Format for ANSWERING REVIEWERS

June 20, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17909-review.doc).

Title: Helicobacter pylori and microRNAs - relation with innate immunity and progression of preneoplastic conditions

Author: Diogo Libânio, Mário Dinis-Ribeiro, Pedro Pimentel-Nunes

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 17909

The manuscript has been updated – format has been updated as per revision policies for reviews and revision has been made according to reviewers' suggestion.

Reviewer 2683167 (Classification B Very Good, Language evaluation Grade A Priority publishing, Conclusion Minor revision): "This is a very exhaustive compilation about the role of miRNAs in Helicobacter pylori infection. This manuscript constitutes an important contribution to the field with the main information included. Only some minor points should be addressed: -Page 12, last paragraph, line 7: "…gastric mucosa bot not in…" -Page 14, line 16: "…mir-370 levels were was…" -Page 21, last paragraph: please, indicate the best microRNAs candidates for markers of disease or therapeutic targets. In addition, methods for potential modulation of miRNAs should be discussed."

Response:
We acknowledge the comments of reviewer 2683167 and we addressed the suggested points:

- "...gastric mucosa bot not in..." was replaced for "gastric mucosa but not in…"
- "...miR-370 levels were was..." was replaced for "miR-370 levels were..."
- We added the following paragraph in the end of the review: "Given the data summarized in this review, we believe that let-7, miR-106 family, miR-146a, miR-155, miR-181b, miR-223 and miR-375 are the miRNAs most consistently reported to have important roles in gastric Hp-related carcinogenesis and thus we suggest that these miRNAs deserve greater attention in clinical studies to found if they can be used as disease markers. Future studies on this topic should focus on both miRNA serum and tissue levels in patients in different stages of gastric carcinogenesis (not infected with Hp, chronic Hp gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, invasive carcinoma and metastatic carcinoma). Furthermore, we believe that the modulation of miRNAs by Hp eradication and chemoprevention with COX-2 should also deserve attention in future studies".

Reviewer 2445638 (Classification Grade A Excellent, Language evaluation Grade A Priority publishing, Conclusion Accept): "Libanio et al. have written a detailed informative review of the role of Helicobacter pylori (HP) and microRNAs in specific immune response, and resulting cancer progression of the stomach. The paper is

very well written and referenced, and deals with a fascinating subject that is timely, and new. They begin with an introduction dealing with the interaction of (HP) factors and their interaction with host genes involved in inflammation and gastritis, the generation of micro RNAs and how they might play a role in genetic control and subsequent development of cancer. Specific micro RNAs and how they are influenced by HP infection and toxin production have been discussed. Over and under expression of specific micro RNAs and their ramifications are given. A possible role for epigenetics is addressed with the suggestion that global and CpG hyper-methylation involved in chromatin remodeling and gene expression may be regulated by differential expression of microRNAs. Specific microRNAs implicated in the control of cancer pathways such as TGF-β and MAPK are referenced, as well as RB1 and the E2F, and Forkhead box M1 family of transcription factors. Most of these studies are correlative as opposed to definitive, but the possibilities are real and the review of them is instructive. The review itself is a lot to take in as it presents a great deal of information- and this is both its strength and weakness. You cannot just sit and read it through, it takes a lot of time. I would not suggest changing that though. For those in the fields of gastric carcinoma, microRNA, immunology, and microbiology it will be a real plus to have a cogent explanation of the interaction of these fields, and for the reader who is less involved- it is readable, comprehensive, and thorough."

Response:
We thank the interesting and favorable comments.

Reviewer 2682232 (Classification Grade D Fair, Language evaluation Grade A Priority publishing, Conclusion Major revision): "Dear authors, I think your paper similar a review paper, But very short,in fact its a collection,so This paper should has analize for control And patient group. Regards"

Response:
We thank reviewer comments. In fact our paper is intended to be a review paper and is in fact a review paper. Given this we could not analyze for control and patient groups.

We hope that the revisions made meet the reviewers' comments.

Best regards.

In behalf of all authors,

Diogo Libânio, MD