ANSWERING REVIEWERS

December 15, 2013

Dear Professor Ma,

Please find enclosed the edited manuscript in Word format (file name: WJG_2013_Esposito_Review_Revision_Final).

Title: Pathology of Pancreatic Ductal Adenocarcinoma: Facts, Challenges and Future Developments
Author: Irene Esposito, Björn Konukiewitz, Anna Melissa Schlitter and Günter Klöppel
Name of Journal: *World Journal of Gastroenterology*
ESPS Manuscript NO: 7393

In the revised version of the manuscript we have performed all the needed editorial changes and we have addressed all the reviewers' suggestions. In particular, the relationship between IPMN and PDAC was discussed and detailed information about the exocrine-like subtype were added.

In detail, the manuscript has been improved according to the suggestions of reviewers:

1 Author contributions have been included.

2 Revision has been made according to the suggestions of the reviewer

> ***2A.*** *"In the discussion of precursor lesions, the authors mentioned about IPMN and its genetic alteration, "the presence of KRAS mutations as common characteristics of PDAC precursors." However, it is known that gastric subtype IPMN, which is mostly low-grade, has more frequent KRAS mutation than intestinal subtype IPMN, which is frequently high-grade or sometimes IPMC. Moreover, branch duct IPMN patients (most of them are low-grade gastric subtype) frequently have PDAC at the distinct area in the same pancreas. Therefore, the relationship of IPMN and PDAC is not so simple. The authors should have comments on this."*
> Response: This relevant aspect has been now discussed in the revised version of the manuscript (page 6) and three references (Dal Molin et al., Annals of surgical oncology 2013; Mohri et al., Journal of gastroenterology 2012; Ideno et al., Annals of surgery 2013) have been added.
>
> ***2B.*** *"The authors mentioned about three molecular subtypes of PDAC, classical, quasi-mesenchymal, and exocrine-like subtypes. They discussed differences between the classical and quasi-mesenchymal subtypes, but not exocrine-like subtype at all. The authors should explain a little more about the exocrine-like subtype for readers to understand."*
> Response: We agree that this is an important point that requires further explanation. Collission et al. defined three molecular subtypes of PDAC: classical, quasi-mesenchymal and exocrine-like with prognostic relevance and distinct treatment response between classical and quasi-mesenchymal subtypes. The clinical relevance of the exocrine subtype, a subtype characterized by high expression of digestive enzymes, remains questionable. Although the exocrine subtype was identified in primary tumor samples, no representative tumor cell line could be identified among the investigated cell line collection, raising the possibility of an contamination artifact

with normal pancreatic tissue (Collison et al). These details have been now included in the revised version of the manuscript.

3 Spelling mistakes were corrected

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

Sincerely yours,

Irene Esposito, MD