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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 65531

Title: Hepatitis B virus infection modeling using multi-cellular organoids derived from human induced pluripotent stem cells

Reviewer's code: 00213926
Position: Peer Reviewer
Academic degree: PhD
Professional title: Doctor
Reviewer's Country/Territory: China
Author's Country/Territory: Japan

Manuscript submission date: 2021-03-09
Reviewer chosen by: AI Technique
Reviewer accepted review: 2021-03-11 02:10
Reviewer performed review: 2021-03-21 01:02
Review time: 9 Days and 22 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

This review summarized the advances in HBV modeling reported thus far and discussed the limitations and ongoing challenges in the application of liver organoids, particularly those with multi-cellular components derived from human iPSCs. The research status and challenges in this field are fully discussed, and the research prospects summarized are reasonable. Some of the existing details need further modification. 1. The topic discussed in this manuscript is Hepatitis B modeling system, but the introduction begins with Hepatitis C, which deviates from the theme of the review and is recommended to be deleted. 2. In the middle part of the Introduction, the existing in vitro model system, especially the IPSCS3D organ, is rarely mentioned in the application of the in vitro model of hepatitis B. It is suggested to discuss it in combination with the current situation of the study on the modeling system of hepatitis B, instead of just mentioning the research status of the in vitro modeling system in isolation. 3. Some references are too old, so it is suggested to update them. 4. On the part of Transplantation and gene editing, it is suggested that the three paragraphs be condensed into one paragraph for discussion. It is not necessary to write in such detail separately, as it is easy to deviate from the main idea.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 65531

Title: Hepatitis B virus infection modeling using multi-cellular organoids derived from human induced pluripotent stem cells

Reviewer's code: 02374599
Position: Editorial Board
Academic degree: PhD
Professional title: Director, Doctor, Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Japan

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Reviewer accepted review: 2021-03-16 07:47
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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The authors reviewed the in vitro modeling systems for HBV infection, especially organoid-generating strategies derived from human induced pluripotent stem cells (iPSCs). A robust cell model that permits the investigation of the virus-host interaction and therapeutics screen is crucial for the current study. A review article underlying this topic is timely and adequate. There are a few issues the authors should consider in a revision. First, The Introduction section is too wordy. It is suggested to focus on the theme: (1) HBV infection modeling in vitro; (2) using of iPSCs on in vitro modeling; and (3) multi-cellular liver organoids. The content should be concise. Second, in the part of Cell sources, a lot of hepatic cell models have been summarized. But non-hepatic cell lines can also be HBV models, such as 293T overexpressing human NTCP, HNF4α, RXRα, and PPARα. The authors should mention it. The conclusion ends with a sentence: "We have discussed general concepts for the establishment of clinical-grade patient iPSC-derived multi-cellular liver organoids for further applications in modeling and treatment of hepatitis virus infection and other liver diseases simply summarized as the schema in Figure 1.". This sentence has appeared in the preceding text. The conclusion should lead from the rest of the piece, not repeat the content of the text.