

We wish to thank you for considering this manuscript for publication in *World Journal of Gastroenterology* and the reviewers for their comments. We address below each point raised by the reviewers.

**Reviewer code: 01714224**

“The paper by Van der Jeught et colleagues entitled "Drug resistance and new therapies in colorectal cancer" reviews current data on chemotherapy for CRC, focusing attention on resistance mechanisms and molecules, such as  $\alpha$ -amanitin, possibly overcoming this problem. The review is interesting and well written, with high quality figures, literature updated. Only minor criticism is the presence of multiple typewriting mistakes in the text to be corrected. “

We appreciate the reviewer's comment on pointing out multiple typewriting mistakes in the text. We screened the entire manuscript and have corrected them.

**Reviewer code: 00044333**

“The authors presented the mechanisms of drug resistance and new therapies in colorectal cancer, especially, in the aspects of drug metabolism, tumor microenvironment, and immunotherapy. The manuscript includes many detailed contents with a lot of clinical and basic evidence, and was well organized. Because one of the main issues in chemoresistance is cancer stem cell theory, adding the content of cancer stem cell would improve your manuscript.”

We completely agree with the reviewer that one of the main issues in chemoresistance is the presence of cancer stem cells. Therefore, we wrote an additional paragraph of cancer stem cells into the manuscript in the section “Chemotherapy Resistance and their Potential Mechanisms”.

**Reviewer code: 02505493**

“This review focuses to the drug resistance in colorectal cancer, evaluates major resistant mechanisms and discuss new therapeutic approaches, highlighting new developments with clinical potentials. The field is very interesting, and the review gives substantial information to the reader. However, there are several points requiring clarification and/or correction. Major point Tables should be introduced in sections “Hurdles and New Avenues for Targeted Therapy”, “The Tumor Microenvironment, Microbe Biofilm, and their Contribution to Drug Resistance and Tumorigenesis” and “Immunotherapy development” to highlight in brief the various findings with the respective refs.”

We believe that the text is clear and contains the majority of the current approaches with their respective references. The further addition of a table in each section as mentioned is superfluous and would not benefit the clearness of the manuscript. Therefore, we did not include any additional tables in the manuscript.

Minor points

1. In a lot of cases (about one hundred) there is no space between adjacent words (see, for example, page 3, lines 22, 25, 26, 27).

We appreciate the reviewer’s comment on pointing out multiple lack of spaces between adjacent words. We screened the entire manuscript and have corrected them.

2. Page 3, line 20: Replace the word “focusses” with either “points of focus” or “foci”.

We replaced the word “focusses” by “point of focus”.

3. Page 9, line 12: Replace “remaining” with “remains”.

We replaced the word “remaining” by “remains”.

4. Page 14, line 12: Replace “currently” with “currently”.

The word in the manuscript is currently.

**Reviewer code:** 00503442

“I read with great interest the manuscript entitled " Drug resistance and new therapies in colorectal cancer" by Kevin Van der Jeught et al. The manuscript is excellent, timely and very well written. It is quite appropriate and well written. I am not able to see Figure 1 but all the images well describe the field. I have no amendments to required to the Authors.”

We are delighted to see the reviewer’s appreciation of our manuscript. The Figure 1 should be in the manuscript. It might have been a technical issue. Therefore, no further modification was required.