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April 2, 2014

Qi, Yuan

Science Editor, World Journal of Gastroenterology

Re: ESPS Manuscript NO: 9676

Dear Dr. Qi,

Appended please find a revised version of manuscript 9676 titled, "Immune evasion strategies used by *Helicobacter pylori*". We are very thankful to the reviewers and the editor for the insightful comments and suggestions, which we followed to improve this invited manuscript for the special issue on *Helicobacter pylori*. The comments are addressed below by either explanations and/or modifications to the manuscript where indicated.

**Title:** Immune evasion strategies used by *Helicobacter pylori*.

**Authors:** Taslima T. Lina, Shatha Alzahrani, Jazmin Gonzalez, Irina V. Pinchuk, Ellen J. Beswick, Victor E. Reyes.

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 9676

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

A comment by comment response is addressed below:

**Reviewer 1:**

**Comment:** "The manuscript is well written and figures are useful. Importantly, the manuscript would improve its impact if there would be a discussion of the immune evasion strategies used by *Helicobacter pylori*"

*and how to manipulate them in order to perform immune system based therapy. The point would not be to discuss extensively but at least give the reader the basic aspects on these points in a small paragraph”.*

**Response:** Changes have been made in the revised manuscript following this reviewer’s suggestion.

**Reviewer 2:**

**Comment:** *“In general, this is a nicely written review article. However, in my opinion it would benefit from re-writing to become more succinct - as it is now, its rather long in relation to content. Many words are not needed - as an indication of what i mean: if the sentence does not change meaning when words are removed, it generally means that the words are not needed. Also, many sentences can be summarized”.*

**Response:** Changes have been made in the revised manuscript to improve clarity and make it more succinct.

**Comment:** *“One issue is that many statements are missing reference – possibly the authors mean that the reference after a line of 4 or so sentences covers all four sentences, but better to put it out on each sentence as this is not clear. In addition, it seems to me the review is under referenced - but I think also it would be good if a reviewer with more expertise in immunology would work over this manuscript”.*

**Response:** References have been added where credits were missing in the revised manuscript.

**Comment:** *“Why is “modified Kdo (3- deoxy-d-mannoctulosonic acid)-lipid A structure tetra-acylated with a phosphoethanolamine added at the 1 position of the dissacharide.” within ""? Again, ref missing”.*

**Response:** Changes have been made and reference has been added in the revised manuscript.

**Comment:** *“H. pylori type I strain were shown to reside in a compartment with early endosome properties and did not fuse with lysosomes. – It appears an A or s is missing in the sentence?”*

**Response:** This typo has been corrected.

**Reviewer 3:**

**Comment:** *“This article summarized the immune evasion strategies used by H. pylori in detail. It will be more helpful if figures can be provided for each section. Some typos should be corrected”.*

**Response:** In the interest of space limitations, we have not added any new figures in the manuscript. However, we tried to provide a clearer text and correct the typos.

**Reviewer 4:**

**Summary:** *“This is a very well-written, organized and extensive review on both innate and adaptive immune evasion mechanisms by H. pylori, with both bacterial and host factors nicely considered”.*

**Major suggested changes:**

*“A nice overview figure depicting major innate versus adaptive immune evasion mechanisms should be shown, with both host and bacterial factors (where known), then follow up for Fig 1 and 2 that get into more specifics”.*

**Response:** We tried to divide the manuscript into two major sections that are, as alluded to by the reviewer, evasion of innate responses and evasion of adaptive responses. Where the virulence factors are known they were described mechanistically in the text. The figures suggested would include too much information that is already in the text. We thought it may be more beneficial to the reader to illustrate, in a focused manner, in the two figures appended novel mechanisms that are less well known.

**Minor suggested changes:**

**Comment 1.** *“Numerous minor wording changes throughout are suggested a. p3. Change to “establishes” in “H. pylori successfully...” b. p4. Change “gycolipid” to glycolipid c. p5. Insert “that” after acute phase reactants; add period after in vitro. d. p9. Delete of in the sentence “despite of the presence of iNOS”. In ref 36, it is arginase not urease that inhibits NO production. e. p 10. Delete “phenotype” after APC in bottom sentence. f. p15. Delete “interrupts IL-2 signaliing and” as previous sentence already implies VacA interrupts IL-2*

signaliing. g. p16. Change principal to principle. h. p16. The sentence *Interestingly, a study in mice...* is confusing and unclear. i. p18 delete *"were in the stomach"* and add *"stomach"* before *CD4+*.

**Response:** Changes have been made in the revised manuscript to address the reviewer's suggestions.

**Comment 2.** *"P4. Provide reference for the quote at bottom of page"*.

**Response:** Reference has been added in the revised manuscript.

**Comment 3.** *"p6. The section on CLR's seems too long and generic and not specific for H. pylori. Consider reducing to most important points as they relate to H. pylori immune evasion mechanisms"*.

**Response:** Changes have been made in the revised manuscript.

**Comment 4.** *"p 9-10. Should the authors consider adding information to this macrophage section on the M1/M2 area? eg, Fehlings 2012 Infect Immun, 80:2724; and Guiding Plos One 5:e15018."*

**Response:** Information regarding this topic has been added in the revised manuscript.

**Comment 5.** *"p11. Provide reference(s) for the sentences 'It was shown that E2F1 expression is downregulated'...and 'However, Hp VacA was shown to inhibit DC maturation...'"*

**Response:** Reference has been added.

**Comment 6.** *"p19. The autoantibodies section could be improved by addition of the well-known observation of autoantibodies directed against the H. pylori LPS, which bears Lewis antigens the molecularly mimic the host cell surface glycoproteins"*.

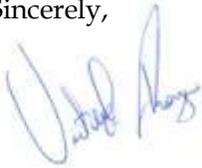
**Response:** We actually discussed the issue regarding the Lewis antigen in another part of the manuscript where we discussed about "Evasion of Recognition by PRR".

**Comment 7.** *"References- ref 7 missing author's last name. Many references should have bacterial/gene names italicized"*

**Response:** We appreciate the reviewer for catching this oversight and changes have been made accordingly in the revised manuscript.

We feel we have responded constructively to all of the comments and valuable suggestions made by the reviewers. Their suggestions certainly improved the quality of the manuscript. Again, we are grateful for their insightful comments and advice.

Sincerely,

A handwritten signature in blue ink, appearing to read "Victor Reyes".

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