Author’s response to reviews

Title: The FATZO mouse, a next generation model of type 2 diabetes, develops NAFLD and NASH when fed a western diet supplemented with fructose

Authors:

Gao Sun (gaogao_36@hotmail.com; gao.sun@crownbio.com)

Charles Jackson (vjackson@crownbio.com)

Karen Zimmerman (kzimmerman@crownbio.com)

Li-Kun Zhang (zhanglikun@crownbio.com)

Courtney Finnearty (cmfinnea@umail.iu.edu)

George Sandusky (gesandusky@umail.iu.edu)

Guo-Dong Zhang (guodong.zhang@crownbio.com)

Richard Peterson (rpeterson@crownbio.com)

Yi-Xin Wang (yxwang@crownbio.com)

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Reviewer reports:

Gianluca Svegliati-Baroni (Reviewer 1): In this study, Sun et al. fed FATZO mice with an high-fat diet (HFD) enriched in fructose in drinking water. In the first part of the study they evaluated mostly the histological picture of liver injury, while in the second part they evaluated the effect of OCA on the degree of liver injury.

This is a well done study, however the Authors should better define at the experimental level the differences between their model and what has been already published in the literature.

-GS: We have added discussions for the difference between FATZO model and several other rodent models, such as db/db, MCD induced, DIO model with C57BL/6J mice, etc. in the Discussion section.

Finally, both Introduction and Methods are too long. The Discussion should more focus on the real novelties of this paper and it is too much speculative.
-GS: The introduction and methods sections are trimmed now and the novelties of the paper are further discussed (page 14 and paragraph 1).

A detailed explanation of the protective effect of OCA, different from what is already known in the literature, should be provided.

-GS: The further discussion of protective effects of OCA is now included (page 14 and paragraph 2, page 15, paragraph 1).

Cláudia Pinto Marques Souza De Oliveira (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

This is an very interesting NASH animal model that can use to test new drugs.

Reviewer 2 (Reviewer 3): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

Statistics - Is the use of statistics in the manuscript appropriate?

Not sure - I am not able to assess the statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Yes - current version is technically sound

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: This study is conducted appropriately to determine if the FATZO mice fed a western type diet supplemented with fructose is a suitable clinical NASH model. The authors have used suitable animal numbers, allocated them randomly to the different treatment groups and had someone blinded to the study design perform the histology analysis.

REQUESTED REVISIONS:

Authors need to clarify the statistical analysis used here as it is unclear if they used a one way ANOVA or a t test. If they used both they need to precise in the figure legends which analysis is used for which figure.

-GS: The statistical analysis used in the study is now included in each figure legend.

In addition, it is surprising not to see histology data for the liver of the mice on diet for 8 and 12 weeks as they were planned in the study design and blood was used for blood chemistry. It would be interesting to see the progression of the liver pathology along the full time of the study rather than just seeing endpoint.

-GS: In this study, we did not evaluate the histological changes of the liver from the mice on diet for 8 and 12 weeks because we got the impression from the separate pilot experiments that the significant liver histopathological changes would take time to develop during WDF induction.

Finally, how can the authors explain that the mice lose fat mass after 4 weeks of diet while their body weight steadily increases?

-GS: The body fat presented in the Fig. 1B is the % fat over total body mass. The flat curve in the % fat mass after 4 weeks on diet while the body weight steadily increases indicates that the gain in fat mass is faster than the non-fat mass in the first weeks on diet, which becomes similar after 4 weeks on diet.

ADDITIONAL REQUESTS/SUGGESTIONS:

Get grammatical check as they are some typos in the manuscript
-GS: We have carefully gone through the revised manuscript by elimination of grammatical errors and typos.