Answering Reviewers

Responses to Reviewer #1

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.

1. 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.

Response: We appreciate the reviewer's comments. We have rearranged the content to focus on the theme according to the suggestion: (1) HBV infection modeling in vitro; (2) using of iPSCs on in vitro modeling; (3) iPSCs derived multi-cellular liver organoids.

2. 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.

Response: Thank you for raising this insightful point. As suggested, we have added the research on this non-hepatic cell line and discussed its potential uses in future in "Cell sources".

3. 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.

Response: Thank you for this kind suggestion. Accordingly, we have revised this sentence in "Conclusion".

Footnote: And all the changed or re-arranged in this revision version are highlighted with yellow.

Response to Reviewer #2:

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.

Response: We appreciate the reviewer's comments. We intended to show the evidence that in vitro modeling had led to successful HCV drug development, which also highlight its importance in HBV modeling. As suggested, we have deleted the redundant introduction about Hepatitis C, and rearranged the content in "Introduction".

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.

Response: We agree that the introduction of iPSC-derived liver organoids is very important. Accordingly, we have added the related information in "Introduction".

3. Some references are too old, so it is suggested to update them.

Response: As suggested, we have updated with recent references. In detail, we reduced the old ones (>10 years) from 15% to 6%, updated in recent 5-10 years from 32% to 38% and in recent 5 years from 53% to 56%. Finally, the references in recent 3 years are reached up to 32% in total 107 references.

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.

Response: We appreciate the reviewer's helpful suggestions. We have deleted some unimportant details and rearranged the part of "Transplantation and gene editing".

Footnote: all the changed or re-arranged in this revised version are highlighted with yellow.