Cover letter.
Manuscript NO.: 28328

Aline Awad and Ama Gassam-Diagne
INSERM U 1193
F-94800 Villejuif, France.

Dear Editor,

We are pleased to resubmit our review manuscript, after revision, to the World Journal of Hepatology. Our manuscript is entitled "the PI3K/SHIP2/PTEN pathway in cell polarity and HCV pathogenesis" (Manuscript NO.: 28328).

I) First, we have revised the manuscript according to the reviews (Reviewer code: 03537078), and here are the modifications we have done:

1- What happens to this pathway when HCV-related chronic hepatitis is present in a patient with Metabolic Syndrome and NAFLD?

To answer this question, we developed a paragraph (page 14-16) discussing the PI3K/SHIP2/PTEN pathway in NAFLD and HCV infected patients. We have highlighted that PI3K/SHIP2/PTEN pathway alterations are responsible of the disruption of phospholipid metabolism generating a NAFLD.

2- Still, what is the role of antiviral therapy and insulin resistance at the light of ..... Does a lower insulin resistance affect antiviral therapy.....Gut 2006 .

For this issue, we developed first a paragraph discussing the relationship between insulin resistance and HCV infection (page 11-12). This paragraph show that insulin resistance is very common in the context of chronic HCV infection, and it causes liver steatosis in patients infected with genotypes 1, for this reason antiviral therapy is not sufficient in HCV genotype 1 infection. We cited the two articles in Gut 2006 describing how insulin resistance reduces the biological

response to IFN-α, (Walsh M J *et al.* Gut 2006) and confirming that by improving metabolic syndrome ameliorates the foundations for a good antiviral response (Tarantino G. *et al.* Gut 2006). Then, we highlighted a new clinic trial using metformin as insulin sensitizers to improve the response to HCV treatment, and decrease liver fibrosis in this patient population.

Finally, we developed a paragraph discussing The PI3K/SHIP2/PTEN pathway and Insulin resistance (page 12-14). This part shows that deregulations of this pathway are very linked with insulin resistance. Several insulin resistance treatments act via the PI3K/Akt pathway.

II) We added a figure (figure 2) to illustrate the difference between simple epithelial cell polarity and hepotocytes polarity which are described in the text.

III) We updated the manuscript according to the Guidelines and Requirements for Manuscript Revision-Review.

IV) The language of the manuscript has been revised by a professional translator of scientific documents. (Certificate in attachment).

All modifications are highlited in the text.

We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere.

Please address all correspondence concerning this manuscript to us at: ama.gassama@inserm.fr

Thank you for your consideration of this manuscript.

Sincerely,

10 September 2016

Aline Awad and Ama Gassama-Diagne