Answer to Reviewer's Queries

Name of journal: World Journal of Hepatology

Manuscript NO: 40589

Title: Bioengineered functional humanized livers: An emerging supportive modality to bridge the gap of organ transplantation for management of end-stage liver diseases

All the changes have been incorporated in revised manuscript by track change.

Reviewer's Code: 03260503

Query: The article addresses a topic of broad and current interest in the very selective field of liver transplant. In the introduction it is very clearly explained the rationale of the reviewand the context that makes any progress in this direction so important: the increasingly high demand of liver grafts in patients with end stage liver disease in contrast with the shortage of organ donors justifies the need of alternative options. Some alternatives are then briefly reviewed, including intra-peritoneal human fetal hepatocyte transplantation, a procedure in which the hosting clinic is one of the pioneers, as it is interestingly highlighted in the introduction. The second issue of relevant significance that emerges from the review is the organ transplantation in an ectopic site consisting in the omentum, which is a futuristic, yet promising strategy, considering the numerous properties listed in the introduction and supported by recent evidence. The next chapter explains in a detailed manner the current state of regenerative strategies in end stage liver disease, including cell transplantation of liver/bone marrow derived stem cells or induced pluripotent stem cells as well as extra-corporeal liver support systems using both non-biological and bio-artificial liver support devices. The indications and limits of each techniqueis very coherently synthesized, providing the essential, yet comprehensive information supported by previous studies cited as bibliography. Bioengineered organ transplantation is approached the last in the series of regenerative strategies, its importance being implied form the many limitations of the previous techniques. The

process is thoroughly described in a very comprehensible manner. As expected, the process includes fascinating technology such as 3D bio-printing or humanized neo-organ development, depending on the chosen strategy to provide the necessary components.Both techniques are backed up by up to date in vivo and in vitro studies, adding the clinic's exclusive experience in generating acellularized whole liver as well as other organs. The major challenges in generating complete bioengineered functional liver are then listed, highlighting the importance of further research and the endeavor to improve such a complex technique. Another topic of the article of equal importance is the ectopic transplantation site consisting in the omentum. The numerous advantages of this procedure are again mentioned in a more detailed manner, supported by very recent data (some published as recent as a few months ago) and also by very interesting figures and photos collected from the clinic's archive. The conclusion emphasizes one last time the benefits of such a revolutionary breakthrough in the transplantation field and the importance of further research that can potentially change the medical approach of end stage liver disease. Considering language accuracy, some improvement mostly in grammar should be made in the first part of the article. Here are some examples that need to be revised: "considering to this study", following to this", "higher rates of success has been demonstrated", "possess lot of limitations", etc. After the introduction, the article doesn't need much improvement from the language point of view. Considering the bibliography, it is clear that the authors made a full literature review before writing the paper. The citations are up to date, some of them being published in the current year. In conclusion, the article approaches a significant topic of board interest, providing original concepts in bioengineered liver transplantation. The experience of the clinic with such technology is fascinatingly described in a comprehensive way. I therefore recommend that the article should be published after revising very few language errors.

Answer: As per the reviewer's suggestion, language errors have been corrected and incorporated in the manuscript and highlighted.

Reviewer's code: 02936529

Query: The author discuss the recent advances and challenges to create functional secondary livers and their further application in the management of ESLD, perhaps a supportive bridge for liver transplantation.A very concise and well-written text, with a good ordering of ideas, giving the reader a up-to-date informations about functional secondary livers concepts and their future utility.

Answer: No comments found.

Cross check report

1. Page 4, paragraph starting from "In cell transplantation strategies…….durable solution" has been revised and incorporated in texts.

Other specific comments

- As per the suggestion, running title has been shortened and limited to less than six words.
- As per the suggestion, core tip has been reduced to less than 100 words.
- All authors' abbreviation names and manuscript title are provided after core tip in manuscript.