Format for ANSWERING REVIEWERS

February 06, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO_7752 revision highlighted.docx).
Title: Epigenetics and pancreatic cancer – pathophysiology and novel treatment aspects
Author: Daniel Neureiter, Tarkan Jäger, Matthias Ocker, Tobias Kiesslich
Name of Journal: *World Journal of Gastroenterology*
ESPS Manuscript NO: 7752

The manuscript has been improved according to the suggestions of reviewers:
1 Format of the revised manuscript has been updated according to Revision Policies of BPG.

2 Revision has been made according to the suggestions of the reviewer
Reviewer 1
All suggestions were checked and transferred to the revised manuscript (highlighted)

Reviewer 2
1. In section one, the description of epidemiologic and morphological aspects about pancreatic cancer looks too long, it looks better if the authors make them simpler. → as suggested, sections 1.1.-1.2 have been shortened
2. In Table 1, 4-6, the authors should list all of the abbreviations such as MHL1, MSH2, DNMT, HDAC, and HAT et al. → in the revised manuscript all abbreviations are explained when they first appear; all abbreviations have been listed in a separate list of abbreviations
3. As is known to all that pancreatic adenocarcinoma (PDAC) is the most common subtype of pancreatic cancer, it would better they highlight PDAC in this review. → We agree that focusing on PDAC would be more attractive – however as we intended to give a comprehensive overview including all pancreatic cancer subtypes as well as due to the heterogeneous sampling as seen in several studies, we did not differentiate between the specific subtypes.
4. In Table 2, they did not show us up-regulation or down-regulation of the major genetics in association of grade of dysplasia. → As suggested, information about up- versus down-regulation of the major genetics has been added to Table 2
5. It would be better they describe more about YIN and YANG, as this theory may be a little strange to researchers and clinicians. → to avoid confusion and improve readability, the heading of section 1.3. has been simplified
6. In section two, part of "introduction of epigenetics" and "overview of epigenetic mechanisms" could be merged into one part, and would look better if the authors make them simpler. → as suggested, these parts haven been merged into one subheading and been revised to improve readability.
7. In Table 4, should DNA methylation be DNA hyper-methylation? → changed as suggested
Could the table be classified according to material? And cell lines should be displayed, for example, SW1990, BxPC-3 and Panc-1 et al. → as suggested, the table has been improved for readability and differentiation of sample material; furthermore, the particular cell lines have been mentioned in the tables
8. In part of "Histone-based epigenetics in pancreatic cancer" and "epigenetics in pancreatic cancer stem cells", it is recommended that one figure or table be added in each part to illustrated the epigenetic mechanisms. → as the available literature in these sections does not yet provide a comprehensive picture, we

think a summarizing illustration is currently not indicated. However, to improve readability, we have added a new table (#4) to section 2.1 summarizing the general epigenetic mechanisms

9. Table 5 should be made simpler, or classified according to onc/sup, material, or functions. Or it could be converted into a schematic drawing. Cell lines should also be displayed, for example, SW1990, BxPC-3 and Panc-1 et al, or explained below the table. → as recommended, the table has been re-sorted, i.e. classified by onc / sup properties of the affected miRNAs and the particular cell lines have been listed.

Reviewer 3

In the present review, Neureiter et al. well summarized epigenetic events of the pancreatic cancer in detail, although it is still unclear which genetic and epigenetic mechanisms are important targets to cure this intractable disease. Comments from the reviewer have only small needs for revising.

Major comments:

1. The text of the present review feels too long, 23 pages including tables. Can the author make their descriptions as short as possible, e.g., "2.2. Overview of epigenetic mechanisms" which is general findings? → as suggested, the whole manuscript has been revised for readability and shortened where appropriate. The former sections 2.1 und 2.2 have been merged under one subheading. To provide the reader not familiar with epigenetic mechanisms with appropriate basic information, we would like to keep the general findings on epigenetics in this section of the manuscript.

2. The section "1.2. Morphological aspects under respect of the precursor lesions". They stated that it is difficult to distinguish between reactive pancreatic glands and invasive pancreatic cancer, since no definitive and routinely used immunohistochemical markers exists although many biological markers in pancreatic ductal adenocarcinoma were tested as possible diagnostic and prognostic tools [19]. Further approaches for prognostic grading focused on different morphological pattern scheme similar to Gleason's scoring system [20], or include epithelial-mesenchymal characteristics like Vimentin-expression, tumour budding [21, 22] or evaluate several gene expression signatures [23]. It seems very important to differentiate invasive pancreatic ductal adenocarcinoma from reactive pancreatic glands especially in the histopathologic diagnosis of cancer-free margin of the operatively resected pancreatic stump. What gene expressions do the authors mean? → as recommended we have mentioned the key findings of gene and protein expression studies of ASPM (abnormal spindle-like microcephaly associated) as a possible prognostic marker.

Could the author suggest possible gene expression markers or immunohistochemical markers (e.g., CEA, B72.3, CA125, p53, S100A4, mesothelin, claudin, etc.)? → Many of the mentioned and published markers for PDAC are not yet established for routine pathological work. Therefore, we could not suggest definitive markers to distinguish between reactive pancreatic glands and invasive pancreatic cancer which has now been made more clear in the manuscript.

3. Table 6. Are these regimens are used as palliative chemotherapy for patients with unresectable pancreatic cancer or postoperative adjuvant treatment? → as recommended, for those studies where information is currently available, the treatment setting has been added to Table 6. For compounds currently in phase I of clinical development, usually maximum tolerated dose is given as a study endpoint and no label is given for the therapeutic treatment setting here.

Minor comments:

1. Table 2: Concerning photographs of the PanIN, IPMN, and MCN, high-resolution images should be provided. → Table 2 was completely re-designed and now includes high-resolution histological images.

2. The abbreviation "miRNAs, PFS, MTD" should be described when first appears.

→ as recommended, all abbreviations are described when they first appear in the text. Additionally, a separate list of abbreviations has been included in the revised manuscript.

Reviewer 4

All suggestions were checked and transferred to the revised manuscript (highlighted). Changes according to specific comments see below:

Page 2, abstract: This statement makes no sense. → as recommended, we have changed this sentence to "Improvement of pancreatic cancer treatment represents an urgent medical goal".

Page 2 core tip: Please correct this sentence. It does not make sense: → as recommended, we have changed this sentence to "Pancreatic cancer represents a devastating disease with only poor overall survival at advanced stages requiring new and effective treatment options."

Page 2, core tip: How can dysregulation of genes be a novel therapeutic approach? Surely yuo mean targeting the epigenetic alterations offers a novel therapeutic approach, dont you? → as recommended, we have changed this sentence to "Besides genetic events, epigenetic dysregulation of oncogenes and tumour suppressor genes is recognised as a novel therapeutic target."

Page 2, core tip: Please provide the full form of every abbreviation when using them for the first time → as recommended, all abbreviations are described when they first appear in the text. Additionally, a separate list of abbreviations has been included in the revised manuscript.

Page 3, last paragraph: Please proved the unit (/100.000), etc → this are absolute numbers worldwide per year provided by GLOBOCAN; the sentence has been rewritten to improve readability

Page 4, second paragraph: Change this to, ‚delayed'→ as recommended by the other reviewers, this section(s) have been shortened and simplified – this particular recommendation is not further applicable.

Page 7, second paragraph: Plese provide full form when using abbreviations for the first time → According to the instructions for authors by WJG, "DNA" is a standard abbreviation, which can be used without further explanation.

Page 8, legend to table 3: Please provide a reference → changed as suggested

Page 14, second paragraph: Please change this to clear → changed as suggested

Page 15, first manuscript: manuscript → changed to ‚section' as this refers to this particular part of the manuscript

Page 17, second paragraph: please correct this → we regard "stemness" as a standard scientific term already used in this field

Reviewer 5

This is an interesting and comprehensive review of pancreatic cancer and its treatment, with focus on epigentic mechanisms of tumor progression and therapeutics to interfere with these. Minor comments: Close parentheses missing on page 6 (table 2 page 15: change 'As reviewed in the chapter' to 'As reviewed here' or similar,
→ changed as suggested

3 References and typesetting were corrected

We believe that the language of our manuscript has reached Grade A and therefore chose not to make use of additional language editing services.

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

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