

Format for ANSWERING REVIEWERS



April 1, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6599-Review-r.doc).

Title: MicroRNAs as emerging biomarkers and therapeutic targets for pancreatic cancer

Author: Marion Gayral, Sébastien Jo, Naima Hanoun, Alix Vignolle-Vidoni, Hubert Lulka, Yannick Delpu, Aline Meulle, Marlène Dufresnes, Marine Humeau, Maël Chalret du Rieu, Barbara Bournet, Janick Sêlves, Rosine Guimbaud, Nicolas Carrère, Louis Buscail, Jérôme Torrisani, Pierre Cordelier

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6599

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

1 Revision have been made according to the suggestions of the reviewers

(1) Comment #1: this review deals with translational studies about microRNAs in pancreatic cancer. This manuscript was well written and contained extensive review of general issues of microRNAs in pancreatic cancer. This paper will be helpful and useful for readers who want to know current status and clinical role of microRNAs in pancreatic ductal adenocarcinoma. 1) MicroRNAs are new concept for some readers, so it is recommended to introduce general concept of microRNAs about cancer (in introduction part).

Answer by the author: relevant changes are highlighted in yellow in the manuscript.

(2) Comment #2: this is a well organized review about the significance of microRNAs in the diagnosis and potential treatment of pancreatic cancer, the subject and the contents are excellent. 2. However, I believe that the following issues should be addressed: A: The significance of microRNAs in high risk patients for developing pancreatic cancer. B: The potential rations underlying the conflict results reported as indicated out by authors. C: It should be pointed out in the review that it is not here for screening for pancreatic cancer. D: It would be paramount important to comments on the potential changes in other common GI cancer such as gastric/colon cancer.

Answer by the authors: relevant changes are highlighted in yellow in the manuscript. However, we decided not to further comment the potential changes of miRNA expression in other common GI cancers as this is not the scope of the review.

(3) Comment #3: the review entitled "MicroRNAs as emerging biomarkers and therapeutic targets for pancreatic cancer" by Gayral et al describes an increasing important role for miRNAs. The review provides a good overview of the field and is of interest and importance. Specific comments: 1. Page 3 - the number of deaths/year in the US due to pancreatic cancer is higher than 28,000 (~38,000 for 2013). 2. Instead of using the word "chapters", "sections" might be more appropriate. 3. "Benign" is misspelled several times ("begnin"). 4. Should be more consistent use of either "Pr" or "Dr" throughout.

Answer by the authors: relevant changes are highlighted in blue in the manuscript.

(4) Comment #4: the authors are to be congratulated on a thorough review on the role of MicroRNAs in pancreatic cancer, exploring the possibilities of MicroRNAs as emerging biomarkers and potential therapeutic targets for this dismal disease. The use of MicroRNA and the genomic profiling will for sure add benefits in the characterization of pancreatic ductal adenocarcinomas (PDAC). At present, the up- and downexpression of various MicroRNAs is a bit confusing and one would wish a comparison

with other techniques like proteomics, tissue microarray etc. For sure, finding cancer-specific biomarkers in tissue and if possible detectable also in blood in general will improve the possibilities of better (and hopefully earlier) diagnosis, provide us with novel tools for prediction/prognosis and add targeted therapy with the aim of being tumor-specific and personalized. This is not done in the present review (and is not the primary aim either), but could have been of value in summary or discussion, e.g. on prognostic and predictive markers for pancreatic cancer and chemotherapy resistance. For example on page 5 it is quite extensively discussed the role of miR-10b and miR-21 and response to chemotherapy, especially gemcitabine. The fact that lack of response often is due to a non-existing expression of the nucleoside receptor hENT-1 could be worth mentioning. On page 6 (5. Open question) the authors describe IPMNs as precursor lesion of PDAC. For most pancreatologists and pathologists, these are two different entities. Somewhat specific for PDAC is the frequently extensive stromal reaction and the importance of the tumor microenvironment. This fact that the stroma with its proinflammatory-tumor proliferative effects is difficult to read out in the manuscript where most of the work seems to be done on cell lines. The authors foresee MicroRNA to soon be used as therapeutic targets in patients with PDAC. Real examples pointing in this direction are up to now scarce. From both diagnostic and therapeutic Point of view, the future might be a combination of different techniques and thus not only depending on one type of "omics". Despite for some minor linguistic error, the manuscript is well written.

Answer by the authors: relevant changes are highlighted in pink in the manuscript

(5) Comment #5: this is a well written review dealing with an important topic in the field of pancreatic cancer, namely the use of miRNAs as diagnostic tools and/or therapeutic targets. The review includes the key/relevant findings in the field and it is for the most part well organized except the second section on therapies. The role of miRNA in pancreatic biology should be condensed into a single section, same with the role of this molecules in therapy response (section 8 and 11). Also, the epigenetic section should be expanded/developed into a new section describing the targeting strategies for miRNA. Finally, the introduction (after the PDAC section) will benefit from having a short description of what are miRNAs and how they function to control gene expression.

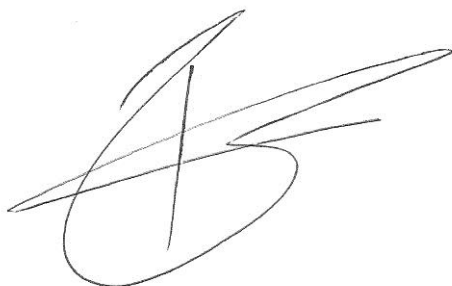
Answer by the authors: we re-organized the manuscript according to reviewer 5's suggestions.

3 References and typesetting were corrected

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

Sincerely yours,

Pierre Cordelier, PhD, P.I.
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A handwritten signature in black ink, consisting of a large, stylized 'P' followed by a series of loops and a long horizontal stroke extending to the right.