February 19, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8140-review.doc).

Title: New Advances in Molecular Mechanisms and Emerging Therapeutic Targets in Alcoholic Liver Diseases

Author: Jessica A. Williams, Sharon J. Manley, Wen-Xing Ding

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8140

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

1. The manuscript format has been updated according to the editor's suggestions. Author contributions have been added, the citation format was changed, and the primary and secondary titles were put into the correct format. The decomposable figures were also included per the editor's request.

2. Thank you to the reviewers for their positive and critical comments. Revision has been made according to the suggestions of the reviewers.

(1) In response to reviewer 1: Williams et al have written a thorough and up to date review of the mechanisms of alcohol related liver disease, focussing on data from animal models of ALD. The discussion of adaptive mechanisms such as IL-22 and autophagy is detailed and particularly interesting. The following minor comments are suggested:

1. Suggestion: The introduction describing ALD pathogenesis in humans is too simplistic. It should emphasise that it is a multifactorial disease involving the interplay of genetic/ethnic factors (eg females and hispanics are more susceptible), the immune system and other lifestyle factors such as obesity and smoking. Animal models may therefore only explain part of the overall development of the disease in humans.

   Response: Thank you to the reviewer for this great comment. The introduction has been expanded to include this information.

2. Suggestion: References are needed for rate of progression to steatohepatitis and cirrhosis (eg Teli et al, Lancet 1995).

   Response: Thank you to the reviewer for this suggestion. References have been added for this.

3. Suggestion: The section on SAM would be made more readable and easier to understand with a diagram of methionine metabolism and where alcohol influences it.

   Response: We agree with the reviewer that this information should be added. A diagram outlining the influence of alcohol on methionine metabolism has been added in Figure 1. The original Figures 1 and 2 are now Figures 2 and 3.

4. Suggestion: The first paragraph of the FOXO3 section (pages 38-39) is unnecessarily detailed

and not relevant to the potential role of FOXO3 in ALD.

Response: Thank you to the reviewer for this suggestion. This paragraph has been revised to include only relevant information pertaining to FOXO3 and ALD.

5. Suggestion: In the concluding remarks it should be reiterated that existing animal models mimic neither the chronic disease process in human ALD nor its complex multifactorial nature. Therefore putative targets may not translate well in human disease. As well as improving and standardising animal models, further work on human tissue and human ALD should also be advocated.

   Response: This is a great suggestion by the reviewer, and this information has been included in the concluding remarks.

(2) In response to Reviewer 2: Dear Dr. Ding, I have read your review entitled "New Advances in Molecular Mechanisms and Emerging Therapeutic Targets in Alcoholic Liver Diseases" with great interest. It is an important topic since alcohol is the third most common preventable cause of death after smoking and hypertension. In this review, Williams and colleagues give a good overview of the molecular factors involved in ALD. The authors also discussed mechanisms underlying ALD-associated diseases and current possible protective pathways in ALD aiming to offer a novel avenue for treating ALD. It is a good and timely review which would be of great interest for the readers of the World Journal of Gastroenterology and others. Giving the fact that the large molecular overview will facilitate the tracing of the most important genes involved in ALD, therefore I advice to give this manuscript a chance for publication.

Response: Thank you to the reviewer for these supportive comments!

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

Sincerely yours,

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