

November 5, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 12776. review.doc).

Title: The thrombospondin peptide ABT-898 inhibits inflammation and angiogenesis in a colitis model
Author: Linda S. Gutierrez, Jun Ling, Derek Nye, Konstantina Papathomas and Catherine Dickinson
Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12776

The manuscript has been improved according to the suggestions of reviewers. Please, find below our point-by-point responses to the reviewers, describing the changes and indicating the page/section where such changes have been made. Most of the changes are underlined in the manuscript as well.

1. *"It is unclear what specific altered parameter relates to the statement on p. 11 regarding Fig 1B that "These results were statistically significant."* Response: Results driving this conclusion have been better explained (page. 13, underlined paragraph). In addition, figure 1e has been labeled.

2. *Panel E in Fig 2 is cited in the Results but not labeled in the figure.* Response: The Panel E is now labeled.

3. *In Fig 2 ABT-898 is clearly inhibiting angiogenesis, but endogenous TSP1 appears to not inhibit angiogenesis under the same conditions. Please discuss.*

Response: This point is discussed on page 14 (underline paragraph)

4. *The y-axis in Fig 3 needs a better label to indicate that IL-6 is being measured.* Response: the y-axis has been labeled as suggested.

5. *In Fig 4 p-STAT3 is elevated in the inflamed TSP1-null tissue, but total STAT3 seems also to be elevated. Is the ratio of p-STAT3/total STAT3 constant or elevated in the null? Has the data been replicated? If so, please present a bar graph with statistics.* Response: The Western blots were repeated three times and the statistical analysis was added as a new panel in Fig.4A. The intensity of p-STAT3 bands was normalized with the total STAT3 bands. The histology of pSTAT3 is now part of a new figure (Figure 5).

6. *It is interesting that endogenous TSP1 appears to be limiting STAT3 expression and activation because others have reported that STAT3 signaling induces TSP1 expression (Am J Physiol Renal Physiol. 2011 Nov; 301(5): F1014-25; Nat Commun. 2014,5:4294). This suggests a negative feedback loop and should be discussed.* Response: This issue is discussed on page 20 of the Discussion (underlined paragraph). In addition, the references provide by the reviewer and few others have been included.

7. *On p. 8 "100 ml of plasma" presumably should read "100 microliters"* Response: this mistake has been corrected.

8. *TSP1^{-/-} is inconsistently superscripted. Technically, to denote the null genotype the italicized proper murine gene name thbs1^{-/-} should be used.*

Response: the reviewer is correct stating that the gene TSP-1 should be indicated as thbs1, which is a more updated nomenclature. However, the HGNC, Entrez Gene and other sites still accept the term TSP-1 or TSP1 as synonyms. Researching the recent literature in Pubmed shows several papers in which the co-authors are still using TSP-1/-/: Soto-Pantoja et al. Matrix Biol. 2014,37:25-34; Kong et al.

Am J Physiol Endocrinol Metab. 2013; 305(3): E439-50 and Shibahara et al. Cancer Res. 2013; 73(1): 459-68. In addition, changing the nomenclature would require the re-entry of all the data to generate new graphs with the new denomination, when our time is very limited. We agree about the inconsistent use of superscript for the term TSP-1^{-/-}. We solved this issue by eliminating the superscript across the entire manuscript, matching the graphs in the figures.

9. Format has been updated, original figures are available and all the references have the required DOI.

Thank you again for reviewing our manuscript, we very much look forward to publish this manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Linda Gutierrez R.", written in black ink on a light-colored background.

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