

## ANSWERING REVIEWERS



January 4<sup>th</sup>, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6771-review.docx).

**Title:** The clinical implications of hepatitis B virus mutations: recent advances

**Author:** Ivana Lazarevic

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6771

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

1 Format has been updated. According to "Format for Topic Highlights", the abstract was lengthened to reach at least 256 words. The added sentences were highlighted.

2 Revision has been made according to the suggestions of the reviewer

**(1) Reviewer No. 00007461**

**Reviewer's Comment:**

Page 5, last paragraph the sentence must be re-written for clarity "During the 1980s, a follow-up study of childhood vaccination in Italy revealed vaccinees who became HBsAg positive, despite the present of a strong antibody response to HBsAg".

**Answer:**

**The sentence was re-written to clarify the meaning and was highlighted in the text.**

**Reviewer's Comment:**

Page 11, please revise sentences as follows, since these are well established functions of HBx: HBx serves as transactivator and is required for efficient transcription of viral RNAs from CCC DNA in infected hepatocytes[4]. Please add the following references in support of this statement: ? Andrisani OM, Barnabas S. The transcriptional function of the hepatitis B virus X protein and its role in hepatocarcinogenesis. *Int J Oncol* 1999;15(2):373-9. ? Bouchard MJ, Schneider RJ. The enigmatic X gene of hepatitis B virus. *J Virol* 2004;78(23):12725-34. HBx protein has a role in HBV-induced carcinogenesis by number of different mechanisms[71,72]. Please add the following references in support of this statement: ? Terradillos O, Billet O, Renard CA, Levy R, Molina T, Briand P, et al. The hepatitis B virus X gene potentiates c-myc-induced liver oncogenesis in transgenic mice. *Oncogene* 1997;14(4):395-404. Madden CR, Finegold MJ, Slagle BL. Hepatitis B virus X protein acts as a tumor promoter in development of diethylnitrosamine-induced preneoplastic lesions. *J Virol* 2001;75(8):3851-8. ? Buendia MA. Genetics of hepatocellular carcinoma. *Semin Cancer Biol* 2000;10(3):185-200

**Answer:**

**The sentences were revised according to reviewer's suggestion and the suggested references were added in support of these statements. The changes were highlighted in the text.**

**(2) Reviewer No. 00742524**

**Reviewer's Comment:**

Addressing the following concerns will significantly enhance the manuscript. 1) Drug-resistant and vaccine-escape mutants as well as occult hepatitis B in patients with HBV/HIV and HBV/HCV co-infection should be described in detail. New papers such as *Hepatology* 58:912-922, 2013 should be cited and discussed.

**Answer:**

**The suggestion for improving the manuscript, by adding information on clinically relevant HBV mutations in HBV/HIV and HBV/HCV co-infected patients, was appreciated and the chapter discussing these matters was added at the end of the manuscript. The suggested reference was discussed and cited.**

**Reviewer's Comment:**

2) A table or diagram summarizing the different mutants would be helpful.

**Answer:**

**The table summarizing mutations mentioned in the text was added at the end of the manuscript. Several references to the table were added in the text and highlighted.**

**Reviewer's Comment:**

3) Truncated HBx is commonly found to be integrated into cellular genome. This should be explained clearly.

**Answer:**

**The sentence clarifying this matter was added in the chapter about X gene mutations and highlighted.**

**Reviewer's Comment:**

4) Some typos such as "weather" (should be "whether") and "CCC DNA" (should be "cccDNA") should be corrected.

**Answer:**

**The typing errors were corrected throughout the text and language polishing was performed.**

**(3)Editor's comments:**

1.) Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

**Answer:**

**The core tip was added to the manuscript to outline the core contents of the paper.**

2.) Please add DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

**Answer:**

**DOI citation was added wherever available. PMID is present for all references.**

3 References and typesetting were corrected throughout the text.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'I. Lazarevic', is placed on a light blue rectangular background.

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