriele Berg. *PLoS ONE* 8, no. 11 (November 26, 2013): e81330. doi:10.1371/journal.pone.0081330. Both manuscript represent important gut microbiome longitudinal survaies after FMT.

Answer:

Thanks a lot for your valuable suggestions. **Abstract:** we have changed “microflora” to “microbiota”. **Introduction:** following your suggestion, we described the “normal microbiota” in the human intestine, the abnormal mcirobiota and disturbed metabolites associated with IBD briefly. Moreover, we revised the Point 7, we want to see that some important environmental factors such as the diet, modern lifestyle, abuse of antibiotics, etc., have an effect on the composition of intestinal microbiota and contribute to the significant increased incidence of IBD. **Disturbance of Intestinal Microbiota in IBD:** in this section, we discussed the recent published paper from Tong et al. (Tong, Maomeng, Xiaoxiao Li, Laura Wegener Parfrey, et al. A Modular Organization of the Human Intestinal Mucosal Microbiota and Its Association with Inflammatory Bowel Disease. *PLoS ONE*, 2013: e80702.). According to your suggestions, we remodified this section and deleted some repetitive descriptions about the characteristics of disturbed intestinal microbiota in IBD. Moreover, we described the reduced butyrate and the butyrate-producing bacteria in IBD definitely. **Host-microbe immunity interactions in IBD:** we revised the inappropriate contents following your suggestions. **Fecal microbiota transplantation:** according to your suggestion, we discussed these two papers in the section of **Potential therapeutic mechanisms of FMT.** (1. Angelberger, Sieglinde, Walter Reinisch, Athanasios Makristathis, et al. Temporal Bacterial Community Dynamics Vary Among Ulcerative Colitis Patients After Fecal Microbiota Transplantation. *The American Journal of Gastroenterology*, 2013,108: 1620–30.) (2. Song, Yang, Shashank Garg, Mohit Girotra, et al. Microbiota Dynamics in Patients Treated with Fecal Microbiota Transplantation for Recurrent *Clostridium Difficile* Infection. *PLoS ONE*, 2013: e81330.)

(3) Comment 3: Wang and colleagues have written a review on intestinal microbiota and its role in the pathogenesis and treatment of inflammatory bowel disease. The topic is important and timely. I have the following comments: The second paragraph of the introduction is totally lacking references although it covers a page. I suggest to include references to the text. VSL#3 is mentioned at the end of the first paragraph in the section on clinical use of probiotics in ibd as a probiotic product that has been studied in patients with ibd. There is also a pediatric study (by Miele E et al in Am J Gastro 2009) which evaluated the effect of VSL#3 on induction and maintenance of remission in children with ibd. I would suggest to include the paper to the manuscript. The section of the history and indications of FMT does not include an eminent paper of Mattila E and his co-workers (published in Gastroenterology in 2012) that clearly demonstrated the efficacy of fmt through colonoscopy in patients with recurrent Clostridium difficile infection. I urge the authors to add the paper. At the end of the section on the route of fmt administration the authors state that 'up to 80% of ibd patients had been administrated FMT by colonoscopy and/or retention enema. I would like to get the reference to be added. Some bacterial species in the table 1 lack references. I suggest them to be added. A pediatric prospective clinical trial (by Kunde S et al. in the Journal of Pediatric Gastroenterology and Nutrition in 2013) on safety, tolerability and clinical response of fmt in pediatric ulcerative colitis has not been mentioned in the table 2. I think it should be included to the table and discussed also in short in the text. Both table 3 and table 4 are lacking references.

Answer:

Thanks a lot for your valuable suggestions. We have added the related references in the second paragraph of the **Introduction**. Following your suggestion, we added the contents on the efficacy of the combined probiotics VSL #3 on induction and maintenance of remission in IBD children in the section of **Clinical use of probiotics in IBD**. In the sections of **The indications of FMT** and **Route of FMT Administration**, we added the paper from Mattila E et al. (Mattila E, Uusitalo-Seppala R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology 2012; 142: 490-496). In the section of **The route of FMT administration**, we added the reference on "up to 80% of IBD patients had been

administrated FMT by colonoscopy and/or retention enema". We discussed the clinical use of FMT in children with IBD in the section of **FMT in the management of IBD**, and the related contents and reference were added in **Table 2**. Moreover, following your suggestion, the references were added into **Table 1, 3 and 4**.

(4) Comment 4: This is an informative review about the fecal microbiota transplantation (not about therapeutics in inflammatory bowel disease, please revise the title) which is probably worthy of publication with some modifications. The text is difficult to correct because the page and the line numbers are missing. The manuscript lacks fluency in English and needs revision by an English-spoken colleague before resubmitting the manuscript.

Answer: Thanks a lot for your comments. We have re-written the title, the changed title is that "Intestinal microbiota pathogenesis and fecal microbiota transplantation for inflammatory bowel disease". Moreover, we have asked an professional english language editing company to edit our manuscript, and a language certificate letter could be provided.

(5) Comment 5: In this manuscript, the authors describe some of the microbiota features associated with IBD. The main focus, however, is on fecal transplantation process and its challenges. General comments: The title and contents of the manuscript are discordant – instead of IBD this review is mainly focusing on the fecal transplantation. Moreover, the intestinal microbiota related to the IBD is insufficiently covered. Terms microbiota, microflora and microbiome are mixed –please select one and use that one throughout the manuscript. The quality of English language is poor and sometimes difficult to understand. The text should be clarified and grammar checked before resubmitting the manuscript. Specific comments. Abstract is obscure and difficult to understand. Please revise to improve clarity. The use of numbering is confusing (page 2, lines 68-81). Please modify. The title "Potential single microbial pathogen in IBD" is confusing –please rephrase. Page 5, Line 142, rephrase word "instigation". Please explain what is meant by term "inter-intestinal" (page 7, line 196). The sentence "In addition, except for the single probiotic strain, some probiotic combinations such as VSL#3, an eight..." is incomplete

(page 8, lines 236-239). Please revise. Word "whatever" is not a scientific term and should be revised. The history of fecal transplantation is out of the scope of this review and could be removed (page 10, lines 277-286).

Answer: Thanks a lot for your useful comments. Following your suggestions: 1. We have changed the title "Intestinal microbiota pathogenesis and fecal microbiota transplantation for inflammatory bowel disease". 2. We finally used "microbiota" throughout our manuscript. 3. We have asked an professional english language editing company to edit our manuscript, and a language certificate letter could be provided. 4. We have re-written the abstract as your suggestion. 5. The numbers in the section of **Introduction** were also modified. 6. The word "instigation" was changed into "pathogenesis". 7. We deleted "inter-intestinal", we want to say the heterogenicity of gut microbiota between different individuals could influence on the investigations of intestinal microbiota in IBD. 8. We revised the incomplete sentence "In addition, except for the single probiotic strain, some probiotic combinations such as VSL#3, an eight..." and the incorrect word "whatever". 9. According to your suggestion, we have deleted the history of FMT and re-written this section, the related title was also changed.

3 References and typesetting were corrected

- 1) According to your suggestion, I have finished the section of Core tip to outline the core contents in my paper.
- 2) This paper (Classification of manuscript language quality evaluation is B) was edited by Jing-Yun Ma Editing Office, and professional english language editing company, and a language certificate letter from Ma Jingyun edit office was provided.

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

Sincerely yours,

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