Author's response to reviews

Title: Assessment of the Toll-like receptor 4 Asp299gly, thr399Ile and Interleukin-8 -251 polymorphisms in the risk for the development of distal gastric cancer

Authors:

Elvira Garza-Gonzalez (elvira_garza_gzz@yahoo.com)
Francisco J. Bosques-Padilla (fbosques58@hotmail.com)
Sandra I. Mendoza-Ibarra (gfb_sandra_mendoza@yahoo.com)
Juan P. Flores-Gutierrez (jufloresmx@hotmail.com)
Hector Maldonado-Garza (hectormaldonadog@yahoo.com)
Guillermo I. Perez-Perez (perezg02@med.nyu.edu)

Version: 2 Date: 21 December 2006

Author's response to reviews: see over
December 20, 2006

Sandra Le, Ph. D.
Assistant Editor of the BMC Cancer Journal
BMC-series journals
BioMed Central Ltd
Middlesex House
34-42 Cleveland Street
London W1T 4LB
UK

Reference: MS1441771149118416

Dear Dr. Le,

Thank you for the review of our manuscript entitled “Assessment of the Toll-like receptor 4 Asp299Gly, thr399Ile and Interleukin-8 -251 polymorphisms in the risk for the development of distal gastric cancer” We have considered all of the reviewers’ suggestions and comments. Our reply to each point is below.

Reviewer: Richard Peek, MD.

We thank Dr. Peek for his constructive comments. Our responses and changes in the manuscript are indicated as follows.

- **What was the prevalence of *H. pylori* infection among the cancer patients?**
  
  **Response:** The estimated prevalence of *H. pylori* among gastric cancer patients was 53.8%. Since the prevalence was determined only by histology, it is possible an underestimation of the real prevalence in this population. This information was added in the manuscript (page 7, Section Study groups characteristics and *H. pylori* status).

- **What is the risk for gastric cancer if only *H. pylori*-infected cancer and infected control patients are studied?**
  
  **Response:** We performed the analysis and the results were quite different. For **IL-8*A** the OR is 1.26 (95% CI= 0.57-2.8), p= 0.66. This was an expected result due to the decrease in the number of patients included in the analysis. We are not including this information in the manuscript because we considered that the prevalence of *H. pylori* in the cancer patient group is underestimated.

- **Were all the gastric cancers intestinal-type or diffuse type as well?**
  
  **Response:** The proportions of diffuse and intestinal gastric cancer were 1.2:1 and the calculated ORs were very similar but not significant (OR= 2.15, p= 0.08 and OR=2.1, p=0.13 respectively). This information was added in the manuscript (page 7, Section Study groups characteristics and *H. pylori* status and Assessment of risk of IL8-251*A, **TLR4 Asp299Gly***2 and **TLR4 Thr399Ile***2 alleles).

- **Were there differences in risk based on histologic subtypes?**
Response: No difference was observed when the distribution of genotypes was compared between patients with intestinal or diffuse types of distal gastric cancer. The genotype and allele frequencies were added in Table 1.

- Needs some language corrections before being published

Response: An English native speaker carefully has revised the English of the manuscript.

Reviewer: Stephan Hellmig

We thank Dr. Hellmig for his constructive comments. Our responses and changes to the manuscript are below.

- The selection of TLR4 and IL-8 SNPs seems to be arbitrary. There is no link between these two molecules. The authors should focus on one gene

Response: The link between these two molecules is that both have been associated to the development of gastric cancer, and for this reason we considered that could be included in one paper.

- Asp299Gly and Thr399Ile of TLR4 are known to be in nearly complete LD. Thus, it does not make sense to genotype both SNPs.

Response: The TLR4 Asp299Gly and Thr399Ile LD has not been demonstrated in all populations. As this information is unknown in our own population, we decided to genotype both polymorphisms. This rationale is now included in the text (page 9).

- The frequency of the rare allele of Asp299Gly and Thr399Ile is known to be around 10%. The numbers of the PUD and AG+IM in table 1 are too small to serve as controls. The only control group that should be used are H. pylori infected patients without cancer (n=191).

Response: We agree with the reviewer that the ideal control population is the H. pylori infected group to compare with gastric cancer patients, but we consider that the information about all controls, including non-infected patients, PUD patients and patients with AG+IM support the role of H. pylori presence for the risk of development of gastric cancer.

- Needs some language corrections before being published

Response: An English native speaker carefully has revised the English of the manuscript.

We believe that the manuscript has been strengthened as result of this process and once again, we thank the reviewers for their comments and we hope that the revisions will help clarify the manuscript.

Thank you for considering this work.

Sincerely yours,

Guillermo I. Perez Perez. DSc.
Associate Professor of Medicine