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Madrid, September 1st, 2018

Dear Editorial Office, World Journal of Gastroenterology:

Please find attached the revised form of our Editorial titled "**Extracellular vesicles in liver diseases and beyond**" that we would like to resubmit to WJG.

We thank the Reviewers and the Editors for their comments and hope that now our article is now acceptable for publication in **World Journal of Gastroenterology** and look forward to your reply.

Sincerely yours,

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REPLY TO REVIEWERS

Reviewer 1 (02537773):

The present editorial by Moran et al. provides overview on the topic of extracellular vesicles. The topic deals primarily with EV in liver disease. Overall it is well written and systematic. The topics other than liver are very brief and certain topics (ex. Oncology) are very brief. Nevertheless, since the main focus is the liver disease, I would recommend to include/change the title- with focus on the liver. Abstract: "However" is used 2 times. I would recommend to rephrase the second sentence. The current figures have bad formatting and are not readable completely. Unless the authors prepared each figure them self- please consider obtaining the rights for using the images.

REPLY: Thank you for your comments. We have now changed the title to "Extracellular vesicles in liver diseases and beyond" to be more specific. The mistakes in the abstract are now corrected. We have supplied high resolution TIFF images of our figures which have been done by us.

Reviewer 2 (00053441):

This manuscript focus on a hot topic in these days. It is easy to follow and well written. However, in the scope of extracellular vesicles (EV) and liver, a topic referring to viral hepatitis is missing. A recent review (Sato et al, 2016, Journal of Hepatology 65, 213-221) nicely addressed this topic. A table encompassing the EV important for each pathological scenario (for liver and extrahepatic diseases) would facilitate the reading. Minor points: page 7: demonstrating that there was a significant increase in levels of Hsp90 EVs SECRETED from hepatocytes in ALD page 8: metalloproteinase-2 and -9 which FACILITATE the invasion of HCC cells[31]

REPLY: Thank you for your comments. As suggested by the Reviewer, we have added the topic referring to viral hepatitis and the table with a summary for each disease has been added. Additionally, the mistakes are now corrected.

Reviewer 3 (03633577):

This paper summarizes current understandings regarding relationship between extracellular vesicles (EVs) produced in the liver and diseases. I have a few suggestions. 1) I felt that manuscript title should be more specific given that this paper focuses on relationship between liver-derived EVs and related diseases. 2) Regarding comment 2, papers regarding similar topic have already been published (For example, Sato et al., J Hepatol., 65, 213-221, 2016; Masyuk et al., J Hepatol., 59, 621-625, 2013). This reviewer suggests that authors cite these papers and expand Abstract or Introduction section by adding statement regarding what is already argued about this topic and what is newly added by this editorial paper. This would be helpful for readers and improve manuscript.

REPLY: Thank you. We have changed the title to "Extracellular vesicles in liver

diseases and beyond” to be more specific and added the citations. Additionally, we have included a statement in the Abstract to clarify the novelty of our Editorial.

Reviewer 4 (03538158):

Moran and Cuvero reviewed the EVs. Manuscript seems written well. 1. Please mention the EVs in liver fibrosis. See: Sasaki R, Devhare PB, Steele R, Ray R, Ray RB. Hepatitis C virus-induced CCL5 secretion from macrophages activates hepatic stellate cells. Hepatology. 2017 Sep;66(3):746-757. doi: 10.1002/hep.29170. 2. Add EVs in viral hepatitis section. 3. In page 6, line 18, What is “APAP-induced”?? Also making corrections are needed in abbreviations section.

REPLY: Thank you for your comments. We have added a specific topic about viral hepatitis including the article you suggested. Additionally, the abbreviations section is now corrected. Regarding your question in relation to APAP-induced, we are referring to acetaminophen overdose as a model of drug-induced liver injury (DILI).