



Florence, 28th June 2022

To the Editors of World Journal of Gastroenterology

Dear Editors,

Thank you for the opportunity to reply to your comments about our manuscript submitted for publication in *World Journal of Gastroenterology* (titled "**Impact of microbiota-immunity axis in pancreatic cancer management**", manuscript number 75245). Your interest in this work is highly appreciated.

We will try to clarify all the issues raised in the emails dated May the 29th, as follows.

Reviewer #1:

1 Title. Does the title reflect the main subject/hypothesis of the manuscript? The present review does not fully reflect the issues of "Impact of the microbiota-immunity axis on the treatment of pancreatic cancer".

R. The manuscript was revised to address the issue.

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? Introduction It modestly describes the current state of the issue. The name of the work sounds "the effect of the axis of the microbiota-immunity on the treatment of pancreatic cancer", however, it is precisely this issue in the introduction of very little space.

R. Respectfully, being a minireview, the introduction section was thought to provide general information. However, the section was revised and shortened to give more space to the main topic.

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? The manuscript is dedicated to the review of existing research. However, there are no indications on which the principle was selected by the published works that were taken for the review.

R. Respectfully, being a minireview and not a systematic review, this information is not required.

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? The objectives of the study research are not fully achieved. After reading "the effect of the axis of the microbiota-immunity on the treatment of

pancreatic cancer" remained a "mystery". There are many phrases such as "...seem to contribute to PanCa initiation and development...", "... mitis appeared to be reduced...", "... H. pylori could also have a role in development of this cancer.", "...It could elicit chronic mucosal inflammation...", "... while Candida, Aspergillus, or Saccharomyces species did not seem to cause cancer development...", "...while high levels of anti-commensal microbes' antibodies seem related to a reduced risk of PanCa", "...Several factors can unbalance the microbiota biodiversity..." etc. But many of these statements have long been proven. Why such uncertainty in the text? Thus, it seems that the author did not introduce anything new.

R. Most of the studies are made on animal models and cancer pathogenesis is a complex process thus explaining the uncertainty, mostly in humans. However, the manuscript was revised to address the issue.

12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? The text of the manuscript requires more precise structuring. The figure shows very well the relationship between microbiota and carcinogenesis (pancreatic cancer). However, in the text, these data are scattered and it is difficult to understand what is interconnected with what.

R. The manuscript was revised to address the issue.

13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? The manuscript is a review. However, it is not clear, is it a systematic review, meta-analysis? It is advisable to allocate the section "Methods", which reflects the principle for which articles were selected for review.

R. See replay to point number 5

Reviewer #2:

The overall scientific information in this review is fairly good, however the only microbiota factor could not be explained for the causative, preventive, or therapeutic impact of pancreatic cancer. The gut microbiota appear to be an alternative way to be included in the main standard treatment of pancreatic cancer, hence the authors should revise the manuscript to reflect this.

R. The manuscript was revised to address the issue.

This manuscript has an excessive number of paragraphs in the abstract, core tip, and main text, which should be summarized as normal.

R. The manuscript was shortened and redundant parts were deleted. Respectfully, we think that the number of paragraphs is adequate to reflect the different steps of cancer development and treatment.

Figure 1 is too tiny to be recognized especially when published and references are required.

R. The figure has been enlarged and references added

Table 1 must be changed to clarify "Higher risk of developing PanCan [michaud13,akshi19,fan18,wei10,farrel12]". The references should be revised as the correct format.

R. Table 1 was modified as suggested

Reviewer #3:

There is no definite conclusion on the occurrence and development factors of pancreatic cancer, and it is also a research hotspot. This paper reviews the current research in this field from the perspective that the complex interaction between the microbiota and the immune system may play a role in the pathogenesis and progression of pancreatic cancer. However, the current research in this field is relatively superficial, and the clinical significance is not large, and further in-depth research is needed.

R. Our aim is to provide the actual state of the art of an evolving theme in order to highlight the necessity and stimulate further in-depth research.

Reviewer #4:

R. Thank you very much for the appreciation

Reviewer #5:



I would like to suggest the authors add a section on comparison with other cancers to show which microbial changes are specific to pancreatic cancer and which are common in pan-cancer.

R. Respectfully, we think that another section should be redundant. However, the specificity or not for PanCa was highlighted through all the article

Reviewer #6:

R. Thank you very much for the appreciation

Science Editor:

(1) Advantages and disadvantages: The reviewers have given positive peer-review reports for the manuscript. This research is innovative and discusses the association between pancreatic cancer and the microbiome. Although there is less research in this area, this topic still holds value for the treatment of pancreatic cancer. However, as the peer reviewer indicated, the manuscript does not adequately reflect the issues of "Impact of the microbiota-immunity axis on the treatment of pancreatic cancer". The current evidence is still insufficient.

R. See answer to Reviewer #1

1.5 Language evaluation: The English-language grammatical presentation needs to be improved to a certain extent. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

R. Language was polished through all the text and a new language certificate was provided, as requested.

(1) The authors should reflect that the gut microbiome is the main standard treatment of pancreatic cancer.

R. See answer to Reviewer #2

(2) This manuscript has an excessive number of paragraphs in the abstract, core tip, and main text, which should be summarized as normal.

R. See answer to Reviewer #2

(3) Figure 1 should be submitted to be recognized.

R. See answer to Reviewer #2

(4) Table 1 must be changed to clarify "Higher risk of developing PanCan [michaud13,akshi19,fan18,wei10,farrel12]".

R. See answer to Reviewer #2

(5) The references should be revised as the correct format.

R. References were revised.

(6) The present review should fully reflect the issues of "Impact of the microbiota-immunity axis on the treatment of pancreatic cancer".

R. See answer to Reviewer #2

(7) The authors should add a section on comparison with other cancers to show which microbial changes are specific to pancreatic cancer and which are common in pan-cancer.

R. See answer to Reviewer #5

Company editor-in-chief:

Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should



be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

R. References have been updated.

The main modifications were highlighted in the text in yellow.

We are looking forward to receiving your comments about the revised manuscript.

Sincerely,

Amedeo Amedei

On behalf of all the Authors

Corresponding Author:

Prof. Amedeo Amedei

Department of Clinical and Experimental Medicine, University of Florence

AOU Careggi, Largo Brambilla 3, 50134, Florence, Italy.

amedeo.amedei@unifi.it, phone: +39 055 2758330