December 1, 2021

Dr. Jin-Lei Wang, Vice General Manager
& Science Editor
Baishideng Publishing Group Inc; E-mail: j.l.wang@wjgnet.com

RE: Editorial Decision on our manuscript: 73265.

Dear Dr. Ma and Dr. Jin-Lei Wang,

Thank you for your Editorial Decision regarding our manuscript #73265: “Endothelial Cells & Blood Vessels are Major Targets for COVID-19-induced Tissue Injury and Spreading to Various Organs. (subtitle) Implications for Digestive System; the Newest Oral COVID-19 Therapy.”

We thank you for conditionally accepting our work and for inviting us to respond to the reviewers’ comments and revise the paper. We agree with all the comments and recommendations.

We have addressed them in the enclosed point-by-point response. In brief, in response to the reviewer, we have revised the Discussion section to include more information on Molnupiravir and Paxlovid. We also revised the manuscript to include the Author contributions and formatted the tables as per the journal’s guidelines and reduced self-citation references to 9%. We have introduced all these modifications/revisions into the revised manuscript and provided the figures in a PowerPoint file.

We feel that these changes have significantly strengthened and improved our manuscript.

**Enclosed is a point-by-point response to the Reviewers’ comments.**

We thank you, Science Editor, the Editorial Board, and Reviewers for evaluating our manuscript and for the insightful comments and suggestions.

Thank you for your consideration.

Respectfully,

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A point-by-point response to the Editors' and Reviewers' comments.

Company Editor-in-Chief's comments:

"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. … 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."

**Response:** We thank the Editor-in-Chief Reviewer for kind comments and suggestions to improve our paper. In response, we have included the figures in a PowerPoint file. We have also formatted the tables as per the above specifications.

Science Editor's comments:

We thank the Science Editor- for the comments and suggestions to improve our paper.

There are 20 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e., those that are most closely related to the topic of the manuscript) and remove all other improper self-citations.

**Response:** In response, we removed several citations of our previous papers to limit self-referencing to 9%. Only 9 of the 100 references in the revised paper are citations of our previous work.

The "Author Contributions" section is missing. Please provide the author contributions;

**Response:** In response, we have completed the "Author Contributions" section.

The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**Response:** In response, we have provided the figures as PowerPoint files.

Reviewer #1 comments

Overall, the article is well organized and concise. Understanding and preventing extrapulmonary manifestation, including VTE, plays a critical role in improving outcomes of COVID-19. The present article stresses the importance of endothelial standpoint in COVID-19 development.

We thank the Reviewer for the kind comments and suggestions.

1. Comment: Pathophysiological investigation and clinical trials are both essential to advance the knowledge of today. My concerns about this article are that the pathophysiological benefits of the two novel drugs, Molnupiravir and Paxlovid, were unclear. It is remarkable that we can keep the disease progress at bay by oral drugs. However, the endothelial effects of Molnupiravir were a bit vague. In addition, the results of Paxlovid study from Science were a little misleading because the main experiment was in vivo and did not demonstrate substantial efficacy in humankind. Considering the context of endothelial contribution to COVID-19 severity, I believe that the relationship between the two drugs and endothelial cells should be more clarified and emphasized.

**Response:** We thank the Reviewer for the comments and suggestions aimed to improve our paper. In response, we have revised the Discussion section to include more information on Molnupiravir and Paxlovid. Studies published on November 2, 2021 by Owen DR et al. in Science (PMID: 34726479; DOI: 10.1126/science. abl4784) reported the discovery and characterization of PF-07321332 (Paxlovid). Those studies demonstrated that Paxlovid inhibits SARS-CoV-2 replication in vitro in human adenocarcinoma-derived alveolar basal epithelial (A549) cells, and in differentiated normal human bronchial epithelial (dNHBE) cells. This drug showed in vitro coronavirus antiviral activity against all coronaviruses infecting humans and excellent off-target selectivity and in vivo safety profiles. That study also showed the efficacy of orally administered 300 or 1000 mg/kg PF-07321332 against SARS-CoV-2 infection in vivo in a mouse model challenged intranasally with SARS-CoV-2 MA10 (CCID50). PF-07321332 limited cellular infiltration by SARS-CoV-2 and protected lung tissue from damage compared to placebo treatment in that study. Most importantly, the interim analysis of the Paxlovid human clinical trial demonstrated a dramatic - 89% reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in high-risk patients treated within three–five days of symptom onset. Since this drug inhibits virus replication the chance of endothelial infection and dissemination of virus via blood vessel is reduced. Therefore, we postulate that the EC and blood

vessels are likely important part of this drug clinical efficacy. Naturally, this contention requires further careful analysis, confirmation, and in-depth insight, since the biological effects these drugs remain largely unknown [95, 96]. This sentiment and discussion regarding these oral drugs are summarized in November 10, 2021 Nature article titled: “COVID antiviral pills: what scientists still want to know” (*Nature* 2021; **599**(7885): 358-359; PMID: 34759341 DOI: 10.1038/d41586-021-03074-5).