**AMERICAN
UNIVERSITY OF BEIRUT**

FACULTY OF MEDICINE
Department of Anatomy, Cell Biology and
Physiological Sciences

October 2022

Re: <u>Manuscript Revision</u>

<u>Thursday, October 13, 2022</u>

Re: <u>Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: updates and beyond</u>

Dear Editors-in-Chief,

On behalf of my colleagues, I am returning to *World Journal of Gastroenterology* a revised version of a manuscript entitled: **"Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: updates and beyond."**

The authors thank the editor and the reviewers for the constructive suggestions they provided. We sincerely appreciate all valuable comments and suggestions, which helped us to improve the quality of the manuscript. We have studied and evaluated the comments carefully and have made the amended corrections. We believe that this version has addressed all the editor's and reviewers' concerns. Accordingly, we have modified our manuscript to address all these comments. Please find below a point-by-point reply to all comments. We have provided the revised manuscript file with tracked changes.

I sincerely hope that this manuscript will meet your requirements for publication.

Sincerely Yours,

Wassim Abou-Kheir, PhD
Associate Professor
Department of Anatomy, Cell Biology and Physiological Sciences
Faculty of Medicine
Director of Graduate Student Affairs
American University of Beirut
Bliss Street, DTS Bldg, Room 116-B, Beirut-Lebanon, 1107-2020
Tel: 961-1-350000, Ext. 4778; Mobile: 961-76994308; Fax: 961-1-744464
E-mail: wa12@aub.edu.lb

American University of Beirut
Diana Tamari Sabbagh Bldg., 1st Floor, Room 130
P.O.Box 11-0236 / Anatomy, Cell Biology and Physiological Sciences
Riad El-Solh / Beirut 1107 2020, LEBANON

Editors

American University of Beirut
3 Dag Hammarskjold Plaza, 8th Floor,
New York, NY 10017-2303, USA

' comments:

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Authors' response: We thank the science editor for his/her comment.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Authors' response: We thank the editor-in-chief for the comprehensive revision of the manuscript and the constructive remarks. We have taken these comments on board to improve and clarify the manuscript.

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

Authors' response: Thank you for your comment. We have used uniform presentation when applicable.

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Authors' response: Thank you for your comment. We have provided the editable version of Figures and organized them into a single ppt file, as requested.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Authors' response: We thank the editor-in-chief for his comment. We have provided standard three-line tables and fixed the contents and carriage returns.

Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference sourc e and

copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Authors' response: We thank the editor-in-chief for this input. We confirm that the Figures provided in this manuscript are original, and therefore "Copyright ©The Author(s) 2022" was added to each Figure.
In addition, tables provided in the manuscript are also original.

Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Authors' response: We thank the editor-in-chief for this comment. We have added some of the latest cutting-edge research results to the manuscript using the RCA database, especially in the "targeted therapy" and "beating resistance to targeted therapy" sections.

Reviewers' comments

Reviewer #1:
 This review is well-written and easy to understand. The authors reviewed in detail the mechanisms of resistance to conventional therapies for mCRC, discussed the molecular mechanisms and efficacy of new targeted therapies, and further discussed the problems and solutions of resistance to these targeted drugs. This article summarizes the results of a large number of clinical trials, with sufficient demonstration and clear logic, which meets the requirements of this journal. I recommend that the manuscript should be accepted.

Authors' response: We thank the reviewer for his/her comprehensive revision of the manuscript and his/her constructive remarks. We feel encouraged by your positive feedback on our work. We have taken your comments on board to improve and clarify the manuscript.

there are several minor problems in the article, which can be further optimized:

1. The author lists many tables to summarize the targeted drugs in the paper, but only one figure describes the targeted drugs. Considering that traditional drug resistance mechanisms, targeted drug resistance, and solution strategies are also
2. Very important components of the article, I suggest that several additional summary figures can be drawn based on these contents to facilitate readers' understanding and reading.

Authors' response: Thank you for your suggestion. We have added two figures to summarize the traditional drug resistance mechanisms, targeted drug resistance, and strategies to overcome resistance.

2. In the last part of the article, the author emphasizes the importance of implementing better preclinical models for research, but this part is not explicitly mentioned in the abstract and introduction, which is slightly out of place.

Authors' response: Thank you for your input. We have added statements in the abstract and introduction, in order to highlight the importance of using these models.

3. In the end, the author can elaborate on his understanding of "personalized" treatment of CRC and optimization of existing targeted therapy strategies (such as drug combination) in more detail, and summarize some meaningful suggestions or opinions to show his unique insights.

Authors' response: We thank the reviewer for his/her comments. We have incorporated the suggestions made to improve the last part of the manuscript.

4. In addition, there are some grammatical problems and formatting problems in the manuscript (such as the space before paragraphs), which need to be carefully considered by the author and modified. Some of the possible inappropriacies are listed below. I hope the author can review the whole paper carefully. (1) Please check the spelling of "5-flourouracil (5-FU)" in the third paragraph of the introduction. (2) Please check the verb "has" in the sentence " New drugs whose action is directed at specific pathways implicated in CRC pathogenesis, including the epidermal growth factor (EGFR) pathway, has been tested in preclinical models and in clinical trials. " in the fifth paragraph of the introduction. (3) Please check the "leading" in the first sentence in the "Tumor Microenvironment" section for grammatical errors. And please check if "mediates" is correct in the sentence "During tumor formation, interactions between tumor and stromal cells and secretion of soluble inflammatory molecules mediates the attraction of the above-mentioned cells, which goth tumor cell survival and metastasis.". Please check for any ambiguity before and after the sentence "One of the most important components of tumor stroma are TAMs and CAFs." (4) Please check the use of "include" in the penultimate sentence and "have" in the last sentence of the "Gut microbiota" section for mistakes. (5) Check whether the phrase "Adverse events rates" in the last sentence of the fourth paragraph Targeting EGFR is wrong. (6) Please check whether the phrase "is implicate" in the last sentence of the first paragraph Targeting HER is wrong. Please check the correct noun form of "subgroup" in the sentence " Several factors may account for this variability, including small sample size, different antibodies used for immunohistochemistry (IHC), and analysis of different subgroup of patients with multiple clinical characteristics." in paragraph 2. Please check whether

there is an

extra "the combination of" in the sentence " HER2 amplification was detected in clinically unresponsive KRAS WT patients, and the combination of the combination of lapatinib (a dual EGFR/HER2 tyrosine kinase inhibitor) and pertuzumab induced an increase in response rate and tumor regression, in agreement with clinical studies in patients with similar clinicopathological characteristics." in the second paragraph. (7) Consider whether "table" in the article should be "Table". (8) In

the part of "MEK and Mutant BRAF," please consider whether "are" should be changed to "is" in the last sentence " BRAF, along with RAS, are the only available biomarkers for advanced CRC that are used in clinical practice." of the first paragraph considering" along with ". (9) Please check the use of "were" in the penultimate sentence of the "Immune checkpoint inhibitors".

Authors' response: We thank the reviewer for his/her comments. We have thoroughly revised the manuscript and made the necessary corrections.

Reviewer #2:

This manuscript could be accepted.

Authors' response: We thank the reviewer for taking the time to revise the manuscript.

Reviewer #3:

1. **The manuscript focus on Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: updates and beyond, after checked the references in Pubmed, many references focus on drug-resistance in CRC including review artices such as Drug resistance and new therapies in colorectal cancer. Van der Jeught K, Xu HC, Li YJ, Lu XB, Ji G.World J Gastroenterol. 2018 Sep 14;24(34):3834-3848. doi: 10.3748/wjg.v24.i34.3834.**

Authors' response: We thank the reviewer for taking the time to review and comment on our manuscript.
We agree with the reviewer that many references focus on drug-resistance in CRC. In this manuscript, we chose to focus on both drug-resistance and metastasis in CRC, because there is an association between the two phenotypes, whereby they both affect the response to traditional and targeted therapies.

2. **This topic focus on drug resistance Molecular mechanisms and metasis, but the article consisted with RESISTANCE TO THERAPY Or TARGETED THERAPYor BEATING RESISTANCE TO TARGETED THERAPY, very strange？**

Authors' response: Thank you for your comment. The title indicates that the paper focuses on molecular mechanisms of targeted therapy in drug-resistant and metastatic colorectal cancer. In this paper, we highlight mechanisms of resistance to traditional treatments, then we present an overview of current and novel targeted therapies that are tested against resistant

American University of Beirut
Diana Tamari Sabbagh Bldg., 1st Floor, Room 130
P.O.Box 11-0236 / Anatomy, Cell Biology and Physiological Sciences
Riad El-Solh / Beirut 1107 2020, LEBANON

American University of Beirut
3 Dag Hammarskjold Plaza,
8th Floor,
New York, NY 10017-2303, USA

and metastatic colorectal cancer. We finally emphasize challenges of targeted treatment and strategies to overcome resistance to these therapies.

3. **The structure of the article was confused, I think firstly introduce the targeted therapy and drug resistance phenomenon, then discuss the possible mechanisms such as Cancer stem cells, Tumor microenvironment。。。then disucuss beating resistance strategy.**

Authors' response: Thank you for your suggestion. We would like to clarify that the "resistance to therapy" section was placed before the "Targeted therapy" and "Beating resistance to targeted therapy" sections because it highlights resistance to traditional therapy (we focus on conventional chemotherapy) and the need for a more targeted therapy that would overcome this resistance.

We then introduce the targeted therapy and its efficacy in treating drug-resistant and metastatic colorectal cancer. We also focus on intrinsic and acquired resistance to targeted therapy and solution strategies to overcome this resistance.

4. **The manusrcipt foucus on mechanisms, but so many words introduce the targeted therapy, so please highlight the mechanisms part.**

Authors' response: We thank the reviewer for his/her comment. We have highlighted the mechanisms part as requested.

5. **The mechanisms of drug -resistance I hope add a Figure, this is very important.**

Authors' response: Thank you for your suggestion. We have added two figures that summarize traditional drug-resistance mechanisms and resistance mechanisms to targeted therapies.

6. **The English need much more polish.**

Authors' response: We thank the reviewer for his/her comment. We have had our manuscript further checked and edited by a native speaker.

American University of Beirut
Diana Tamari Sabbagh Bldg., 1st Floor, Room 130
P.O.Box 11-0236 / Anatomy, Cell Biology and Physiological Sciences
Riad El-Solh / Beirut 1107 2020, LEBANON

American University of Beirut
3 Dag Hammarskjold Plaza,
8th Floor,
New York, NY 10017-2303, USA