

November 18, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6373-review.doc).



Title: CANCER STEM CELLS IN COLORECTAL CANCER: FROM PATHOGENESIS TO THERAPY. Controversies and perspectives.

Author: Caterina Fanali, Donatella Lucchetti, Marisa Farina, Maddalena Corbi, Valerio Cufino, Achille Cittadini and Alessandro Sgambato

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6373

The manuscript has been improved according to the reviewers' and editor's suggestions:

1 Format has been updated

2 Revisions has been made according to the suggestions of the reviewers.

(00037223) We were very pleased with the comments of this reviewer who found the manuscript nicely written and did not manifest any criticism.

(02496361) This Reviewer suggested to cite the general survival time in CRC after treatment with classical therapy. We now included this information in the INTRODUCTION section on page 3 where we indicate that CRC display"a median survival time ranging from less than one to more than five years depending on the stage of disease at the diagnosis and the surgical techniques and/or chemotherapy used, especially for metastatic CRC".

This Reviewer suggested to improve the description of Paneth-like cells. We have revised the sentence stating that: A fourth differentiated type, the Paneth-like cells, resides at the bottom of colon crypts and has been shown to synthesize and secrete a variety of antimicrobial factors^[3].

This Reviewer suggested to add some references which were missing and to revise some sentences. We did it, as requested. Moreover, we also thoroughly revised the entire manuscript for grammatical errors and typos and for English style.

This Reviewer suggested to described CD44+CD54+ cells. We did on page 16 where we now state: "The association of CD44 with CD54 (a member of the immunoglobulin super-family also called

intercellular adhesion molecule-1) has been shown to specifically identify rectal CSC displaying the ability to self-renew *in vivo* and *in vitro*, form spheres and recapitulate tumor bulk^[66].

As suggested, we have deleted the References not in English.

(00672270) We were very pleased with the comments of this reviewer who described the manuscript as a well done work and had no comments.

(02446073) We were very pleased with the comments of this reviewer who found the manuscript an interesting and nicely written review article on colorectal cancer stem cells.

This Reviewer suggested to provide a brief or concise statement of the main purpose/aim of this review article at the end of the INTRODUCTION. We now included the following sentence at the end of the INTRODUCTION section: “Mounting evidence suggests that stem cells might play an important role in the process of tumor development being able to acquire a tumorigenic potential and giving rise to the so-called cancer stem cells whose potential role as tumor initiating cells as well as targets of cancer therapies is discussed in this review.”

This Reviewer found the CONCLUSIONS section too long and suggested to revise it and to make it more concise and easier for readers to catch up the main points of the article. We thoroughly revised the CONCLUSIONS section and shortened it highlighting the main points of the article.

This Reviewer noted some grammatical errors in the text. We corrected the errors indicated and we also thoroughly revised the entire manuscript for grammatical errors and typos.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

With my best regards. Sincerely,



Alessandro Sgambato, MD, PhD

Istituto di Patologia Generale

Università Cattolica del Sacro Cuore

Largo Francesco Vito 1, 00168 Rome, Italy. Phone: +39-06-3016619; E-mail: asgambato@rm.unicatt.it