

## Format for ANSWERING REVIEWERS



March 13, 2014.

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8801-review.doc).

**Title:** Targeting Autophagy in Breast Cancer

**Authors:** Paola Maycotte and Andrew Thorburn

**Name of Journal:** *World Journal of Clinical Oncology*

**ESPS Manuscript NO:** 8801

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

1 Format has been updated

2 Attached is our point-by-point response to the reviewer's suggestions (our responses in red).

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'A. Thorburn'.

Andrew Thorburn, DPhil  
Professor and Chair, Department of Pharmacology  
Deputy Director, University of Colorado Cancer Center  
Grohne Professor of Cancer Research

Reviewer #1

Provide a summary figure(s) regarding autophagy and breast cancer and breast cancer STEM cells will help readers.

A summary figure on autophagy and cancer/ breast cancer is included in Figure 3. Here, we describe the different roles that have been proposed for autophagy in cancer and specifically in breast cancer, including the promotion of cancer stem cells.

Reviewer #2

The work by Maycotte & Thorburn about cancer and autophagy is interesting and well written. It points out the dual role of autophagy in cancer being pro-tumoral and anti-tumoral depending on cancer stage. However, there are a few points that needed to be addressed before manuscript publication:

1) There is more recent data about new cases of breast cancer, numbers of 2012 shows an increase of diagnosed cancers and 1.7 million cases, representing 11.9% of total cancer cases;

We updated the information in agreement with the 2012 reference.

2) Figure 01 shows insulin and insulin receptor, the role of these components are not explained during the manuscript. Please clarify;

We added the following sentence in the text in order to clarify the role of insulin and insulin receptor: mTORC1 is inhibited when amino acids are scarce, when growth factor signaling is reduced (e.g. decreased insulin/insulin receptor signaling as shown in Figure 1) and/or ATP concentrations fall, resulting in a de-repression of autophagy.

Additionally, the whole pathway is explained in the Figure Legend.

3) Beclin-1 and its role in autophagy and breast cancer are well explored throughout all the text, I believe that one figure dedicated to this molecule would be very informative to this journal's readers.

As the reviewer says, we explore the role of beclin 1 in autophagy and breast cancer. In this regard, we included a recent reference (that was published while the paper was being reviewed) that questions the tumor suppressor role of beclin 1 and included the information requested by the reviewer in Figure 2.

4) A table containing main molecules and its respective functions would enhance this manuscript.

The main autophagy related proteins as well as other proteins mentioned in the text were included in Table 1.

Reviewer #3

This is a well-written and timely manuscript on the topic of autophagy as a target for breast cancer therapy. The manuscript is (largely) well-structured, and the topic is novel and important. The referencing is up-to-date and well-balanced. The figure is a useful addition to the manuscript. I have one minor concern/suggestion: The introduction on breast cancer and breast cancer subtypes is useful and well-written, but it looks a little isolated at the current position. It may be a better idea to move the section behind the section "autophagy in cancer" and to shorten it a little bit. Much of the information in this section is not directly linked to autophagy, and therefore, this part could be focussed a little bit in my opinion.

The Breast cancer section was moved after the section Autophagy in Cancer and was shortened to make it more concise.

Reviewer #4

The review manuscript titled "Targeting autophagy in breast cancer" reports the recent studies on the role of autophagy in breast cancer. It is aimed to focus on the breast cancer therapy. However, the breast cancer treatment, in particular the review of novel drugs mitigating cancer prognosis, is not highlighted as compared to that of the basic biology of autophagy and cancers in the former part of the manuscript.

We included a paragraph in the breast cancer section that enlists novel drugs in current clinical trials in breast cancer.

Besides, the authors are advised to synchronize abbreviations such as "beclin 1" throughout the manuscript and to provide a table of abbreviation.

We double checked and corrected for gene and protein names in order to standardize our nomenclature. We only used a different nomenclature when referring to the protein or gene (gene names were italicized) or when referring to the mouse or human gene/ protein.

The incidence data of breast cancer used in this manuscript is out of date. Please update to the most current cancer epidemic.

The incidence data was updated to the 2012 reference.

Lastly, the conclusions of the manuscript should be convergent because of a new reference (No. 94) used in the paragraph which is not a common practice of journal article.

We think this point might be a misunderstanding. We agree that most of the evidence in the literature proposes that autophagy should be inhibited together with breast cancer treatment and that is what our manuscript suggests. However, in our conclusions we wanted to mention and discuss some studies with opposing results like the one mentioned by the reviewer (Ko, A. *et al*, Cell Death Differ, 2014; which changed reference number after the revision and is now No. 98). We are not proposing that autophagy should not be inhibited or even induced during breast cancer treatment and we only wanted to raise awareness to the fact that autophagy inhibition could have undesirable effects. Thus, we did not change our conclusions.