UNIVERSIDAD DE MÁLAGA

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Re.: Re-submission of an amended invited review manuscript (Ms 39634) to *World Journal of Gastroenterolgoy* (ID: 00398050)

To the Editor-in-Chief

June 28th, 2018

Dear Dr.,

Please, you can find enclosed an amended versio of our manuscript entitled ***The HGF/c-Met axis in hepatocellular carcinoma and its therapeutic implications*** (formerly entitled ***Updates on the HGF/c-Met axis in hepatocellular carcinoma***) to be submitted as a review manuscript to ***World Journal of Gastroenterology*** in response to a kind invitation sent to me via email. The number ID for this invitation is 00398050.

In the preparation of the amended version of our manuscript, we have taken into account the comments and criticism raised by reviewers.

REPLY TO REVIEWER 1

Reviewer #1: It is a very good review about the HGF/c-Met axis signaling pathways in hepatocellular carcinoma, and compounds already used or showing potential to be used in clinical trials.

Our reply: Thank you very much for your positive comentary and evaluation.

REPLY TO REVIEWER 2

Reviewer #2: The authors have reviewed the role of HGF/c-Met axis in hepatocellular carcinoma (HCC) and its therapeutic potential in the treatment of HCC. This is a detailed review, however the following issues needs to be addressed.

MAJOR CRITIQUES 1. There have been more than half a dozen reviews published in this field in the last five years. Therefore the authors have to explicitly state how this review differ from the previous reviewers and what this review adds to the literature.

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Our reply: Some reviews have been published in the previous years in the HGF/c-Met axis. This trend shows the raising interest of this signaling pathway for liver cancer research. However, the previous reviews already published neither cover overall the same topics about hepatocellular carcinoma as we do, nor do it with the same depth. For example, some of them are regarding risk factors and HCC diagnosis (Waller L.P, et al. 2015), epidemiology and molecular mechanisms (El-Serag H.B. & Rudolph K.L. 2017), signaling pathways involved in HCC (Whittaker S. et al. 2010; Kawaguchi M. & Kataoka H. 2014; Viticchiè G. & Muller P.A.J. 2015), microenvironment and HCC development (Hernández-Gea V. et al. 2013; Owusu B:Y: et al. 2017; Margetts J. at al. 2017; Yagci T. at al. 2017), epigenetic (Shukla S.D. et al. 2013; Callegari E. et al. 2013; Laurent G. et al. 2015; Wilson C.L. at al. 2017), novel therapies against HCC (Chan S.L & Yeo W. 2012) or the evaluation of potential diagnosis biomarkers for HCC (Goyal L. et al 2013). However, no of them gather all those topic in the same review, as we have tried to do. We did an effort to link all the topics related with HCC and build a broad scope review.

2. The authors should consider re-structuring the manuscript. At present the first half of the manuscript concentrates purely on the biochemical aspect of HGF/c-Met axis (pages 6 - 11). It would be better to include these into various aspects of liver disease and HCC (the second half of the manuscript), so that it would keep the reader engaged, as most readers would be Hepatologists.

Our reply: The key aim of the biochemical aspects of this review is to organize the knowledge regarding c-Met signaling pathway, avoiding possible misunderstanding about c-Met activation. we think that describing the signaling pathways separately could help lectors to realize easily about possible novel therapies or researches using inhibitors on the proteins involved in c-Met signaling pathways. We are confident that with this structure the reader can be kept engaged, as implicitly acknowledged by the positive evaluations provided by other reviewers.

REPLY TO REVIEWER 3

Reviewer #3: The manuscript # 39634 entitled, "The HGF/c-Met axis in hepatocellular carcinoma" reviews the HGF/c-Met Signaling in Hepatocellular Carcinoma and available treatments against HCC based on HGF/c-Met inhibition. The review manuscript also included discussions on the novel explored treatments targeting the microRNAs, methylases, and acetylases which are involved in cancer genes expression regulation. Comments: Collectively, the manuscript is wellwritten/ organized and the summarizing tables and figure are conclusive.

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Our reply: Thank you for your positive evaluation of our review work.

However, taking into consideration the excellent review article published recently with almost the same title and content (Hu CT, et al, The Therapeutic Targeting of HGF/c-Met Signaling in Hepatocellular Carcinoma: Alternative Approaches. Cancers (Basel). 2017), I would suggest that authors consider the following comments in a revised (review or mini review version) of their manuscript for clarification of the updates and novel discussions included in their manuscript compared to this recent preceding manuscript:

- Title of the manuscript might be remained in a general form as it appears but the phrase "updates on" might be added. Alternatively, authors might consider a more specific title to indicate the message and novel emphasizing points of their review manuscript. For example: "the novel explored treatments on The HGF/c-Met axis in hepatocellular carcinoma".

Our reply: According to your suggestion we have changed the title. In the present version the tile is: ***Updates on the HGF/c-Met axis in hepatocellular carcinoma and its therapeutic implications.***

- Authors might quote the above mentioned recent review article and addressing this manuscript properly, try to summarize the repeated materials in the text (which are already well-discussed in the prior recent review article) and clearly indicate the aim and novelty of the materials that have been added (updates and/or discussions on the novel explored treatments targeting the microRNAs, methylases, and acetylases which are involved in cancer genes expression regulation).

Our reply: The previous review entitled "The Therapeutic Targeting of HGF/c-Met Signaling in Hepatocellular Carcinoma: Alternative Approaches" is a nice review specially focused in the pharmacological point of view of HGF/c-Met on small molecules kinase inhibitors of c-Met. That review also comments other topics, such as resistance in c-Met targeting, side effects in c-Met targeting, and endosomal signaling of c-Met, that we do not mention in our review. However, our review manuscript is more related with the biological relevance of HGF/c-Met axis in hepatocellular carcinoma. Furthermore, we mention novel therapeutic approximations, not only focused on small molecules kinase inhibitors of c-Met, but also in novel therapies with siRNAs, HDAC inhibitors, and DNA methylase inhibitors, among others.

- English edition of the manuscript is recommended throughout the manuscript.

Our reply: A native English speaker colleague, Dr. Michael J. Hendzel (Univerity of Alberta, Canada), has carefully read the manuscript for English grammar and has made editing suggestions that we have taken into account in the amended version of our manuscript. We have added an Acknowledgement section to thank him for this valuable help.

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REPLY TO REVIEWER 4

Reviewer #4: This is a good review article on a relevant topic that needs a careful revision of the English language.

Our reply: Thank you very much for your positive comentary and evaluation. A native English speaker colleague, Dr. Michael J. Hendzel (Univerity of Alberta, Canada), has carefully read the manuscript for English grammar and has made editing suggestions that we have taken into account in the amended version of our manuscript. We have added an Acknowledgement section to thank him for this valuable help.

REPLY TO REVIEWER 5

Reviewer #5: this review has good knowledge on hcc pathogenesis in regards c-Met and HGF. I think it deserve publication.

Our reply: Thank you very much for your positive comentary and evaluation.

I am confident this amended, new piece of work from our research group could be of interest for the redearship of the journal.

Looking forward to hearing from you soon, I remain

Best regards,

Dr. Miguel Ángel Medina

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Suggested reviewers:

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*Dr. Gabriele Bergers (an expert in angiogenesis research). She belongs to the Department of Neurological Surgery, Brain Tumor Research Center and UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, 513 Parnassus Avenue, San Francisco, CA-94143-0520, USA. E-Mail: gabriele.bergers@ucsf.edu

*Dr. Theodore Fotsis (some of his articles -as those published in PNAS, 1993, and in Nature, 1994- were pioneer scientific works in the area of identification and characterization of anti-angiogenic compounds from natural sources). Laboratory of Biological Chemistry, Medical School, University of Ioannina, Greece. E-Mail: thfotsis@cc.uoi.gr.

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