

July 26, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Pathogenic Mechanisms - APS Review - Updated.doc).

Title: Title: "Pathogenetic Mechanisms of Antiphospholipid Antibody Generation"

Author: Rohan Willis, Emilio Gonzalez

Name of Journal: *World Journal of Rheumatology*

ESPS Manuscript NO: 12291

The manuscript has been improved according to the suggestions of reviewers. Please find our response to the reviewer's comments below:

1. Reviewer 00503045

Comments: The issue of pathogenic/genetic mechanisms in the induction of aPL antibodies is important and is not investigated sufficiently. However this review needs some revisions: 1. As stated in "Introduction" "we need to highlight the effect of classical thrombotic genetic factors on disease expression in APS patients". This is indeed the main issue and most important but is not discussed properly. 2. Section "Human genetic associations-HLA associations" is full of detailed information on how many HLAs are associated with aPL (aCAL, anti-Beta2 ...) but almost nothing on clinical aspects such as any associations with thrombosis? frequency? reccurency?. Even if the information on that is limited this should be at least discussed 3. The section "Non-HLA associations" Here, the authors did well by discussing some data on the association between G/691A-FVL and G20210A and thrombotic events and not only aPL frequency!! 4. The section "Environmental factors" Here also the information is almost on associations with aPL frequency and infections and much less with possible associations with thrombosis?. Again even if limited this information should be better stated.

Response: We thank the reviewer for his/her comments. As the reviewer states, there is not very much published data on HLA associations with clinical aspects of antiphospholipid syndrome. The few studies that have addressed this issue were already included in the article. We did not highlight the lack of studies looking at this association since the focus of our article was discussing the genetic and environmental factors that lead to the production of pathogenic antiphospholipid antibodies, not the manifestations. As the reviewer suggested, we have added statements highlighting that limited information is available. These changes have been highlighted.

2. Reviewer 00506590

Comments: The current review analyzed different aspects that could lead to development of autoantibodies production in the Antiphospholipid Syndrome. I think it is an excellent review that

contributes with up to date information and in a very elegant writing display. It was a pleasure to read it and I cannot criticize any portion of the review; on the contrary I strongly support its immediate publication. Thanks

Response: We thank the reviewer for his/her kind comments.

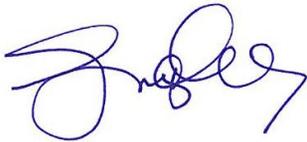
3. References and typesetting were corrected

4. A new version of the figure has been uploaded. We do not have the option of saving the figure as a ppt, so if this new version does not work – please discard the figure.

5. Running title, core tip and keywords have been added to the article.

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

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Emilio B. Gonzalez', with a stylized, cursive script.

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