UNIVERSITY OF ATHENS MEDICAL SCHOOL
Department of Biological Chemistry

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World Journal of Gastrointestinal Oncology

RE: Submission of REVISED Manuscript NO.:* 47888

Dear Editor,

please find enclosed our REVISED Review entitled "Pancreatic ductal adenocarcinoma: treatment hurdles, tumor microenvironment and immunotherapy" to be considered for publication. We would like to thank you and the reviewers for your thoughtful evaluation of our manuscript and for your most welcome comments/suggestions. Accordingly, we have now revised thoroughly our manuscript to reflect these comments.

Please find below a point-by-point **response** to ALL the issues raised by the Reviewers:

Reviewer's Comments

Reviewer #1:

this is an important review discussing a hot topic in the field of gastroenterology and cancer treatment.much is still needed for understanding of the pathogenesis and treatment of pancreatic ductal adenocarcinoma.a metaanalysis is needed to discuss the issue of immunotherapy in pancreatic ductal adenocarcinoma.a few corrections are highlighted in the uploaded file

AUTHOR'S RESPONSE:

We appreciate this reviewer's comments and suggestions as wells as for the corrections he kindly made.

Reviewer #2:

1."CSCs account for 1%–5%", you may need footnote here.

AUTHOR'S RESPONSE:

We thank the reviewer for his comment.

We have corrected the percentage and we have added the specific reference.

<<Pancreatic CSCs account for 0.5%-1.0% of all pancreatic cancer cells [18] Lee CJ, Li C, Simeone DM. Human pancreatic cancer stem cells: Implications for how we treat pancreatic cancer. Transl Oncol. 2008;1:14-18.

2."many PDAC tumors" of "many PDAC tumors are characterized by the invasion of MDSC and the upregulation of PD-L1 through INF-γ", which refers to those, please indicate them.

AUTHOR'S RESPONSE:

We appreciate the insightful comment made by the reviewer. With the term "many" we are referring to the percentage of PDAC tumors characterized by the invasion of MDSC and the upregulation of PD-L1 through INF-γ. This percentage is approximately 50% according to bibliography. << Moreover, approximately 50% of PDAC tumors are characterized by the invasion of MDSC and the upregulation of PD-L1 through IFN-γ [36]. Karakhanova S, Link J, Heinrich M, Shevchenko I, Yang Y, Hassenpflug M, Bunge H, von Ahn K, Brecht R, Mathes A, Maier C, Umansky V, Werner J, Bazhin AV. Characterization of myeloid leukocytes and soluble mediators in pancreatic cancer: importance of myeloid-derived suppressor cells. Oncoimmunology. 2015 Jan 22;4(4):e998519.

3.“Current treatments fail to exhibit a severe efficacy and beneficially affect clinical outcome, as they do not adequately target CSCs.” Is that just one of reasons? The statement is inappropriate, please explain it.

AUTHOR’S RESPONSE:

We would like to thank the reviewer for his comment. In order to clarify the exact meaning of this phrase and specify that targeting CSCs is an additional reason among other, we have slightly amended the sentence in to <<One more reason why current treatments fail to exhibit a severe efficacy and beneficially affect clinical outcome, is that they do not adequately target CSCs [19].>>

4.The format of references is inconsistent.

AUTHOR’S RESPONSE:

We thank the reviewer for his apt comment. Hence, we have made all the required changes at the references.

Trusting that we have adequately **addressed** the Reviewer’s concerns, we would like to thank you for your help in improving significantly our work.

Kind regards,

Associate Prof. Michalis V. Karamouzis
Corresponding author