ANSWERING REVIEWERS

December 7rd, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6521-review.doc).

Title: Pancreatic cancer stroma: understanding biology leads to new therapeutic strategies

Authors: Agnieszka Anna Rucki and Lei Zheng

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6521

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Revision has been made according to the suggestions of the reviewers:

Reviewer 1

a) The authors should correct miss spell in your title; stoma to stroma.
Response: Thank you for finding this error. Misspelling in the title (stoma) was corrected to stroma.

b) Desmoplastic reaction is popular in PDA, suggesting the cancer-stromal interaction. Cancer-stromal intraction is interesting in the biology of PDA, however, it is important to demonstrate the relationship between the survival and cancer-stromal interaction. I recommend adding the consensus of relationship between the survival and cancer-stromal interaction in the authors' Introduction section.
Response: Thank you for this helpful comment. Relationship between survival and cancer-stromal interaction was added to the **Introduction** section

c) Epithelial to mesenchymal transition (EMT) is sometimes demonstrated in PDA tissue. Elevated levels of TGFβ drive EMT process, believed to be the initial step of metastasis, cell proliferation, immunosuppression and activation of PSCs. I recommend describing the summary for molecular research concerned with EMT.
Response: Thank you for this helpful suggestion. We included summary of research concerned with EMT in the *TGFβ* signaling subsection. Specifically, we described the cellular and molecular characteristics of this process. We also included EMT marker correlation with PDA survival.

d) I recommend describing whether Th17 cells contribute desmoplastic reaction or not.
Response: Thank you for this helpful recommendation. It is a wonderful point to investigate the role of Th17 in desmoplastic reaction in pancreatic cancer in future studies. Th17 cells were shown to be involved in the liver fibrosis, which have many similarities to pancreatic desmoplasia. We discussed the role of Th17 in liver fibrosis in the *Immune cells* subsection

Reviewer 2

a) The title (misspelled "stoma") looks too ambitious at the present stage, as it is formulated: "understanding biology leads to therapy". Perhaps to replace "therapy" by "novel therapeutic targets" or "new therapeutic strategies"?
Response: Thank you for finding this error and your helpful recommendation. Misspelling in the title (stoma) was corrected to stroma. The title of the manuscript was changed to: ***Pancreatic cancer stroma: understanding biology leads to new therapeutic strategies***

b) Targeting the tumor stroma (rather than tumor cells) is not that groundbreaking concept anymore. We may not forget that anti-angiogenic drugs have been already studied in PDA, and this therapy appeared to be not effective. We suggest to mention about this strategy, and to briefly discuss the possible mechanisms of resistance.
Response: Thank you for this helpful comment. The mechanism of resistance to antiangiogenic therapy (in the *Stromal Components* section) and brief review of clinical trial was added.

c) Since a decade, constitutive NF-kB activation (both the canonical and alternative pathways) is considered to be a major link between chronic inflammation and pancreatic carcinogenesis, and therefore remains to be a promising target. The group of Peter Storz demonstrated that macrophage-secreted cytokines drive pancreatic acinar-to-ductal metaplasia through NF-kB and MMPs. This signaling pathway deserves to be overviewed.
Response: Thank you again for this helpful suggestion. NFκ-B signaling pathway was briefly reviewed in the *Signaling Networks* section and clinical trial information added to the new table.

d) In our view, this manuscript would benefit from an illustration that summarizes the tumor-stroma interaction in terms of critical signaling pathways and potential therapeutic targets.
Response: Thank you for this recommendation: Summary Table was added in addition to the existing Figure

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Lei Zheng, MD, PhD
Department of Oncology
Johns Hopkins University School of Medicine
1650 Orleans Street, CRB1 Room 488
Baltimore, MD 21287, United States
Telephone: +1-410-502-6241; Fax: +1-410- 416-8216
E-mail: lzheng6@jhmi.edu