

## ANSWERING REVIEWERS

November 25, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 6100-review.doc).

**Title:** Chemopreventive Drugs: Mechanisms via Inhibition of Cancer Stem Cells in Colorectal Cancer

**Author:** Tae Il Kim

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6100

The reviewer's comments have significantly improved the quality of our manuscript.

Reviewer 1.

1. The Review article is well written with very few grammatical and typographical errors, but it still requires some proof reading.  
→ The revised manuscript has been proofread by professional agency.
2. Statements made in the first two paragraphs of the review require citations.  
→ Some references were added (highlighted).
3. In the third paragraph on page 3 the statement should be "aspirin and other non-steroidal anti-inflammatory drugs (NSAID)" instead of "aspirin, non-steroidal anti-inflammatory drugs (NSAID)" as aspirin also belongs to the class of NSAID  
→ Correction was done as the reviewer mentioned (highlighted).
4. Use of a schematic or a diagram to represent the role of cancer stem cells in CRC should be added to the review. A picture showing how attacking CSC can be useful in prevention of CRC will be useful. Both the ideas can be represented using a single or two separate figures.  
→ Two figures (figure 1, figure 2) were added according to the reviewer's suggestion.
5. Recently published studies have also mentioned DCLK1 and LGR5 also as potential CSC markers and they should be mentioned within the review.  
→ The references about DCLK1 and LGR5 were added (page 7, highlighted).
6. Multiple dietary agents have also been reported to have potential anti CSC activity in CRC. Mentioning few of those will also add to the content of the review.  
→ The effects of dietary compounds on CSC were added in page 9 (highlighted).

Reviewer 2.

Colorectal cancer remains despite therapeutic advances, one of the leading causes of morbidity and mortality from cancer. Therefore, prevention is today the best strategy to reduce the incidence of colorectal cancer. Advances in recent years have demonstrated the essential role of cancer stem cells and their niche in the process of colorectal cancer in both tumor initiation and tumor progression. Therefore, as the author of this article, the identification of components of the microenvironment of the stem cells and to study signaling pathways should facilitate the development of specific drugs and no side effects, which can prevent the development of cancer. This article describes the main drugs that have been shown to be protective against colorectal cancer through epidemiological studies. Further, the author smartly discusses as the beneficial effects of these drugs are associated with their ability to interfere with the signaling pathways of

cancer stem cells , to alter tumor metabolism , or to inhibit activity of inflammatory cells residing in the tumor microenvironment.

Reviewer 3.

General comments (1) The importance of the research and the significance of the research contents This manuscript describes about chemopreventive effects of aspirin, NSAID, statin, PPARgamma agonist and metformin on cancer prevention. This is an important topic for cancer treatment. (2) The novelty and innovation of the research The research has the novelty in terms of the points focusing on chemopreventive drugs and cancer stem cells. (3) Presentation and readability of the manuscript. The readability of the manuscript is quite well, although there are some incomplete sentences. (4) Ethics of the research. There does not seem to have any specific problem in ethics. Specific comments Title accurately reflects the major topic and contents of the study. Abstract describes about the aim of the research to investigate the chemopreventive drugs on cancer prevention.

In the 8th paragraph of the section “chemopreventive drugs of colorectal cancer and future direction,” please consider to mention about Apc(Min/+) mice with the intestinal-specific ablation of Pparg.

→ This was mentioned already in original manuscript (page 4, highlighted).

The first paragraph of the section “Effect of chmopreventive drugs on cancer stem cells, and its related mechanisms” is incomplete.

→ This paragraph was corrected (page 7, highlighted).

Please cite the reference indicating PI3K/Akt/mTOR pathway is activated for maintenance and proliferation of CSCs in the 4th paragraph of the section “Regulation of altered metabolism of tumor and AMPK-mTOR pathway.”

→ The references were added according to the suggestion of the reviewer (page 10, highlighted).

Some abbreviations such as NSAID may be described at the first time they appear. Some terms such as “cancer stem cells” are not always abbreviated.

→ The corrections about the abbreviations were done as the reviewer mentioned.

Please check again. Please check references again whether they are appropriately cited.

→ I checked references again.

Thank you again for your kind review.

Sincerely yours,



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