

Dear Editor, Dr Gong:

We appreciate very much our reviewers' constructive comments and your detailed inspection to improve our manuscript. We have incorporated the required files and revised according the recommendations. FYI a portion of this paper is accepted for presentation in the Metabolic and Genetic Liver Disease Session at the Digestive Disease Week 2016 in San Diego CA which will help to increase the visibility of paper and the journal. The paper was carefully edited and revisions are highlighted.

Attached please find required files as follow:

- 1) Our revised highlighted and unmarked manuscript according the recommendation in Doc format.
- 2) Graphics number 1 through 4 in Prism format
- 4) Micrographs number 5-7 in PowerPoint format
- 5) Audio Core Tip in mp3 format
- 6) Copyright signed in PDF
- 7) References: are completed and PMID numbers are added.
- 5) Other files include: a) Conflict-of-Interest Statement, b)Institutional review board statement (Not applicable for basic research), c)Biostatistics statement, d) Institutional Animal Care and Use Committee Statement, e) Animal Care and Use Statement, f)Data sharing statement.

We thank and appreciate the favorable comments and interest expressed by the reviews.

Yes. Naïve controls and Sham treated animals did not lose weight.

Yes. Naïve controls and sham-treated animals and wildtypes did not develop any histopathological symptoms, and similar to previous studies discussed and added in results.

Yes, we agree with the reviewer. The results of the current study at the same dose confirmed the same effect of orally administrated DBTC in wildtypes (no multiorgan chronic disease) and as explained before. But the effect was exceptional for the TNFR1/R2 defiant animals. As they demonstrated severe chronic multiorgan disease with low oral dose administration which are extensively discussed in this paper.

Yes, we appreciate the comment from reviewer and agree the analysis sensibility with von Frey filaments is not the most sensitive analysis and rather subjective. However, the “von Frey test is an standard comparison commonly used in the field of pain research.” Therefore, we have included this statement in the Methods section and Results. Additionally, we have used other measurements including, posture, Gait Disturbance, and Spontaneous Visceral Pain Assessment to substantiate the findings.

We appreciate very much your efforts to facilitate publication of this manuscript.

Sincerely;

Helieh S. Oz, DVM, PhD, AGAF

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