

Dear editor,

I write with regard to submission of manuscript NO 31069 originally titled “Emerging Role of Nucleolar Stress in the treatment of advanced pancreatic ductal adenocarcinoma”.

Following reviewer comments, the appropriate changes have been made as outlined below.

1. *My first consideration is about the title: two-thirds of the manuscript are not about the role of nucleolar stress...Thus, the authors are encouraged to revise the title to something more generic.*
 - a. The title of the review has been changed to:
 - i. Advanced pancreatic ductal adenocarcinoma – Complexities of treatment and emerging therapeutic options.
 - ii. The short running title is:
 1. Diwakarla et al. Treatment complexities in advanced pancreatic ductal adenocarcinoma
2. *The authors should consider minor English revision (e.g. “back bones” in the abstract)*
 - a. The language used has been polished in places to incorporate the reviewers comments.
3. All gene names have been italicized.
4. *In the section “Genetic basis of PDAC” the authors mention KRAS, TP53, CDKN2A and SMAD4, citing Figure 1. However, not all these genes are not mentioned in this Figure. Please, consider to cite the Figure in another moment.*
 - a. The section titled “genetic basis of PDAC” previously referred to figure 1 which did not depict all the mentioned genes. Therefore, this figure has been cited in a separate paragraph.
5. *BRCA2 or PALB2 mutations...could be better discussed.*
 - a. More detail has been provided regarding the role of BRCA2 and PALB2 mutations and their implications on treatment decisions.

Further to the above changes, the attached manuscripts contains tracked changes which have been made. The figures have been added as per guidelines with titles and legends on a separate page and the corresponding author details have been provided along with conflict of interest statement and core tip.

We trust these changes will be adequate and look forward to further communication.

Yours sincerely,

Dr Chandra Diwakarla
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