Reviewer's report

Title: Dimethylaminoparthenolide and gemcitabine: a survival study using a genetically engineered mouse model of pancreatic cancer

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Reviewer: David Cano

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General

The manuscript by Yip-Schneider et al. evaluates the effect of two antitumoral agents (DMAPT and gemcitabine) on pancreas tumor formation in a genetic mouse model of pancreatic cancer. The authors conclude that the combination of DMAPT and gemcitabine decreases tumor size as well as the incidence of metastasis to the liver.

The results reported in this study do not contribute a major advance in the field. Indeed, this report extends previous observations made by the same authors in a similar mouse model of pancreatic cancer. Still, the study should be of interest to researchers specialized in pancreatic cancer.

In general, the conclusions are well supported by the presented results. However, a few minor issues need to be clarified and the main results should be presented with more clarity. The methodology used is appropriate although some methods need to be explained in more detail.

Major Compulsory Revisions

1. The main findings of the paper need to be presented more clearly. Certain parts of the manuscript overlap with previous published data (e.g. Figure 3 and Figure 4). The paper could be significantly shortened focusing on the main novel results presented, namely those regarding the effect of gemcitabine on survival and tumor incidence (in contrast to previous studies) and the effect of the DMAPT/gemcitabine combination on tumor size and metastasis incidence.

2. The effect of gemcitabine on survival and tumor incidence was somewhat unexpected. Several studies have reported that gemcitabine treatment does not have any effect on tumor formation in a genetic mouse model of pancreatic adenocarcinoma. The authors argue somewhat vaguely "gemcitabine was administered earlier and for a longer duration". These results are so unexpected that the authors should discuss them in more detail and offer some possible explanations for this discrepancy. For example, an accurate comparison of the age of the mice and the duration of the treatments between this report and previous studies could be informative.

3. Have the authors determined whether NFKB activity (by IHC or qPCR of target
genes) is decreased in tumor tissue upon DMAPT and DMAPT/ gemcitabine combination?

4. More details should be included in the methods section. What's the origin of the PDA mouse model? What's the origin of the luc reporter mouse? Is the luc transgen a reporter to monitor Cre-recombinase mediated recombination? If so, why bioluminescence could not be detected earlier than 6 weeks of age in p53f/f;LSL-KrasG12D;lucl/l;Pdx-1-Cre mice? The proper references for this mice should be included in the text. As mentioned above, the age of the mice when the treatment started should be more clearly stated in the methods section. How was the quanification for PanIN lesions performed (number of sections, number of mice of each group analyzed, etc...)

4. The authors have previously demonstrated that DMAPT enhanced the anti-proliferative effects of gemcitabine in pancreatic cancer cells in vitro. However, this effect was not observed in the genetic mouse model. Do the authors have an explanation for this apparent discrepancy?

Discretionary Revisions

5. Some discussion about how the DMAPT treatment could decrease liver (but not lung) metastasis seems pertinent (even if entirely speculative at this point)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests