

Re: World Journal of Gastroenterology Manuscript NO: 55347 – Notification on manuscript revision

Dear Prof. Ma,

Thank you for your email regarding the opportunity to revise this manuscript.

We thank the referees for their positive comments and constructive suggestions, which have been addressed in our point-point response below. The relevant changes have all been incorporated into the revised version as specified in each response, and marked in red fonts.

We hope you agree that the comments raised by the referees have been appropriately addressed, allowing the revised manuscript to be suitable for publication in *World Journal of Gastroenterology*.

Yours sincerely,

Mr. Wei-Kun Huang and Dr. Tong-Zhi Wu

On behalf of all co-authors

Reviewer #1

The paper by Huang WK describes the in vivo and in vitro models for the investigation on the hormone secretion from the gastrointestinal tract for the development of novel therapies for metabolic diseases. The review was structured and organized. The description may be arranged more concise. In each section, the overview of the methods and novel findings were described. The reviewer thinks that it is better to describe new therapy or strategy found by these models, if possible. Some abbreviations were used without spelling out at the first appearance. All abbreviations need to be spelled out at the first appearance. There are a couple of strange sentences and wordings. The manuscript needs to be polished up.

Response: We thank the reviewer for positive comments on our manuscript, and apologize for the lack of clarity about the abbreviated terms (including Lgr 5, NEUROG3, Arx and SCFAs on page 7 and 8 respectively), which have now been appropriately defined at their first appearance.

The application and outcomes of respective technique for investigation of nutrient-gut interaction have been outlined in the relevant section where appropriate, but are not given more detailed discussion, since this invited review was designed to provide an update on the technical development in relation to the investigation of nutrient-gut

interactions. The manuscript has been thoroughly checked by Prof Christopher Rayner, Prof Karen Jones and A/Prof Richard Young who are native English speakers, with longstanding experience in medical research on gut function. To ensure its readability to readers with interdisciplinary background, the manuscript has also been carefully revised by co-authors, Prof Heike Ebendorff-Heidepriem and Dr Jiangbo Zhao, who are researchers in material science and physics, respectively.

Reviewer 2

In this manuscript, Huang et al reviewed that the evolution of in vitro and in vivo models and the integration of innovative techniques that will ultimately enable the development of novel therapies for metabolic diseases. The manuscript is well written and the aim of this study is clear. However, the authors should summarize more clinical studies of nutrient-gut interactions by using innovative techniques and models for therapies of metabolic diseases.

Response: We thank the reviewer for the positive comments. We have not elaborated on clinical studies and the models for therapies of metabolic diseases, given that this invited review was set to provide an update on the technical development of nutrient-gut interactions.

Reviewer #3

The authors summarized the research tools and the in vitro and in vivo models used to investigate nutrient-gut interactions, and discussed their advantages and limitations for clinical translation of findings in an organized structure. A better understanding of the mechanisms underlying nutrient-gut interactions is fundamental to the development of gut-based therapies for major metabolic disorders. This makes the present manuscript quite valuable for both basic and clinical professionals. I would appreciate if the authors can mention some further research direction in the field. Moreover, a good review is expected to have brief summary except a detailed literature review. A table is always a great way to present the core information to the readers in an easy way. Finally, when making reference, the original articles instead of review articles should be cited. For instance, reference 2 and 111 are review articles. Overall, the manuscript shows novel interesting and comprehensive highlights with a good quality and the overview given is fairly informative.

Response: We thank the reviewer for the positive comments and suggestions on our manuscript, and have made the following revisions:

1. We have now added a table to provide an overview of the platforms/techniques described in this manuscript (Table 1 on page 34).
2. In the Conclusion, we have highlighted some future priorities in the field (page 13).
3. We have replaced the citations of reviews with original research articles where appropriate.

Reviewer 4

This is a narrative review about novel tools for investigation of nutrient-gut interaction. It discussed the evolution of in vitro and in vivo models and the integration of innovative techniques that would enable the development of novel therapies for metabolic diseases. The manuscript is well written and contains important data regarding the main focus of review. It could be accepted after minor English editing.

Response: We thank the reviewer for the very positive feedback. As per our response to review #1, the manuscript has been carefully edited by all co-authors to achieve both accuracy and broad readability.