UNIVERSITY OF CRETE
FACULTY OF MEDICINE
DEPT. OF GASTROENTEROLOGY

Elias Kouroumalis MD PhD
Professor of Gastroenterology
Head of the Department

P.O. Box 2208, Heraklion,
71003, Crete, Greece
Phone: +30 2810 392355
Fax: +30 2810 542085
E-mail: kouroum@med.uoc.gr

November 13, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Kouroumalis_Notas WJGPT R1.docx).

Title: Primary Biliary Cirrhosis: From Bench to Bedside

Authors: Elias Kouroumalis, George Notas

Name of Journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

ESPS Manuscript NO: 12454

The manuscript has been improved according to the suggestions of reviewers and the notes on the Edited manuscript:

1. Full names of the authors have been provided
2. Postal code has been added
3. Abstract has been reformed according to the journal policies (>200 words)
4. Extensive language polishing (grammar check and spelling) has been performed
5. All changes in the manuscript have been highlighted
6. Revision has been made according to the suggestions of the reviewers (response in *italics*)

(1) Reviewer 1

Dear Editor, I have read with great interest the enclosed manuscript entitled "Primary Biliary Cirrhosis : From Bench to Bedside" in which the authors reviewed basic and clinical evidences on pathophysiology and treatment of PBC. The high quality of the

text and the field of interest give to the manuscript a high priority for publication. However, I suggest some minor changes in manuscript:
Epidemiology; Row 2; refuse: a tendency
Corrected

In my opinion, a table reporting data of prevalence and incidence from available studies could clarify and simplify the text.

A table (Table 1) with indicative studies and metanalysis has been included in the manuscript.

The genetic and environmental factors are well reported and described. The authors included the sub-title "Pathogenesis" two times.

The second subtitle "Pathogenesis" has been deleted from the revised manuscript

The pathogenetic unifying model is very interesting and give to the manuscript a further appeal, over the simple systematic review of the literature in the field; I should stress it and outline it in the abstract and introduction.

We would like to thank the reviewer for his feedback. We have stressed the presence of the hypothesis in the abstract and the introduction as suggested by the reviewer.

In my opinion, within the chapter "diagnosis" the description of non-invasiveserum markers for PBC staging is not need; however, if the Authors want to include it, I suggest to talk also about the use of liver tissue elastography (LSM, Fibroscan, etc..).

We would like to thank the reviewer for his point. We decided to keep the description of non-invasive markers and we have also added a paragraph regarding elastography in the revised manuscript.

Natural history, row 3, refuse: increased
Corrected

Pag. 30, 1st row, refuse: values above
Corrected

Treatment, 1st row, refuse: medical management in PBC
Corrected

Treatment: refuse 12-15 mg/kg/day
Corrected

There are too may clinical data reported on UDCA treatment, while the effects of the other drugs is only cited.

It is true that the greatest part of the "Treatment" section of the manuscript has focused on UDCA which is the standard therapy for PBC. However a number of other treatments are discussed in pages 33-36 including liver transplantation in PBC, bezfibrate, colchicine, methotrexate, glucocorticoids, chrorambucil, tetrathiomolybdate, rituximab, CTLA-4 Ig and obeticholic acid. These therapies are not only cited but are also analyzed to a reasonable extend for a review of such size.

UDCA treatment effect is clear and completely described.

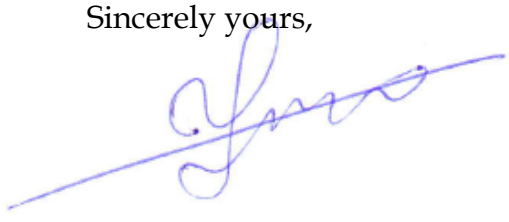
(2)Reviewer 2

Comments to authors: In this review, KOUROUMALIS and NOTAS address that Primary Biliary Cirrhosis: From Bench to Bedside. The authors reviewed that the various epidemiologal and geoepidemiological data as well as the complex pathogenetical aspects of this disease. PBC is considered a multifactorial disease with a strong genetic background and influence by various environmental factors. The role of innate and adaptive immunity, including cytokines, chemokines, macrophages and the involvement of apoptosis and reactive oxygen species are outlined in detailed. The current pathogenetical aspects are presented and a new pathogenetic theory is formulated. A review of clinical manifestations and immunological and pathological diagnosis was presented. Treatment modalities, including the multiple mechanisms of action of ursodeoxycholate (UDCA) were finally discussed. COMMENTS This review has a comprehensive and good reviewer about PBC. It is worthy of publishing in this journal. There is no any comment.

We would like to thank the reviewer for his appreciation of our work

Thank you again for publishing our manuscript in the World Journal of Gastrointestinal Pharmacology and Therapeutics

Sincerely yours,



Elias Kouroumalis MD, PhD