Format for ANSWERING REVIEWERS

December 17, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14585-review.doc).

Title: Mitochondrial uncoupling protein 2 and pancreatic cancer: a new potential target therapy

Authors: Massimo Donadelli, Ilaria Dando, Elisa Dalla Pozza, and Marta Palmieri

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14585

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 Reviewers

Response to Reviewer code 00503469:

-Manuscript has been carefully examined for English language.

Response to Reviewer code 00069082:

-In this Editorial, we examined in depth recent advances in the relationship between cancer development, especially pancreatic cancer, and mitochondrial UCP2 activity through a critical analysis of the literature. We analysed more than 100 articles and we selected the most recent ones and those describing the main biological processes involving UCP2. Some not recent key references have been also added for their specific relevance in the field. We reported data showing the link between UCP2 and cancer metabolism, oxidative stress and cancer. We attempted to give to the reader a wide overview of the current knowledge about UCP2 and cancer, with a critical vision based on our experience in the field.

-As for the suggestion to implement the chapter "UCP2 and pancreatic cancer", we should point out that the Editorial already includes all the literature available in the field. Indeed, our purpose was to stimulate further experimental research in pancreatic cancer by analysing UCP2 expression level on human tissues and cell lines as well as on humans by clinicopathological studies, with the final aim to define UCP2 as a new potential therapeutic target. To clarify this point we have added the following sentence at the end of the chapter: "*Despite the availability of the above described data on the relationship between UCP2 expression/activity and PC, we believe that further studies need to be performed in order to better clarify the functional role of UCP2 in PC tumorigenesis and progression. Of crucial importance will be analyses on proteome and metabolic profiles of pancreatic cancer cells after knock-down or over-expression of UCP2 and clinical studies correlating UCP2 expression with clinicopathological factors and prognosis outcome on PC patients*".

Response to Reviewer code 00058446:

-The Editorial includes all the literature available on the topic "UCP2 and pancreatic cancer" and has the purpose to stimulate experimental research on clinicopathological studies in PC patients, with the final aim to define UCP2 as a new potential therapeutic target. The following sentence referring to this item has been added at the end of "UCP2 and pancreatic cancer" chapter: "*Despite*

the availability of the above described data on the relationship between UCP2 expression/activity and PC, we believe that further studies need to be performed in order to better clarify the functional role of UCP2 in PC tumorigenesis and progression. Of crucial importance will be analyses on proteome and metabolic profiles of pancreatic cancer cells after knock-down or over-expression of UCP2 and clinical studies correlating UCP2 expression with clinicopathological factors and prognosis outcome on PC patients".

-We have modified Figure 3, in order to give a more comprehensible illustration.

Response to Reviewer code 01497562:

-We would like to point out that although UCP2 is the topic of both our previous Review published in Cell. Mol. Life Sci. (2014) and the present Editorial, the message of the two manuscripts is completely different. The former manuscript carefully describes the molecular mechanisms of UCP2 regulation at multiple levels while the present manuscript analyzes the role of UCP2 as a new potential target for pancreatic cancer.

-In this Editorial, our aim was to give an overview about the current knowledge concerning UCP2 and cancer, especially pancreatic cancer, although in this last case only few papers have been published. Nevertheless, our experience strongly suggests that UCP2 could be a target to selectively kill UCP2 overexpressing cancer cells, including pancreatic cancer cells, without affecting normal cells.

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

Sincerely yours,

Prof. Massimo Donadelli, PhD
Department of Life and Reproduction Sciences
University of Verona
Strada Le Grazie, 8
37134 Verona, Italy
Fax: +39 045 8027170
E-mail: massimo.donadelli@univr.it