

Klinikum der Universität München
Medizinische Klinik und Poliklinik II – Großhadern
Direktor: Prof. Dr. med. Burkhard Göke

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Dr. Lian-Sheng Ma, Beijing
President and Editor-In-Chief
World Journal of Gastroenterology

Munich, November 16th, 2013

Re: ESPS Manuscript NO: 4179

Dear Editor,

Thank you for the very helpful review of our manuscript Ms. No.: NO: 4179. Enclosed please find our revised manuscript in word format (4179-Review) embodying our answers to the editors and reviewers. We appreciate the helpful comments and have carefully followed all your suggestions. We do hope that the revised manuscript is now suitable for publication in the "*World Journal of Gastroenterology*".

Title: Aspirin inhibits cell viability and mTOR signaling in neuroendocrine tumor cells

Author: Matilde Spampatti, George Vlotides, Gerald Spöttl, Julian Maurer, Burkhard Göke, Christoph J Auernhammer

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4179

Thank you for your consideration.

Sincerely

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Response to editor's comments:

1. Could you give the word document version of the article

The word document version of the article is now included in the submission package.

2. Provide language certificate by a professional English language editing company

A language certificate by a professional English language editing company is provided.

3. Please provide title (Christoph Auernhammer)

The title "Dr." has now been added to Christoph Auernhammer.

4. An informative, structured abstract of no less than 336 words should accompany each paper. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim in the form: "To investigate/study/...; MATERIALS AND METHODS (no less than 140 words); RESULTS (no less than 150 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$; CONCLUSION (no more than 26 words).

The abstract of the manuscript has been modified accordingly.

5. Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

A summary (core tip) of less than 100 words is now provided.

6. HYPERLINK "http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T3B-4VBC3VD-2&_user=1090508&_coverDate=02%2F28%2F2009&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000051494&_version=1&_urlVersion=0&_userid=1090508&md5=da1f686af31226c856136f64efe7e59b" \ "bib1#bib1" The Authors should put the number of the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability^[1,2]".

The references have been modified accordingly.

7. **Comments: Writing requirements**
(1) BackgroundTo summarize concisely and accurately the relevant background to the article to enable the readers to gain some basic knowledge about the article and better understand its significance.
(2) Research frontiersTo introduce briefly the hotspots or important areas in the research field related to the article.
(3) Innovations and breakthroughsTo summarize and emphasize the differences, particularly the advances, achievements, innovations and breakthroughs, from other related or similar studies, to allow the readers to assimilate the major points of the article.
(4) ApplicationsTo summarize the practical applications of the research.
(5) TerminologyTo describe concisely and accurately any terms that may not be familiar to the majority of the readers, but are essential for understanding the article.
(6) Peer reviewTo provide the comments from peer reviewers that most represent the characteristics, values and significance of the article, and allow the readers to have an objective point of view toward the article.

A comment has been added to the manuscript according to guidelines.

8. Please provide **PubMed citation numbers** for the reference list, e.g. PMID and DOI, which can be found at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed> and <http://www.crossref.org/SimpleTextQuery/>, respectively. The numbers will be used in the E-version of this journal. Thanks very much for your co-operation

PubMed citation numbers have been added to the references.

Response to the reviewers:

Reviewer 1:

1. The manuscript explores an interesting and actual topic. However, the paper is not well structured nor clearly written. Both the introduction and the discussion section should be largely reviewed. Some sentences are quite confusing and do not appear to be rationally related to the context. Particularly, in the introduction, the sentence about MEN1 (lines 8-14) and its link with the background are not clear. The link between MEN1 and the aim of this study emerges only from the last sentence of the discussion section. This sentence should appear in the introduction.

Thank you for this comment. Because of the unclear link to MEN1-associated neuroendocrine tumors (the cell lines used are derived from sporadic tumors), we have now focused on sporadic disease and have removed the link to MEN1 in the introduction and discussion section of the manuscript.

2. Again, in the introduction, the sentence regarding possible antitumoral mechanisms of aspirin should be anticipated prior to report the studies on its efficacy.

Thank you for this comment. We have now placed the sentence on possible antitumoral mechanisms of aspirin (introduction, paragraph 2) prior to the studies on its efficacy.

3. In this study, only human pancreatic neuroendocrine and bronchopulmonary cells were treated with aspirin. These tumors largely differ between them. It should be advisable as well as more sensitive from a clinical perspective to study and compare intestinal and pancreatic neuroendocrine tumors rather than bronchial cell lines. The lack of intestinal neuroendocrine tumors is a dearth of the study.

Thank you for this comment. We have now performed additional experiments (cell proliferation and Western blot) with the use of the midgut neuroendocrine tumor cell line GOT1 with similar results (results section, figures 3, 4C, 5C and 6C).

4. Specific comments: Introduction, page 3, 13rd row: the authors mention in branches “Thakker, Newwey 2012”, but the number corresponding to the reference is lacking (cited below ref #3). Please correct.

Thank you for this comment. We have corrected the reference accordingly.

5. Too many acronyms without explanation have been included in the text (only as an example in the abstract there are at least 15, and some are not commonly used by everyone –i.e. TSC2, AKT, ERK). An extensive English- mother tongue review is required.

Thank you for this comment. We have added a full explanation to each acronym used.

Reviewer 2:

Congratulations for your paper. Excellent work. You have done a powerful step towards the NETs cell biology understanding. Only minor english review must be done before publication.

Thank you for this comment. A language certificate by a professional English language editing company is provided.