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April 15, 2018

Dr. Ze-Mao Gong
Science Editor, Editorial Office
World Journal of Gastroenterology
Baishideng Publishing Group Inc.

Dear Dr. Gong

Re: Manuscript No. 38855 "Emergence of immunotherapy as a novel way to treat hepatocellular carcinoma" by Mukaida and Nakamoto.

We express our sincere gratitude to your invaluable recommendations on our above mentioned manuscript. We have revised the manuscript in response to the reviewers' comments as follows. We indicate the major modifications in red in the text.

Review 03664082
#1. The number of the words should be less than the current version. This is more likely to be a lecture or chapter book! It is strongly recommended that delete unnecessary and less essential sentences. If below recommendations be considered, and more importantly, the unnecessary sentences and unrelated to immunotherapy of HCC be omitted, it may be qualified for publication in "World Journal of Gastroenterology".

In response to the comment, we deleted the section on drug therapy in the previous manuscript, in order to focus on immunotherapy.

#2. It could be recommended that authors revised the subheads to have a more systematic structure. For example, after the introduction, tumor immunity should be placed. Then start a section with multiple subsections, which cover treatment strategies. The topics should be ordered based on their importance. The recommended subheads are as below 1- Introduction (note: it is also too wordy. It also could be subdivided into different sections, such as introduction, genetics, and risk factors) 2- Tumor immunity; 3- Current and emerging immunotherapy approaches (note: according to the focus of the manuscript on emerging immunotherapy of HCC, "chemotherapy and "Molecular targeted therapy" should be deleted. a. Promotion of anti-tumor immune responses i. Dendritic cell-based therapeutic cancer vaccines ii. Adoptive cell transfer of immune cells (note: cover NK, NTK, CAR-T cells, etc.) iii. Peptide vaccine therapy b. Reversing T-cell dysfunction and exhaustion i. immune checkpoint inhibitors ii. Blockade of immune suppressor cells 4- Future perspectives

In response to the comments, we shorted the introduction section. However, we are afraid that the subdivision of the introduction may make each subdivision too short and therefore, we dared not make any subdivision of the introduction.

We also rearranged section 3 as follows.
3. Current and emerging immunotherapy approaches
3.1 Promotion of immune effector cell functions
3.1.1. Peptide vaccine
3.1.2. DC-based vaccine therapy
3.1.3. Adoptive transfer of immune effector cells

3.2. Reversal of T cell dysfunction
3.2.1. Immune checkpoint therapy
3.2.2. Blockade of immune suppressor cells

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However, we placed the section on peptide vaccine before that on DC-based peptide vaccine, because this sequence can help the readers to understand the principle of these immunotherapies more easily.

#3. In Table 1, only clinical trials related to targeting PD-1 have been pointed. What about other targets, such as CTLA-4? Take a look at NCT03062358 and search for more phase 3 clinical trials. Also, include clinical trial(s) that target PD-L1. Take a look at NCT03298451 and search for others.

We already listed NCT03062358 in Table 1 and mentioned it in the first paragraph of page 21. We introduced one more clinical trial on anti-CTLA-4 antibody (NCT02821754) in the first paragraph of page 19. We enlisted phase III clinical trial (NCT03298451) to Table 1. Because this clinical trial examines the combined effects of anti-CTLA-4 and anti-PDL-1 antibodies, we discussed it in the third paragraph of page 23.

#4. Keywords need to be revised. Using abbreviations in parenthesis in the keyword section could be omitted.

We corrected as requested.

#5. Having a Table to summarize the immunotherapeutic approaches could make the manuscript easier to read.

We made the new Figure 3 to demonstrate the immunotherapeutic approaches schematically and accordingly we added the legend to the new Figure 3.

Reviewer 00188507
“his manuscript is good written and summarized the current status and discussed the future perspective on immune therapy for hepatocellular carcinoma. Manuscript contains good represented and simple figures and recent publications in this research area”
Reviewer 02994003
“Well written excellent review focusing on the immunotherapy for HCC.”

Thank you for agreeing to accepting the manuscript.

We believe that we have responded to the comments fully and hope that the paper is now acceptable for the publication in World Journal of Gastroenterology.

Yours sincerely,

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