

July 29<sup>th</sup>, 2015

Dear Editor

Thanks for your message containing the peer-review of our manuscript (20968, Topic Highlight, World Journal of Gastroenterology) entitled “Inflammatory status in human hepatic cirrhosis” by María Martínez-Esparza, María Tristán-Manzano, Antonio J Ruiz-Alcaraz and Pilar García-Peñarrubia.

We have found all the criticisms raised by the reviewers very relevant and constructive. Indeed, they improve the scientific content and the presentation of our manuscript. Accordingly, they have been incorporated in the revised version.

I enclose all the documents required except the language certificate as we previously agree. The detection of plagiarism has been performed with “The Pensters” software instead of “Cross Check”, with your consent too. The name of that file is now 20968-Plagiarism detection instead of 20968-CrossCheck. It is a PDF file with the complete report of the plagiarism search instead a screenshot of the first page. We also provide the revised manuscript file, highlighting the changes as requested (20968-Revised manuscript) and additional file where are marked the deletions performed on text (20968-Revised manuscript with marks). In addition we provided the .pptx files of the figures as requested (see “Answers to the comments raised by the scientific editor in the edited document”).

We hope our manuscript will be now considered suitable for publication in *World Journal of Gastroenterology*

Looking forward to hearing from you soon,

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## **Answers to the queries raised by the Reviewers**

### **Reviewed by 00053580 (Review Time 2015-07-04 06:10)**

This is a very well written and relevant manuscript, and may be accepted after minor revisions. The manuscript is very extensive, and some paragraphs must be suppressed. There are many abbreviations or acronyms, some are abbreviated many times and must be reviewed. Others are used only one time and may be suppressed.

Thank you very much for your comments.

- “some paragraphs must be suppressed” We have reduced the extension of the manuscript in the revised version.

- “There are many abbreviations or acronyms, some are abbreviated many times and must be reviewed. Others are used only one time and may be suppressed”. We have corrected this accordingly in the revised version of the manuscript. We have also deleted the extended names of some molecules, and included a list of abbreviations as suggested by the reviewer 03260869.

### **Reviewed by 00068156 (Review Time 2015-07-07 09:26)**

In this paper, the author provided an overview of the current evidence-based information on the new findings about the inflammatory status implicated in the development of human liver cirrhosis induced by the two main causes, infection with HCV and chronic alcohol abuse, avoiding results obtained from animal models. The author demonstrated that the predominant features of HCV-related cirrhosis are more related with those that allow viral evasion of the immune defenses, especially although not exclusively, inhibition of IFNs secretion, NK activation and T cell-mediated cytotoxicity. On the contrary, the inflammatory status of alcohol-induced cirrhosis is determined by the combined effect of direct hepatotoxicity of ethanol metabolites and increases of the intestinal permeability, allowing bacteria and bacterial products translocation, into the portal circulation, mesenteric lymph nodes and peritoneal cavity. This paper is described in detail, which, as a valuable information, could help the readers that have better understand the first-hand knowledge of this topic to start novel studies.

Thank you very much for your comments.

### **Reviewed by 03260869 (Review Time 2015-07-10 16:47)**

A very well-written manuscript on a very tough subject. There are very few points that need editing: page 6: patient's dead change to patient's death page 10: dow-nregulated change to down-regulated page 11: capital letters not needed for Myeloid (myeloid); Reactive (reactive); HCV-Core protein (HCV-core protein) miRNAs in the title; change

to MicroRNAs page 17: titters of antibodies change to titers page 23: BT change to: bacterial translocation (BT) page 25: Furthermore, it has been described the predominant activated state of peritoneal macrophages from cirrhotic patients[159,165,166]. Needs re-phrasing. page 26: sIgA, change to secretory IgA (sIgA) page 27: Abdominal inflammation after increased permeation of viable bacteria; title that needs modification This lengthy manuscript needs a table of abbreviations. Figure 1 is innovative. Figure 2 is less informative.

Thank you very much for your comments.

- “patient’s dead change to patient's death”. This change has been included in the revised version (page 7, lane 20)

- “dow-nregulated change to down-regulated”. This change has been included in the revised version (page 11, lane 1)

- “capital letters not needed for Myeloid (myeloid); Reactive (reactive)”. These changes have been included in the revised version (page 11, lanes 22 and 23).

- “HCV-Core protein (HCV-core protein) miRNAs in the title; change to MicroRNAs”. These changes have been included in the revised version (page 12, lanes 1 and 16).

- “titters of antibodies change to titers”. This change has been included in the revised version (page 17, lane 20).

- “BT change to: bacterial translocation (BT)”. This change has been included in the revised version (page 23, lane 23).

- “Furthermore, it has been described the predominant activated state of peritoneal macrophages from cirrhotic patients[159,165,166]. Needs re-phrasing” This change has been included in the revised version (page 25, lane 9).

- “sIgA, change to secretory IgA (sIgA)”. This change has been included in the revised version (page 26, lane 5).

- “Abdominal inflammation after increased permeation of viable bacteria; title that needs modification”. This change has been included in the revised version in agreement with the relative title (Page 27, lane 15).

- “This lengthy manuscript needs a table of abbreviations”. We have deleted the extended names of some molecules, and included two list of abbreviations at the end of the manuscript in the revised version, one with the abbreviation of terms extended on text, and other with the names of molecules whose abbreviations are not extended on text (page 54)

- “Figure 1 is innovative. Figure 2 is less informative”. We think that Figure 2 is key to understand and visualize the inflammatory process emphasizing in the vicious circle that aggravates the situation leading to the exhaustion of the immune system defenses. The differences between the inflammatory status of alcohol- and HCV-induced cirrhosis

presented here, summarizes the available information and highlight the interest of performing new studies to gain further insights into the cellular and molecular mechanisms implicated in this disease.

### **Answers to the comments raised by the scientific editor in the edited document**

- “Please provide language a certificate letter from a professional English language editing company (Classification of the manuscript language quality evaluation is B). For manuscripts submitted by non-native speakers of English, please provide a language certificate from one of the professional English language editing companies mentioned in ‘**The Revision Policies of BPG for Article**’.” The results of language evaluation of our manuscript is “Grade A: priority publishing” for the three reviewers. After consult, the scientific editor decided that we don’t need to provide a language certificate from one of the professional English language editing.
- “Please add conflict of interest, which must be provided, otherwise the manuscript will be unaccepted finally”. This information has been included in the revised version and the signed document and its corresponding file (20968-Conflict-of-interest statement) has been provided.
- “Please read the core tip then provide the audio core tip: Acceptable file formats: .mp3, .wav, or .aiff. Maximum file size: 10 MB. To achieve the best quality, don’t allow to have the noise”. We have change the core tip text in the revised version of the manuscript (page 4, lane 4) to better fit to oral communication and the audio core tip file has been provided (20968-Audio core tip).
- “For the figures, the fonts and lines can be edited or moved. It can be made by ppt” We provide the pptx files for Figure 1 and 2 (20968-Figure 1.pptx and 20968-Figure 2.pptx respectively).