In this paper, Xu et al investigate a novel method of generating differentiated hepatocytes from two sources of mesenchymal stem cells and test their ability to recover liver damage in an experimental mouse model. The paper thus adressed an important question as stem cell therapy could help overcome current limitations of Treatment for metabolic liver diseases and liver injury. Yet, several Points Need to be adressed, the paper is not considered adequate for publication at this time.

Response Letter

1. The BALB/c mouse model of CCl4 induced liver damage was used. Yet, the authors describe rats and rat diet in the methods section.

We have corrected the mistake in the Experimental animals. we are sorry that this is a clerical error.

2. Is it correct that the cell phenotype of the isolated populations was tracked only after P2 and P3?

Yes. We have described the results in the supplement Figure1 in our another article "Mesenchymal Stem Cell-Seeded Regenerated Silk Fibroin Complex Matrices for Liver Regeneration in an Animal Model of Acute Liver Failure". The PMID is 28409921.

3. Concentrations are sometimes given as mM or uM and sometimes as e.g. 10^-7. Please use uniform Formats. Also language editing is needed.

We have corrected it.

4. The part on osteogenic Differentiation of the cells is not relevant here. The detailed results are neither shown nor used for any of the conclusions relevant to the paper. This can be deleted.

We have removed these results as you suggested.

5. How was the cell fate tracked in the mouse model? Was a mixed-sex-Transplantation Approach used? Otherwise it is unclear how this was really done specifically.

We didn't use the mixed-sex-transplantation approach. We used CM-Dil staining to track the transplanted cells. CM-Dil is one common dye used for cell tracing, and the labeling rate can be higher than 95%. The labeled cells still can be tracked after one month.

6. All histological microphotographs are very difficult to read and higher power magnifications are needed to Support the Claims from the results text part.

We have improved the quality of the Figs.

7. FACS Scans should be shown for the phenotypic characterization and not only listed in a supplementary tabl.e

We have showed the related pictures in our published article, so we think that it isn't necessary to repeat the results again. [PMID: 28409921]

8. Results for Primary hepatocytes should be included into Fig 1. As different scales are used between ADSCs and BMSC, it is difficult to compare the data. It is unclear for which

markers the controls were stained in Fig 1C. This Looks as if only nuclear staining was performed and no other marker applied and the Statement may thus be misleading. PLease verify and correct.

We will show the result in fig1. We used the same scale. At the same lens, ADSCs are larger than the BMSCs. We chosed one control makers to list here for if we list all the figures, the figure will become too large. We will delete it to avoid misleading .

9. Results for Fig 2 are difficult to see, too. Data should be quantified.

We transplanted the CM-Dil labeled MSCs to the mouse and after 1, 2, 3 and 7days after the transplantation, we used the fluorescence microscope to observe the engraftment of the CM-Dil labeled MSCs. So Fig 2 showed the engraftment of the transplanted cells in liver.

10. The Statement on p 16 on the ability to provide protection against CCl4 induced liver injury should be corrected. Actually, cells were applied after the injection of CCl4 so the observed results are rather a repair than a protection effect in my view.

Yes , our depiction is not accurate,we have corrected it and highlighted it .

11. Data in Fig 3 are unclear. There seems no difference at all between the two cell type Systems and CCl4 injection! Also CCl4 Groups Shows a return to baseline after day 3 to 7. Therefore, the Major Claim on this work seems not to be supported by this finding.

Fig3 shows the improved liver function of different experimental groups compared with the CCl_4 group. The experiment showed that there is no different between the ADSCs group and the BMSCs group. And our conclusion is that there is no different between the two groups. Mouse has self-healing capability and our result showed that the transplanted MSCs could reduce the recovery time of the liver injured mouse. Besides, the histological staining(Fig4) showed that compared the CCl_4 group, the inflammatory infiltration and congestion of the MSCs groups are much better than the CCl_4 group too.