

Format for ANSWERING REVIEWERS

September 3, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 20751-Review.doc).

Title: Role of histone deacetylases in pancreas: Implications for pathogenesis and therapy

Author: Eckhard Klieser, Stefan Swierczynski, Christian Mayr, Johanna Schmidt, Daniel Neureiter, Tobias Kiesslich, Romana Illig

Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript NO: 20751

Reviewer report (ID 1832)

We thank the reviewer for his/her thorough assessment of our manuscript and the specific suggestions for improvement. Please find below the detailed response to the particular issues.

The manuscript by Klieser and co-workers entitled "The role of histone deacetylases in pancreas? Implications for pathogenesis and therapy" is a comprehensive, up-to-date and well written review. There are some minor points to consider:

? On occasion, the authors could better separate the disease entities. For example, pancreatitis comprises two different disease entities. This, statements such as "therapeutic options for pancreatitis ... are limited" sound somewhat awkward. I would suggest to clearly separating acute from chronic pancreatitis.

The reviewer thought that the statement "therapeutic options for pancreatitis...are limited" would sound awkward. In order not to disregard all up to date treatment approaches (surgical or medicinal) we added the adverb medicinal in order to underpin that the use of HDACis (as described in the following text) could be an addition to the up-to-date medicinal treatment approaches.

We did not follow the suggestion to separate the pancreatitis chapter into (a) acute and (b) chronic pancreatitis chapter³. In our opinion this would not lead to a benefit for readers but would require some redundancies within the text of the newly created chapters.

? Is there any information regarding HDAC inhibitors and the formation of ADM lesions (acinar to ductal metaplasia)?

Additional literature research revealed no information about the use of HDAC inhibitors and the formation of ADM. What we did find was information about the role of SIRT1 and its inhibition by Leptomycin B and nicotinamide, both of which, however, are not HDAC inhibitors.

? The authors state that "Neoplasms of the pancreas are defined by their line of differentiation: pancreatic tumors can derive either from ductal, endocrine or acinar cells". This statement is not true

inasmuch as there is an ongoing debate regarding for example cell of origin/carcinogenesis of pancreatic ductal adenocarcinoma (i.e. acinar to ductal metaplasia, PanIN, PDAC). Therefore, this statement should be changed accordingly.

We agreed with the reviewers note that the statement " Neoplasms of the pancreas are defined by their line of differentiation: pancreatic tumors can derive either from ductal, endocrine or acinar cells." is not correct (especially considering recent debates "regarding for example cell of origin/carcinogenesis of pancreatic ductal adenocarcinoma "). Thus we deleted the whole sentence.

? The authors state in the conclusion that "HDACis were shown to have diverse anti-tumor effects in PC, especially in combination with standard chemotherapeutics"; however, this is not described in depth in the manuscript. Could the authors present more data regarding this statement?

In the opinion of the reviewer the statement "HDACis were shown to have diverse anti-tumor effects in PC, especially in combination with standard chemotherapeutics." has not been described in depth in the manuscript. What we were trying to say is that the anti-tumor effects are multifariously. So we changed the adverb in this sentence. Furthermore, in our opinion, these multifariously anti-tumor effects are described in detail within the chapter " HDAC-INHIBITOR: FROM THE BENCH TO THE BED".

? In figure 2, activation of pancreatic stem cells is mentioned. Could the authors describe what exactly is meant by "pancreatic stem cells" in this context?

In figure 2 the reviewer was wandering what exactly was meant with "stem cells" (see figure 2 below). What we wanted to show in this figure is the activation of pancreatic stellate cells similar to the explanation in the manuscript. According to that we improved Figure 2.

? In the summary, the authors mention "nitrosative stress"; however in the following text, this is barely mentioned. I would suggest omitting this in the summary.

The reviewer suggested to omit the mention of the nitrosative stress within the summary (core tip) and we agreed with him.

? I would also suggest omitting the question mark in the title.

Regarding the reviewer comment so avoid the question mark in our reviews title we changed it into a colon.

? The term "Deregulated epigenetic regulation" in the abstract sounds awkward; better e.g. epigenetic deregulation.

We accepted the reviewer's suggestion to change the term "deregulated epigenetic regulation" into "epigenetic deregulation".

? There is a typo in part II: (ev. auch representative).

Kindly, the reviewer indicated this typo: "(ev. auch representative)". We deleted it.

Dear Editor,

thank you very much for the efforts during handling our manuscript

"The role of histone deacetylases in pancreas: Implications for pathogenesis and therapy. (Minireview)" authored by Eckhard Klieser, Stefan Swierczynski, Christian Mayr, Johanna Schmidt, Daniel Neureiter, Tobias Kiesslich, Romana Illig.

Please find enclosed the following files:

- 1 20751-Revised manuscript
- 2 20751-Answering reviewers
- 3 20751-Copyright assignment
- 4 20751-Audio core tip
- 5 20751-conflict-of-interest statement (handwritten signed)
- 6 20751-Google Scholar
- 7 following 20751 figures 1,2,3,4

During revision of our manuscript, the following changes were incorporated into the revised manuscript (highlighted by track changes):

- The manuscript has been carefully revised for English language - we believe that the language of our manuscript has reached Grade A and therefore chose not to make use of additional language editing services.
- As mentioned (comment 2) we changed the author contributions list according to the editor's suggestion.
- As mentioned (comment 4) we adapted the suggested spelling of the telephone and fax number.
- As mentioned (comment 12) we deleted all Roman numerals in the headings of each chapter.
- According to the changes in the revised manuscript we adopted the italic font for authors named in the manuscript.
- Changing the font of our manuscript to Book Antiqua lead to incorrect special symbols and we had to change them correctly.
- Changing the design of Table1 made us change the text colour of the first line into white so that this line was readable again.
- Thanks to the reviewer's question if there was any information about HDAC inhibitors and the formation of acinar-to-ductal metaplasia -ADM (see below), we found pieces of information about the role of SIRT1 in the formation ADM and decided to add a new paragraph within the chapter "HDAC EXPRESSION IN PANCREATIC TUMORS".
 - By adding new paragraph, we had to add two abbreviation more.
- Furthermore we improved some not yet detected spelling errors.

As required, we added the conflict-of-interest statement handwritten signed (file number 5), although we already provided it within the first submission.

Figures 1, 2, 3 and 4 were prepared in COREL Designer X5, a professional vector-based graphics program. Above mentioned file number 7 and following contain three different file formats for each figure which may be used for your further editing.

The manuscript has been carefully revised for English language - we believe that the language of our manuscript has reached Grade A and therefore chose not to make use of additional language editing services.

As our institution does not have institutional access to 'Crosscheck', no systematic plagiarism detection has been performed - see enclosed for 'Google Scholar'-based assessment of the manuscript title.

We hope that the manuscript is now suitable for publication.

Thank you for your efforts.
Yours sincerely,

Daniel Neureiter