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World Journal of Stem Cells, Ms. No. 64490

Immunotherapy against PD-1/PD-L1 in hepatocellular carcinoma: Importance of molecular variations, cellular heterogeneity, and cancer stem cells

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March 25, 2021

Prof. Tong Cao - National University of Singapore, Singapore

Prof. Shengwen Calvin Li – Children's Hospital of Orange County Research Institute, USA

Prof. Carlo Ventura - National Institute of Biostructures and Biosystems, Italy

Editors-in-Chief

World Journal of Stem Cells

Baishideng Publishing Group Inc.

Pleasanton, CA, USA

Dear respected Editors,

We submit the revised version of our Ms. 64490 for publication in World Journal of Stem Cells. We thank the overall positive comments of the editors and reviewers. We are pleased that this Ms is conditionally accepted. In response to the letter of the editorial office, we carried out minor revision of the previous version and prepared a point-by-point answer (As) which addresses the comment (Cs) by the editors and reviewers. We hope to have comprehensively and successfully dealt with the critiques, which further helped to improve the quality of the Ms and expect this may be now officially accepted for publication.

The revised Ms includes the text with track changes containing revision based on the previous version. The format had been updated according to the guidelines and requirements for revised Ms.

On behalf of all the co-authors, I thank you for your attention and send you our best regards.

Sincerely yours,

Caecilia Sukowati, PhD

Corresponding Author

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ANSWERS TO THE EDITORS

Company editor-in-chief

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

We thank the Editor-in-Chief for the acceptance of this Ms.

Science editor

C1: Scientific quality: This manuscript is a Review, and it does not reach the publication standard of the WJSC. (1) Classification: Grade A and Grade D; (2) Summary of the Peer-Review Report: Reviewer 05121819 pointed out that authors would very concisely discuss current knowledge in basic sciences and then provide a clearer picture on its clinical application. This can also include a well-made infographic showing clinical translational aspects with molecular variations and response/cellular heterogeneity and response and ultimately role of cancer stem cells.

A1: We thank the Editor for the comment. As our response to the Reviewer 1 (below), this Ms is a review of basic science and less of clinical. We are confident that our Ms is in concordance with the Journal mission statement to publish high quality articles, basic and clinical, in order to showcase and promote research in the field of stem cells.

C2: Language quality: Classification: Grade A and Grade B.

A2: This is good classification. We, however, had re-checked our revised Ms for any error and/or typos.

C3: Recommendation: Transferring to the World Journal of Meta-Analysis.

A3: We thank the Editor for the suggestion of the transferring. However, this Ms is an in-depth review and absolutely is not a meta-analysis. As in A1, we sincerely consider that World Journal of Stem Cells is the appropriate journal for its publication.

ANSWERS TO THE REVIEWERS

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Answer to Reviewer 1

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

C1: The authors have exhaustively written on the aspects of PD-L1/immune check point blockade in HCC and responsiveness related current knowledge. The paper is well written. It is a very good paper for basic sciences. For a clinician, there is very little to understand and make sense of in here. This paper is more suited for a basic sciences journal rather than a clinical one. However, this decision is left to the editors. I wish the authors would very concisely discuss current knowledge in basic sciences and then provide a clearer picture on its clinical application. This can also include a well made infographic showing clinical translational aspects with molecular variations and response / cellular heterogeneity and response and ultimately role of cancer stem cells. As a clinician who would want to get to the core of the matter, reading through so much of basic sciences jargon and material is quite tedious. If this was meant to be a pure basic sciences paper, then I have no comments, but for a clinician this is a very difficult read, because the flow in simplification is lost.

A1: *We thank the Reviewer for their comments, especially in pointing out that this Ms is well written and a very good paper for basic sciences. We are sorry for the difficulties in readability due to immense biological jargons and terms, that might be exhaustive. We completely agree that this Ms is a review of basic science and less of clinical; we did mean to write a basic science paper. Nevertheless, we certain that the World Journal of Stem Cells is a proper journal for its publication since it is in concordance with their mission to publish high quality basic and clinical articles.*

From clinical science point of view, so far, the international guidelines for the management of the HCC (staging, allocation of the patients' treatment, type of drugs, etc.) is still based on the clinical findings and tumor parameter (e.g. size, single/multiple nodules, performance status test, and liver function) (EASL, J Hepatol . 2018 Jul;69(1):182-236). On the other hand, HCC genetic variability and its molecular classification are mainly explored in basic science, by dissecting HCCs heterogeneity in archived tissue bank or cell lines. The so-called personalized-medicine based on a patient's HCC specific characteristic in clinical application is still very few considered. In fact, regarding the CSC, this cellular population has not considered (yet) as one factor for a treatment choice against HCC, even though increasing data had indicated the role of these cells in therapy resistance. We hope this Ms could give insight, not only for basic scientists but also for clinicians, on the importance of HCC cellular heterogeneity in therapy, in particular in immunotherapy against anti-PD-1/PD-L1.

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We decide not reduce the content and simplify the Ms because we want to give an extensive knowledge on the subject. We consider and we truly appreciate the suggestion of the Reviewer for an article on HCC cellular heterogeneity from clinical aspects. We hope to be able to deliver the paper very soon.

Reviewer #2

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors:

C1: The authors reviewed immunotherapy against PD-1/PD-L1 in hepatocellular carcinoma, which will be beneficial for the selection of patient and the management of the ICIs against PD-1/PD-L1. The manuscript is well written and information is fully explained.

A1: *We sincerely thank the Reviewer for their remarkable comment.*

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