

Dear Editor,

Thank you for your letter. We highly appreciate the valuable comments of the reviewers on our manuscript entitled “*Combined TIM-3 and PD-1 blockade restrains hepatocellular carcinoma development by facilitating CD4+ and CD8+ T cell-mediated antitumor immune responses*”. We have improved our manuscript according to the suggestions, and the amendments are highlighted with yellow color in the revised manuscript. Point by point responses to the reviewer’s comments are listed below. We would like to re-submit this manuscript for your kind consideration.

Yours sincerely,

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**Reviewer #1:**

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Thank you for a useful and important synopsis of this important topic. Due to the complex pathological mechanisms of HCC, ICIs with a single target exhibit poor overall response rate in HCC patients. I’m really appreciate that you investigated the effects of combined blockade of TIM-3 and PD-1 on T cell immunological function and cancer development in HCC mouse model. As you have found, combined blockade of TIM-3 and PD-1 has additive antitumor effects in a mouse model of HCC compared to treatment alone. Your findings will benefit the clinical treatment of HCC. Overall, your study is well conducted with good methodology and intelligible English. The material studied allows to draw the conclusions. SPECIFIC

COMMENTS: What does the special symbol SS, \*\*, ##, && represent in Figure 2 and Figure 3 mean? Please specify. The legend of some figures is not clearly described. It should have a detailed figure legend that provides a clear and comprehensive description of the information presented in the figure, so that I can understand without having to refer back to any other portion of the manuscript.

**Response:** We appreciate for your positive comments and thank you for pointing out this issue. According to your suggestion, we supplemented more details in figure legends and provided a clear and comprehensive description of the information presented in the figures. Moreover, we invited a native speaker to help us modify the typo and grammar errors and improve both grammar and language throughout the manuscript. We really hope that the language level of our manuscript has been substantially improved.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.

**Reviewer #2:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Title: Combined TIM-3 and PD-1 blockade restrains hepatocellular carcinoma development by facilitating CD4<sup>+</sup> and CD8<sup>+</sup> T cell-mediated antitumor immune responses. 1- TITLE reflected the main subject of the manuscript. 2- The ABSTRACT summarized and reflect the described in the manuscript. 3- KEY WORDS reflected the focus of the manuscript. 4- The manuscript adequately described the background and presented treatments of hepatocellular carcinoma, and the general information of immune checkpoint inhibitors targeting PD-1 and TIM-3. 5- The manuscript described methods (acquisition of clinical specimens, animals, and relevant cells, cell processing, and detection of immunohistochemistry and cytokine levels,

Statistical analysis, etc.) in adequate detail. 6- The research objectives are achieved by the experiments used in this study. Authors determined the levels of PD-1 and TIM-3 on CD4<sup>+</sup> and CD8<sup>+</sup> T cells from tumor tissues, ascites, and matched adjacent tissues of HCC patients with flow cytometry. They also treated HCC xenograft mouse model with anti-TIM-3 mAb and/or anti-PD-1 mAb. 7- The manuscript interpreted the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. 8- Manuscript included sufficient, good quality Tables and Figures. Overall, the manuscript is well, concisely and coherently organized and presented and the style, language and grammar are accurate and appropriated. The data are rich and logical, so I recommend that the manuscript can be published.

**Response:** We appreciate for your positive comments. To perfect our manuscript, we invited a native speaker to help us modify the typo and grammar errors and improve both grammar and language throughout the manuscript. We really hope that the language level of our manuscript has been substantially improved.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.