

30<sup>th</sup> October 2018.

Ying Dou,

Science Editor,

World Journal of Gastrointestinal Pathophysiology.

Dear Dr Ying,

### **Revised Manuscript Submission – Minireview-42023**

Thank you very much for inviting us to submit a revised manuscript. We value the reviewer's comments and have revised the manuscript accordingly.

Please find uploaded the revised manuscript titled "Current therapies and novel approaches for biliary diseases".

We have listed below the reviewer's comments followed by our answers.

#### **The Editor**

**Comment:** 1) Please revise the manuscript according to the review report and my comments. And answer all of the reviewers' comments carefully (point-to-point).

**Answer:** The minireview has been revised as per editor's and reviewer's suggestions. Please find the answers for the reviewer's comments below.

**Comment:** 2) Please provide the approved grant application form(s) for each grant.

**Answer:** As per the editor's request two grant application approvals are submitted along with the revised manuscript.

**Comment:** 3) Please add 5-10 key words here, words that could reflect content of the study mainly from Index Medicus

**Answer:** As per the editor's suggestion, 5 key words have been added.

**Comment:** 4) Core tip should be less than 100 words.

**Answer:** As per the editor's suggestion, core tip has been reduced to 100 words.

**Comment:** 5) Please add PubMed citation numbers and 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:** As per editor's suggestions, PubMed citation numbers and DOI citation were added to the reference list and the names of all authors are now listed. The first page of papers where there is no PMID and DOI are also provided.

**Reviewer #1- (Reviewer code-02566971):**

Specific comments: None

**Reviewer #2 - (Reviewer code-02444978):**

Specific comments:

**Comment:** In the description of cirrhosis (section Cirrhosis), the sentence “intrahepatic vascular shunts between afferent (portal vein and hepatic artery) and efferent (hepatic vein) vessels of the liver”, although reported in ref.10, is uncertain. In general, the hepatic artery supplies the peribiliary capillary plexus and in developing fibrosis can supply the fibrous tissue by means of a newly formed capillary network. So, direct connection with the central vein are not ascertained. Other studies on experimental cirrhosis (Gaudio et al, Hepatology 1993, 17(3):477-485; Onori et al, J Hepatol 2000;33:555–63) does not report the presence of shunts between the branches of the hepatic artery and the central vein. I suggest to delete “portal vein and hepatic artery” inside the bracket.

**Answer:** As per the reviewer's suggestion, we have deleted “portal vein and hepatic artery” that was mentioned within brackets and changed the ‘efferent’ to ‘efferent hepatic vein’.

**Reviewer #3 - (Reviewer code-02444931):**

Specific comments:

**Comment:** 1) More attention needed to be payed to the language expression and word spelling. For example, the word “focused” was misspelled in the “Abstract”, and the word “myofibroblasts” was misspelled in the “Liver injury and fibrosis”.

**Answer:** We have gone through the manuscript and corrected the misspelled words.

**Comment:** 2) References were a bit outdated. There were 62 references in the text, of which 19 references were published in the last 5 years, and only 5 references were published in the past 3 years.

**Answer:** As per reviewer's comment, new references (articles published within last 3 years) have been added to the revised manuscript.

**Comment:** 3) The focus of the article was not prominent. The title of the article was "Current therapeutic advances in biliary diseases"; in the abstract, the article mainly described the pathophysiology of liver fibrosis and its progression to cirrhosis with special emphasis on biliary fibrosis and current therapeutic options; in the main body of the article, it devoted much space to discuss the epidemiology and etiology of chronic liver disease, the process of liver fibrosis and basic characteristics of cirrhosis. The focus of this review was not prominent enough, and the background introduction needed to be more concise and clearer

**Answer:** Following the review's suggestion, we have changed the article title to "Current therapies and novel approaches for biliary diseases" to better reflect the contents of the manuscript.

**Comment:** 4) The article structure was unreasonable. The article consisted of seven parts: Introduction, Liver injury and fibrosis, Cirrhosis, Biliary disease, Pathogenesis of cholestasis and biliary fibrosis, Current treatment options for cholangiopathies and ACE2 overexpression in the liver. The content in the "Introduction" was too simple to elaborate on the disease background, and contents of "Liver injury and fibrosis" and "Cirrhosis" actually belonged to the "Introduction". In addition, there was a lack of summary at the end.

**Answer:** As per reviewer's suggestion, we have combined "Liver injury and fibrosis" and "Cirrhosis" sections and described in Introduction section. We have also added a separate section of "summary" at the end of the manuscript.

**Comment:** 5) The contents of the review were a bit vacuous and lacked logic. For example, in the "Liver injury and fibrosis", the article introduced different classifications of liver injury, the process of liver fibrosis and cellular crosstalk. The mechanism of hepatic stellate cells, Kupffer cells, myofibroblasts and mast cells was listed separately, which lacked logic and depth.

**Answer:** We have now made changes to the manuscript. However, the roles of different cell types in the liver during fibrogenesis have been briefly described to suit our mini-review because a detailed description is normally given in a standard review.

**Reviewer #4 - (Reviewer code-01221925):**

Specific comments:

**Comment:** 1) Although this is of significant interest, the title "Current therapeutic advances in biliary diseases" creates an expectation for a more well-rounded presentation, rather than placing too much emphasis on the specific mechanism. Potentially, this paper may be presented as a research paper, other than a mini-review

**Answer:** As per reviewer's comment, we have now changed the title of this mini-review to "Current therapies and novel approaches for biliary diseases" We hope the new title will reflect what has been emphasized in our mini-review.

Yours sincerely,

Chandana B Herath, PhD

Senior Research Fellow

Department of Medicine, The University of Melbourne,

Austin Health, Heidelberg 3084,

Victoria, AUSTRALIA.

Telephone: +61 3 9496 2549

Fax: +61 3 9457 5485

Email: [peter.angus@austin.org.au](mailto:peter.angus@austin.org.au)