Reviewer's report

**Title:** Fluvastatin attenuates hepatic steatosis-induced fibrogenesis in rats through inhibiting paracrine effect of hepatocyte on hepatic stellate cells

**Version:** 2  **Date:** 10 September 2014

**Reviewer:** Silvia Affo

**Reviewer’s report:**

**General comments:**

- It is not always easy to understand the text and a revision of the English is recommended to avoid some confounding data.

- In the discussion too much space is dedicated mentioning the literature data, authors should write a little more about the use of Fluvastatin as potential treatment of NASH induced-fibrosis based on their results.

**Specific comments:**

- Authors show the effects of Fluvastatin on palmitate (PA)-treated hepatocytes, but no data regarding the effects of Fluvastatin alone on untreated hepatocytes are shown; this group is important to show the direct effects of Fluvastatin on hepatocytes

- Authors state that conditioned media from PA-treated hepatocytes induce activation of HSCs by showing the alpha-sma protein expression, but no other data about their activation are shown (i.e. gene expression...)

- When authors treat hepatocytes with Fluvastatin, they show gene expression, ROS production, NFKB nuclear expression, on the other hand, when they treat HSCs with Fluvastatin, they only focus their attention on alpha-sma protein expression, I think more data should be shown to see the real effects of Fluvastatin on HSCs in absence and presence of Fluvastatin and in absence and presence of conditioned media.

Moreover, as before, the group only Fluvastatin is missing.

- In figure 3B the use of TGF-beta as positive control is correct, but the groups Fluvastatin alone and TGF-beta+Fluvastatin are missing, please include these groups

- Before state that PA has no effect on HSCs activation, did the authors check the expression of some gene at mRNA level?

- What happens if you stimulate the HSCs with the conditioned media from palmitate and Fluvastatin-treated hepatocytes? Does it also inhibit the HSC activation?
- For the in vivo model, how do authors choose the dose of Fluvastatin? And how do they know that the dose used is not hepatotoxic?

- Animals with combined CDAA and Fluvastatin show a significant and important reduction in their weight, getting lower than control group. How do authors explain this effect?

- It is not clear how the inflammation and steatosis scores have been assessed in the animals

- Why do not authors use the Oil Red O staining to assess the steatosis in the rats?

- To propose Fluvastatin as a potential drug to be used as a treatment and not only as a prevention, would be very important to include other 2 groups in the animal studies: 1) the group treated only with Fluvastatin and regular diet, to look at the direct effects of Fluvastatin and study its hepatotoxicity and adverse effects (such weights loss, ALT, AST...); 2) induce the steatosis and fibrosis with your diet and then, when it is well established, treat the animals with the drug.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

i declare that I have no competing interests