

November 16<sup>th</sup>, 2020

**NO: 58790 Integrative Analysis of Layers of Data in Hepatocellular Carcinoma Reveals Pathway Dependencies**

Dear Professors Hu, Kang and Pyrsopoulos,

Thank you for your interest in considering the revised version of our manuscript for publication in World Journal of Hepatology Manuscript. We have addressed the comments point-by-point as below, which we hope satisfactorily address the reviewers' concerns.

Reviewer(s)' Comments to Author:

Reviewer #1

*Why did the authors not include data obtained from HCC experimental animal models in the integrative analysis? It would have been interesting to compare this with the analysis from HCC patient tissues.*

We thank the Reviewer#1 for this comment. We recognize that animal models have been of incredible scientific values in studying new therapeutic avenues or molecular mechanisms behind the etiopathogenesis of HCC. The scientific intent of our integrative analysis was, however, to identify, despite the heterogeneity among HCC patients, common molecules and/or pathways in HCC across different layers of data. From our perspective, including animal models in the analysis might be a source of bias due to the fact that usually animal models are used in publications with the specific intent of investigating a specific pathway or drug target more than with the intent of studying HCC heterogeneity in itself.

Reviewer #1

*Discussion would be improved if authors discuss other articles describing this type of integrative analysis of big 'omics' data from other tumor types, for instance, breast cancer, ovarian cancer.*

We thank the Reviewer for this constructive comments and we have now added this part in the Discussion on pages 14-15 ( lines321-329)

Science Editors comments

*1)The highest single-source similarity index in the CrossCheck report showed to be 7%. According to our policy, the overall similarity index should be less than 30%, and the single-source similarity should be less than 5%. Please rephrase these repeated sentences.*

We have reviewed the Discussion part on pages 13-14 (lines 281-284) bring the single-source similarity index to less than 5%. We hope this adequately addresses this comment.

*2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); The study was supported by Ontario Research Fund; and Canadian Institutes for Health Research Fellowship for Health Professionals*

We have now removed them.

*3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;*

We have now created a folder, as for instructions, where all images are provided in their original PowerPoint format and can be modified as needed

*4) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;*

We have now revised all the reference, as for instructions

*(5) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text;*

We have now added this section on pages 15-16 (lines 356-367)

*6) The author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.*

We have now revised the references accordingly.

We hope that the above responses adequately address the reviewers’ comments. Thank you for your interest in our manuscript, and we look forward to your response.

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