

Dear Editor-in-chief,

This is with reference to our manuscript titled “Linking stemness with colorectal cancer initiation, progression, and therapy” (Manuscript no.: 46727). We wish to thank you as well as the reviewers for taking time out to review our manuscript. As per the suggestions provided by the reviewers as well as the Editors, we have revised our manuscript.

Following are our responses for the reviewers:

#### **Comments by Reviewer # 00068559**

In this review, the author gave a research summary of linking stemness with colorectal cancer initiation, progression, and therapy. The manuscript focused on the evolving concepts of colorectal CSCs – from their origin within the intestine, to their roles in cancer development, metastasis, therapeutic resistance, and recurrence. It also provided critical evidence from relevant discoveries, as well as the molecular signaling network that support the existence, self-renewal, plasticity, quiescence, and the overall maintenance of cancer stem cells in colorectal cancer. I think the review is helpful for us to better understand the the biology and the mechanisms of the origin of CRC, influential pathways regulating the colorectal CSCs, and the relevance of stemness in CRC prognosis and therapy.

Response: Thank you very much for your detailed evaluation of the manuscript as well as the positive comments related to its acceptance for publication.

#### **Comments by Reviewer # 00053419**

The review is a comprehensive summary of the most relevant mechanistic information in the field. I would suggest to include in figure 1 some of the most relevant cellular pathways (or gene/protein drivers) involved in the transition across the different stages.

Response: Thank you for your suggestion. We have updated figure 1 to show the relevant molecular pathways. The changes have been shown in yellow.

#### **Editor-In-Chief**

EIC notes: There are numerous typographical/grammatical errors (punctuations)/choices of style throughout the manuscript (examples, but not an exhaustive presentation, were given in the attached manuscript with tracking for locations). Refer to my email separately sent to the editorial office for details as in the attachment with tracking of the changes, as suggested for clarity and coherence.

Response: As per the EIC comments, we have revised the manuscript. Please find attached the revised word document labelled "46727-Review2.docx".

With reference to the comments provided for the Figure 1, we have revised the figure as well as the description to

provide a detailed overview of the stem cell model in normal colon and CRC. We wish to clarify that transit-amplifying cells are not seen in CRC and they generally present themselves as differentiated tumor cells or CSCs. Although an image of the revised Figure 1 has been included in the revised word document, we have also attached a revised figure powerpoint labelled "46727-Figure(s)2.pptx".

We hope that the revised version of the manuscript is suitable for publication in World Journal of Stem Cells. We are happy to respond to any further comments that may arise.

Yours sincerely,

Lui Ng, Ph.D., Research Assistant Professor Department of Surgery, University of Hong Kong, Hong Kong.