Format for ANSWERING REVIEWERS

June 12, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Leporini et al_Revised manuscript.doc).

Title: Targeting Mast Cells in Gastric Cancer with Special Reference to Bone Metastases

Authors: Christian Leporini, Michele Ammendola, Ilaria Marech, Giuseppe Sammarco, Rosario Sacco, Cosmo Damiano Gadaleta, Caroline Oakley, Emilio Russo, Giovambattista De Sarro, Girolamo Ranieri

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18095

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

(1) i) In the INTRODUCTION chapter we have inserted that: *"Recently, it has been reported that bone metastases diagnosed by 18F-FDG PET/CT examinations are 10% of evaluated series. In fact, GC patients die due to metastases to intraperitoneal organs before that bone metastatic sites are revealed* (Ma DW et al. Dig Liver Dis. 2013)". The above reference has been updated;

ii) In the CONCLUDING REMARKS chapter we have inserted that: *"From a therapeutic point of view, it is interesting to remark that tumors injected in mice treated with inhibitors of MCs-degranulation present decreased vascularization and metastasizing. According to these lab data, targeting MCs is currently under investigation especially in gastrointestinal cancer patients"(Deplanque G et al. Ann Oncol 2015).* The above reference has been updated.

(2) i) We have provided the importance of targeting MCs in gastric cancer for both bone metastases and cancer progression. In detail:

- in the MAST CELLS POSITIVE TO TRYPTASE AND ANGIOGENESIS IN HUMAN GASTRIC CANCER chapter we have reported: *"Therefore, MCDPT may possibly exemplify a valuable target of anti-angiogenic therapy by either tryptase inhibitors or c-KitR inhibitors, which may potentially prove useful therapeutic tools in controlling angiogenesis-mediated tumor growth, progression and metastasis in GC";*
- in the ROLE OF MAST CELLS POSITIVE TO TRYPTASE IN BONE METASTASIS ANGIOGENESIS FROM PRIMARY GASTRIC CANCER chapter we have reported: *MCDPT may potentially offer a novel promising target of anti-angiogenic therapy to decrease both angiogenesis-mediated GC cell growth in the bone tissue and tumor-induced osteoclastic bone resorption"*

ii) Although bone is not the most common site of metastases from gastric cancer and metastases are common to peritoneum, liver and lung, we have focused on bone metastases due to the important related symptoms. In detail, in the INTRODUCTION chapter we have inserted that: *"Bone metastases are a relatively uncommon finding, pertaining between 1% and 20% of GCs and notably*

they represent a major discomfort due to the related pain, neurological involvement and hypercalcemia syndrome"

iii) Figure 1 has been deleted. The manuscript reporting this figure has been now cited in REFERENCES chapter (BioMed Research International 2014: 154702)

iiii) English editing has been now performed

iiiii) We have carefully check the manuscript and we have deleted the overlapping with our previous publications

(3) i) We have shortened all manuscript, in particular the first three parts (introduction, mast cells positive to tryptase and tumor angiogenesis, mast cells positive to tryptase, angiogenesis, and immune suppression in human cancers...). We also have cited in REFERENCES our previous publications. In particular, we have deleted figure 1 and 2 and we have now cited references that indicate papers describing the same figures.

ii) We have specified that EMT and cancer stem cells play an important role in tumor metastases, in particular we have reported in that:" *Moreover, cancer stem cells also promote GC metastasis via close physical cellular contact and paracrine signals released from the tumor niche both in vivo and in vitro assay. In fact, it has been demonstrated that stroma-associated cancer stem cells promoted gastric cancer cell EMT attracting circulating cancer cells to self-seed the primary tumor, again though EMT"* (Xue Z. Journal of Cellular Biochemistry 116:618–627 (2015)

iii) We have deleted many old references and we have now inserted more recent references

3 References and typesetting were corrected

4 In reply to you:

i) I certify that the attached manuscript has now been edited by a native English speaker, Caroline Oakley, in our in-house publications department and has reached Grade A standard. In fact, Caroline Oakley is now added and she now edited the manuscript;

ii) The title was shortened to 12 words;

iii) Audio Core Tip (file name attached: Leporini et al_Audio Core Tip.mp3) has been performed;

iiii) Figure 1 has been deleted as reviewers' suggestions;

iiiii) Table 1 was reported on a separate sheet (file name attached: Leporini et al_Table 1.doc);

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

Sincerely yours,

Michele Ammendola M.D.
Department of Medical and Surgery Science, Clinical Surgery Unit
University of Catanzaro "Magna Graecia" Medical School,
Viale Europa - Germaneto
88100, Catanzaro, Italy.
E-mail: michele.ammendola@libero.it
Tel. 09613694191
Fax: 09613647556 - 00393493717326