

Format for ANSWERING REVIEWERS

October 14, 2014



Dear Editor,

Please find enclosed the revised manuscript in Word format (file name: 13589-revised.docx). We have replied to the comments of the reviewers, and we hope we have clarified them in a sufficient way. The comments of the reviewers (in italic) followed by our answer are attached to this letter, and changes in the manuscript are highlighted in the revised version (underlined).

Title: Immune mechanisms of vaccine induced protection against chronic HCV infection in chimpanzees

Author: Babs Verstrepen, André Boonstra, en Gerrit Koopman

Name of Journal: *World Journal Hepatology*

ESPS Manuscript NO: 13589

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

1 The format has been updated, full names of the authors as well as the address and postal code of the authors have been given. All the available information regarding the DOI and PMID in the reference list is included. Unfortunately, this information is not available for all manuscripts. Especially for manuscripts published before 1995, no such features are available.

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

Review 00736297

This very interesting review both for clinicians and R&D workers. Paper met the scope of World Journal of Hepatology and could be published without corrections. Small editorial errors are presented but could

corrected during final revision.

Re: We thank the reviewer for this compliment and in the new revised version we did our best to correct the editorial errors

Reviewer 00503125

Hepatitis C virus remains a major problem for a large number of people. In this manuscript a detailed review is provided regarding the development of a prophylactic vaccine against hepatitis C virus including pre-clinical data in primates along with the experience in patients.

Re: We would like to thank the reviewer for the kind evaluation of the manuscript.

Reviewer 00069773

This manuscript is well written and gives an interesting overview on a very interesting topic. However, the methodology for the collection of the literature is not described. Which type of literature review did the authors wanted to make? The authors must give a substantial overview on how they collected the data, during which time period, using which keywords; what was the evolution of the articles which were withheld,...

Re: We acknowledge the remark of the reviewer about the collection of the literature. To our knowledge we have included all studies in which naïve chimpanzees were used in prophylactic HCV vaccine studies. Due to specialized facilities and personnel, the total number of research groups working on prophylactic HCV vaccines in chimpanzees is extremely limited. Also, literature searches in PubMed combining the keywords chimpanzee(s) and hepatitis or HCV in combination with any of the following keywords; vaccine(s), vaccination, immunization or immunized did not reveal other experiments.

It many cases multiple publication have arisen emanating from a single vaccine study. We have tried to include all of the follow-up research that was directed at the identification of the correlate of protection or the mechanism behind partial vaccine induced protection. Studies addressing other aspects that are more remotely related to vaccine evaluation may not always have been included.

In conclusion, we are not aware of any other prophylactic vaccine efficacy studies performed in chimpanzees or that we withheld any article describing this type of work. However, should we have missed a publication or description on a study from another source then we are very interested in the data and happy to include the reference in the manuscript.

Information was added to the manuscript at page 6 to describe the method used for collection of the data.

Reviewer 00068420

This review article gives an unnecessary detail under each head without drawing a conclusion of all these studies. Instead of describing details, it is better to draw conclusions and organize the findings in author's language to update the readers on the topic of interest. It needs complete write-up in a concise and informative language. The text is too lengthy and may be shortened to one-fourth of the total.

Re: With this review we aimed to provide a complete overview on the work performed with regard to HCV vaccine evaluation in chimpanzees. We feel that this comprehensive overview is justified by the fact that the prospect of future studies in this animal model and therefore generation of new data will be very limited. We have included a paragraph with conclusions at the end, to provide a brief description that can be used by interested readers.

Reviewer 00504045

This manuscript by B.E. Verstrepen et al. reviewed the current progress in prophylactic vaccines against HCV, with focus on the immunity evaluation of various types of vaccine candidates in chimpanzee models. The manuscript is well organized and written and worthy of publication.

Re: We thank the reviewer for carefully reading our manuscript and for the given remarks and suggestions. We have replied to the comments of the reviewers, and we hope we have clarified them in a sufficient way.

1. The lack of line numbers makes it difficult to make a review.

Re: We apologize to the reviewer for the inconvenience.

2. The topics of the paper seen to be a bit scattered and should be more focused

Re: We acknowledge the concerns of the reviewer about the order of the different topics in the manuscript. HCV research and specifically HCV vaccine development was modeled around knowledge gained in the HIV-field, for instance, envelope vaccines were evaluated before it was technically possible to measure HCV-envelope-neutralization. Because of this illogical order of events in HCV research,

many different topic-arrangements were tried during the process of writing of this manuscript and nevertheless, the current order resulted in the most clear story.

3. *the abstract seems to be not informative enough to summarize the main content of the manuscript*

Re: The abstract was modified and now contains the main conclusions of the described vaccine studies.

4. *Some sections, such as Vaccines sections A) and B), are too long and should be divided into smaller subsections*

Re: We agree with the reviewer and therefore we have, like the reviewer suggested, divided the sections into smaller subsections.

5. *The authors are recommended to include a Conclusions and future directions section that deal with the challenges and prospects of HCV vaccine development.*

Re: In the revised version of our manuscript we have added a section describing the conclusions and the future perspectives of a prophylactic HCV vaccine (starting at page 25 of the manuscript)

6. *The manuscript should be subjected to minor language editing.*

Re: All suggestions of the reviewer have been included in the revised version of the manuscript

3 References and typesetting were corrected

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

Sincerely yours,

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