

From:

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To:

Patras, 22 February, 2021

Re: World Journal of Gastroenterology, Manuscript no: 62850-R1
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Dear Editor,

Thank you for reviewing our manuscript titled “Towards a new era of HBV therapeutics: the pursuit of functional cure” by Tsounis et al.

We have now completed the revisions required by the reviewers and the Science Editor. All changes are highlighted in the revised manuscript. Point-by point answers to the comments made by the reviewers and the Science Editor are provided below.

The revised manuscript has been seen and approved by all authors,

We hope that our revised manuscript will meet with your approval,

I remain,

Yours sincerely,

Christos Triantos

REVIEWER 1

Comment

This is an informative and educational review. Authors had better add the comment about necessity or possibility of interferon/pegylated interferon for HBV therapy in the future. Is the possibility of combination therapy with interferon/pegylated interferon left in the future? Minor; The bottom line, page 20; Was ‘GS-6988’ incorrect? The line 16, page 26; ‘INF-medicated’ should be replace to ‘IFN-mediated’, if INF means interferon.

Answer

The discussion section has been revised to include a comment about the necessity or possibility of interferon/pegylated interferon for HBV therapy in the future (page 35, lines 4-15 and lines 17-20).

We have made the suggested corrections: “GS-9688” (page 21, line 18) and “IFN-mediated” (page 27, line 9).

REVIEWER 2

Comment

This is a comprehensive review focused on novel anti-HBV drugs towards functional cure of HBV. This manuscript covered most of the important therapeutic approaches including direct-acting antivirals and immunotherapy in the pipeline or preclinical. I would like to recommend this manuscript for publication after minor revision: 1) Page 9 Line 26: Bulevirtide is an HBV entry inhibitor, and it has been already reported that it is effective on HBV/HDV co-infected patients (ref 41). How is the effect for HBV infected patients without HDV infection? Is it already tested or on the clinical trial? 2) Page 11 Line 23: Please cite the articles which reported that smc5/6 are the substrates of HBx-DDB1 ubiquitin ligase complex. 3) The headlines for the therapeutics in the text, tables and figures are not always similar (for example, “Silencing viral transcripts”, “RNA targeting therapeutics” and “RNA interference”). It would be readable for the readers if they could be unified or expressed similarly. 4) There are some typos to be corrected. For example, Page 10 line 25 and 28 “CRISPR”.

Answer

(1) The effect of bulevirtide in HBV patients without HDV coinfection has been included (page 9, line 31; page 10, lines 1-5).

(2) A citation has been added (ref. 57).

- (3) We have modified the headlines as suggested (text, tables, figures).
- (4) We have made the suggested corrections: “CRISPR” (page 11, line 1; page 11, line 4).

REVIEWER Comment The revised manuscript is much improved, and the authors have addressed my issues. I recommend its acceptance with one very minor correction. As citation ref 57, the first report (Decorsière A et.al, Nature. 2016 Mar 17;531(7594):386-9. doi: 10.1038/nature17170.) would be better. Please replace it.

Reply We have made the suggested correction.

SCIENCE EDITOR

Comment

1 Scientific quality: The manuscript describes a review of the new era of HBV therapeutics. The topic is within the scope of the WJG. (1) Classification: Grade D, Grade A and Grade A; (2) Summary of the Peer-Review Report: The authors a comprehensive review focused on novel anti-HBV drugs towards functional cure of HBV. This manuscript covered most of the important therapeutic approaches including direct-acting antivirals and immunotherapy in the pipeline or preclinical. However, the authors had better add the comment about necessity or possibility of interferon/pegylated interferon for HBV therapy in the future. The questions raised by the reviewers should be answered; and (3) Format: There are 2 tables and 2 figures. A total of 197 references are cited, including 149 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B, Grade A and Grade A. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJG. 5 Issues raised: (1) 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; (2) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (3) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to

withdrawal of the article from BPG publications and may even be held liable. 6 Re-Review: Required. 7 Recommendation: Suggest to transferring WJH.

Answer

The discussion section has been revised to include the comment about the necessity or possibility of interferon/pegylated interferon for HBV therapy in the future (page 35, lines 4-15; page 35, lines 17-20). The questions raised by the reviewers have been addressed. Original figure documents have been provided according to guidelines. Meticulous revision of reference list has been carried out according to guidelines. Finally, we confirm that in our article we are not re-using figure(s) published elsewhere.