



December 2, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6006-review.doc).

**Title:** *Helicobacter pylori* neutrophil-activating protein: from molecular pathogenesis to clinical application

**Author:** Hua-Wen Fu

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

**ESPS Manuscript NO:** 6006

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

1 Format has been updated. The primary titles are written in upper cases, whereas the secondary titles are written in lower cases except that the first character of the first word of the title is written in upper cases.

2 Revision has been made according to the suggestions of the reviewers

**Responses to reviewer 02535996**

(1) Page 4 – when describing the iron binding capacity, the word cavity might not be the appropriate word. This may need to be described in more detail.

**Response:** The wording has been changed according to the suggestion. The revised sentences are shown in the lines 7 and 8 on page 4.

(2) Comma needed on page 5 line 3 before the word “but”

**Response:** A comma was added before in word “but” and is shown in the line 3 on page 5 of the revised manuscript.

(3) Generally, a little more attention could be given to the effect of Hp-NAP on neutrophils. For example, several articles are not referenced that describe meaningful information about Hp-NAP: A. FEMS Microbiol Lett. 2005 Aug 1;249(1):95-103. *Helicobacter pylori* induce neutrophil transendothelial migration: role of the bacterial HP-NAP. Brisslert M, Enarsson K, Lundin S, Karlsson A, Kusters JG, Svennerholm AM, Backert S, Quiding-J?rbrink M. This article describes the continuous influx of neutrophils in a transwell chamber system requires live Hp expressing NAP. This is an important study that should be included in the manuscript. B. Cell Microbiol. 2010 Jun;12(6):754-64. doi: 10.1111/j.1462-5822.2010.01431.x. Epub 2010 Jan 11. *Helicobacter pylori*-derived neutrophil-activating protein increases the lifespan of monocytes and neutrophils. Cappon A, Babolin C, Segat D, Cancian L, Amedei A, Calzetti F, Cassatella MA,

D'Elios MM, de Bernard M.

**Response:** The two suggested articles were referenced and described under the section of "Role of HP-NAP in host inflammation". The descriptions are shown in the lines 11-22 on page 6 of the revised manuscript.

**Responses to reviewer 02527808**

- (1) As regard key words: Please added Immune modulation; Th1-Th2; Immunotherapy  
**Response:** These three key words "immunotherapy", "immunomodulation", and "Th1/Th2" were added according to the reviewer's suggestion. The other two key words "pathogenesis" and "inflammation" were removed to keep only 10 key words.
- (2) Line (14) neutrophil-activating protein, NAP,must be changed to neutrophil-activating protein (NAP)  
**Response:** The changes have been made according to the suggestion and are shown in the line 15 on page 3 of the revised manuscript.
- (3) Page (6) : interleukin-4 (IL-4)-secreting T cells must be changed to interleukin-4 (IL-4) secreting T cells  
**Response:** "interleukin-4 (IL-4)-secreting T cells" was changed to "IL-4-secreting T cells", which is shown in the line 12 on page 8 of the revised manuscript.
- (4) As regard the review article Role of HP-NAP in bacterial protection and survival:( page 4) I think you must clarify that HP-NAP does not possess a positively charged N-terminus but, unlike the other members of the family, is characterized by a positively charged protein surface which has been proposed to be responsible for binding and condensing DNA (Ceci et al.,2007).  
**Response:** The suggested article has been referenced and described according to the reviewer's suggestions. The descriptions are shown in the lines 4-10 on page 5 of the revised manuscript.
- (5) Role of HP-NAP in host inflammation (page 5) You don't discuss how the HP-NAP stimulate the monocyte to synthesize tissue factor (TF) and plasminogen activator inhibitor-2 (PAI-2)& the relation of this action to the development of chronic gastritis (Montemurro et al., 2001)  
**Response:** How HP-NAP stimulates the monocyte to synthesize tissue factor (TF) and plasminogen activator inhibitor-2 (PAI-2) is described in the lines 3-5 on page 9 of the revised manuscript. The relation of this action to the development of chronic gastritis was described in the lines 5-8 on page 7 of the revised manuscript.
- (6) In page (6) before discussing the role of HP-NAP in innate immunity and gastric Th1-polarized response, a brief revision about the role of different types of T-helper cells in immunity against infection is required (D'Elios and Del Prete, 1998).  
**Response:** A brief revision about the role of different types of T-helper cells in immunity against infection has been described and the suggested article has been referenced and described according to the suggestion. The descriptions are shown in the lines 16-25 on page 7 of the revised manuscript.
- (7) In Page (7): The last sentence (A recent study showed that TLR2 was involved in HP-NAP-stimulated) you must delete a recent study because the reference was (Del et al 2008) which is not recent now.  
**Response:** "A recent study showed that TLR2 was involved in HP-NAP-stimulated" has been changed to "In a study using a TLR2-blocking antibody, TLR2 was shown

to be involved in HP-NAP-stimulated” and is shown in the lines 11-12 on page 9 of the revised manuscript.

- (8) Disease associations with HP-NAP (page 8) The finding that HP-NAP shares significant homology with other Dps-like proteins, produced by bacteria associated with chronic inflammation, such as NapA of *Borrelia burgdorferi* must be discussed .

**Response:** The finding that HP-NAP shares significant homology with NapA of *Borrelia burgdorferi*, produced by bacteria associated with chronic inflammation, has been discussed according to the suggestion and is shown in the lines 2-7 on page 10 of the revised manuscript.

- (9) References - You must update old references . - Many references were missed in your review such as 1- The immune modulating activity of the Helicobacter pylori HP-NAP: Friend or foe? de Bernard M & D'Elios MM 2010 Toxicon. Dec 15;56(7):1186-92. Although This review article is more or less similar to your review but it was not found in your reference . 2-Velin D& Michetti P2010 Expert Rev Gastroenterol Hepatol. 2010 Apr;4(2):157-66. 3-de Bernard M & D'Elios 2009 MM Helicobacter. Sep;14 Suppl 1:21-8 4- D'Elios et al 2007 FEMS Immunol Med Microbiol. Jul;50(2):157-64. 5- D'Elios et al 2007 Clin Chim Acta. May;381(1):32-8. 6- Montecucco C,& de Bernard M 2003 Microbes Infect. Jul;5(8):715-21. 7- Dundon et al 2002 Int J Med Microbiol. Feb;291(6-7):545-50. Also the manuscript is devoid from any associated figures or models illustrating the molecular pathogenetic activity of the HP-NAP.

**Response:** All seven references have been cited in the revised manuscript. These references are listed as number 6, 14, 33, 34, 35, 45, and 46 in the REFERENCES section of the revised manuscript. Since the associated figures or models illustrating the molecular pathogenic activity of the HP-NAP are well described in the references 34 and 35 of the revised manuscript, the two articles are referenced and a brief description to refer readers to the references for those models are described in the lines 13-16 on page 8 of the revised manuscript.

3 References and typesetting were corrected.

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

Sincerely yours,



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