

ANSWERING REVIEWERS



April 9, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16758-review.doc).

Title: Novel therapeutic approaches for hepatitis B virus cccDNA

Author: Motoko Ohno, Motoyuki Otsuka, Takahiro Kishikawa, Takeshi Yoshikawa, Akemi Takata, and Kazuhiko Koike

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16758

The manuscript has been improved according to the suggestions of the reviewers:

1 The format has been updated.

2 The revisions have been made according to the suggestions of the reviewers,

(1) Reviewer #3020625:

Comments to Authors:

In this review, the authors reviewed the novel therapeutic approaches for HBV cccDNA, which is favorable for the clinician in various fields. As one of the genome-editing methods, CRISPR/Cas9 system has triggered a revolution in which laboratories around the world are using the technology for innovative applications in biology. Being a potential therapeutic approach, it would be better to list some HBV-specific gRNA in this article. The paper could be accepted by minor revision, such as "INF".

Response:

We thank the Reviewer #3020625 for his/her valuable comments.

First, because HBV genome is not highly-homologous with the human genome, there are too many possible candidates of HBV-specific gRNA sequences to list. Previous reports have already targeted various sites of cccDNA using the CRISPR/Cas9 system, and we cited these studies as much as possible. These settings of gRNAs may influence their efficiency, which remains to be verified. We have added some descriptions about these points in the revised manuscript.

Second, we sincerely apologize for the careless spelling mistakes. We have corrected these mistakes in the revised manuscript.

We sincerely thank the reviewer for pointing out these crucial issues, which greatly helped us to improve our manuscript.

(2) Reviewer #2841615:

Comments to Authors: N/A (accept)

Response:

We thank the Reviewer #2841615 for his/her good evaluation.

(3) **Reviewer #2439938:**

Comments to Authors:

This is a good article and help readers to understand new methods to cure HBV infection. But it will be better for readers to understand if authors can have a picture, which illuminates how the CRISPR/Cas9 system work on HBV cccDNA. And also there are some spellings mistakes within manuscript and need to be revised, such as “INF”, it should be “IFN”.

Response:

We thank the Reviewer #2439938 for his/her valuable suggestions.

According to the reviewer's comments, we added a new figure (as Figure 3) to the revised manuscript, which shows how the CRISPR/Cas9 system works on the double-stranded DNA (including HBV cccDNA) in the nucleus.

Additionally, we sincerely apologize for our careless spelling mistakes. According to the reviewer's comments, we have corrected these mistakes in the revised manuscript.

We sincerely thank the reviewer for these suggestions, which greatly helped us to improve the manuscript.

3 The references and typesetting were corrected.

4 We attached the original decomposable ppt file containing the figures for editing.

We thank the editors and the reviewers again for the kind consideration of our manuscript.

Sincerely yours,

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