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June 23<sup>rd</sup>, 2016

Dear Editor,

Please find attached our revised copy of manuscript titled:

26791 Revised Manuscript.docx

**Name of Journal:** World Journal of Gastrointestinal Pathophysiology

**Number ID:** 03256573

**Manuscript Type:** Review

**Immunobiology of Hepatocarcinogenesis. Ways to go or almost there?**

Patel, P *et al.* Immunobiology of Hepatocarcinogenesis

**Pavan Patel, Steven Schutzer, Nikolaos Pyrsopoulos**

**ESPS Manuscript Number:** 26791

The manuscript has been revised according to the following suggestions from the reviewers:

1. **Reviewer 00503601:** "Fairly detailed and comprehensive review of immunobiology and immunotherapy in HCC. The field is still fairly complex and in its infancy and this review is useful. The writing style is somewhat hard to read and heavy going and may be hard reading for those not so familiar in this area."

*We appreciate the above comments and have edited the manuscript in order to flow smoothly and appeal to readers not familiar with immunobiology to the best of our ability.*

2. **Reviewer 02242399:** "This manuscript summarizes the cancer immunology and oncogenic pathways in HCC. Various immune cells which contribute to establish the tumor microenvironment are listed in this review article. Several oncogenic pathways involved in hepatocarcinogenesis are also under discussed. This manuscript is well described, however, there are still some minor issues need to be further addressed. 1. Pages 6-7, description of the roles of CD8+ T cells in HCC is too little; the authors need to add more references in this part. The correlation between CD8+ T cell, sorafenib sensitivity and PD-1 expression should be addressed in this part. 2. Page 7, the description of CD4+ TH1 cells is not clear. In addition, the two sentences – "TH1 is response for antitumor immune response and they differentiate by response to IL-12 and IFN- $\gamma$  via signal transduction. The loss of the IFN- $\gamma$  receptor expression on the HCC cell surface may lead to HCC progression and metastasis.", may make the readers confuse. The correlation between 「loss of the IFN- $\gamma$  receptor expression on the HCC cell surface」 and 「TH1 is response for antitumor immune response and they differentiate by response to IFN- $\gamma$ 」 should be addressed more clear. 3. Page 9, the introduction of TAM/M1 in HCC is too little. 4. Page 13, reference for NK cells should be added in the second paragraph. 5. Page 14, the sentence "Add the reference and Num/Denom or %." What does it mean? 6. Another two oncogenic pathways have highly correlation with inflammation and immune response, the STAT3 and NF- $\kappa$ B pathways, should be included in this review article."

*We appreciate the above comments with the following revisions:*

- 1) *The CD8+ T cell role was further clarified and additional information was added accordingly and with references.*
  - 2) *The role of CD4+ TH1 cells was revised and information regarding IFN was clarified.*
  - 3) *More information regarding TAM and M1 response was added.*
  - 4) *Reference for NK cells was added*
  - 5) *This was taken out as it was added in error.*
  - 6) *Both STAT3 and NF-  $\kappa$ B pathways were added.*
3. **Reviewer 00503441:** "This manuscript by Patel P et al. elegantly summarizes the current concepts in the immunobiology of hepatocarcinogenesis including the interplay of a variety of immune cells involved in anti-tumor and pro-tumor effects. The Authors highlight the role of the immune system and immunomodulatory therapy against hepatocarcinoma. MINOR 1. The Authors

should add some figures to the manuscript. 2. Transforming growth factor-beta pathway should be also discussed.”

*We appreciate the above positive comments. Two new figures were added regarding the Mechanisms leading to CD8 T cell suppression and the differentiation of naïve T cells. Certain wording regarding the transforming growth-factor beta was also added in the manuscript.*

Thank you for allowing us to work with you and publishing this manuscript with the *World Journal of Gastrointestinal Pathophysiology*.

Sincerely,

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