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Submission of a revised manuscript (invited minireview)

Dear Editors,

Please find enclosed the revised version of our minireview article entitled: *"Polyubiquitination inhibition of estrogen receptor alpha and its implications in breast cancer"* by Angeles C. Tecalco-Cruz and Josué O. Ramírez-Jarquín. We were pleased that the reviewer was positive about our manuscript and found her/his comments helpful in improving it. These changes are also outlined in detail in the attached reply to the reviewer's comments, and marked with blue in the manuscript. We believe that the revised version adequately addresses the concerns raised by the reviewer. We think that this version of our minireview would be of appropriate interest to the readerships of *World Journal of Clinical Oncology*.

Sincerely

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SPECIFIC COMMENTS TO AUTHORS

The review aimed to discuss the mechanisms of ER α polyubiquitination. The Review is well written and comprehensive. Few minor points to address

1. Abstract: ...” .. is inhibited by multiple mechanisms” – it is necessary to be more specific here and list some of the mechanisms.

We thank reviewer for this observation. In this version in our abstract, we are more specific and list some of the mechanisms implicated in the polyubiquitination inhibition of estrogen receptor alpha in breast cancer cells. (Section: *ABSTRACT*. Page: 3).

2. Protein interacting with never in mitosis A – “Never” should be in uppercase

The reviewer is correct. We have changed “*never*” by “*Never*” in “*protein interacting with Never in mitosis A*” (Section: *4.1 ER α POLYUBIQUITINATION INHIBITOR PROTEINS (EPIP) IN BREAST CANCER CELLS*; Page: 7).

3. Figure 3: authors should indicate/accnt whether the amount of ERalpha is being increased or remain the same; indicate that ER signalling is being stimulated as well.... The ER stability does not indicate this.

We have modified this figure to clarify these observations. In this new figure, and its legend, these aspects have been integrated. In this new version, this modified figure is the number 4; page 29.

4. MUC1 -related mechanism is the most attractive. Authors might should consider extending the paragraph and draw the separate figure for this topic. The recently shown association between ERalpha - MUC1 – cancer progression is complex. Authors should cite and discuss this new paper: Kotzsch M, Kirchner T, Soelch S, Schäfer S, Friedrich K, Baretton G, Magdolen V, Luther T. Inverse association of rab31 and mucin-1 (CA15-3) antigen levels in estrogen receptor-positive (ER+) breast cancer tissues with clinicopathological parameters and

patients' prognosis. Am J Cancer Res. 2017 Sep 1;7(9):1959-1970.eCollection 2017.
PubMed PMID: 28979817; PubMed Central PMCID: PMC5622229.

We thank reviewer for all these recommendations. We have added a new section for MUC1 (5.1 MUC1 IS AN EPIP IN BREAST CANCER). For this reason, we have added new information, including the important paper suggested by the reviewer (Page 11). We have also added a separated figure for this topic (Figure 3; page: 28).

Thank for all suggestions, we believe that all these recommendations have improved our manuscript.