Reviewer’s report

Title: Differential modulation of nicotine-induced gemcitabine resistance by GABA receptor agonists in pancreatic cancer xenografts and in vitro

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Reviewer: Amir Avan

Reviewer’s report:

The manuscript by Banerjee et al., evaluated the effect of GABA-B-receptor agonist baclofen and GABA in pancreatic cancer to overcome nicotine induced gemcitabine resistance. They found that GABA effectively reversed nicotine-induced gemcitabine resistance of pancreatic cancer and enhanced the antitumorogenic effects of gemcitabine in the absence of nicotine exposure. They observed the modulation of p-ERK, p-Src, p-CREB, p-AKT and caspase-3 status after treatment with gemcitabine and GABA. Moreover, They reported that baclofen did not improve the efficacy of gemcitabine and also did not inhibit the growth of xenografts when used as single agent treatment and might also increased gemcitabine resistance.

Overall idea: the manuscript deals with an issue of interest, however there are several aspects that should be considered and further clarified:

Major Compulsory Revisions

1) What was the rational reason for starting treatment only one day after cell implantation?

2) The Authors observed that gemcitabine and GABA significantly reduced the phosphorylation status of Akt, CREB and ERK1/2 in vivo, do they have any rational explanation for these modulations or whether there is any indirect, or direct (?) interaction between gemcitabine and Akt, CREB and ERK1/2? Can the authors elaborate on this in the discussion?

3) In the results part, specifically Figure 1 A, the Authors showed the effect of gemcitabine and GABA on tumor volume. Their findings illustrated that the effects of these two drugs are more or less same and GABA didn’t significantly improve the antiproliferative activity of gemcitabine! But in the abstract/discussion part they mentioned “further studies are needed to evaluate the effect of GABA in combination with gemcitabine in pancreatic cancer”. On the one hand no improvement has been found in combination group (Gem+GABA), compared to the gemcitabine group; do they have any explanation for this issue?

Minor Essential Revisions:

- I would suggest to rephrase the following sentence in page 11, line 20-22.
- The following statement “….greater than expected by chance” is repeated for
more than 5 times in the results part, so I would suggest to rewrite this statement.

Discretionary Revisions:

- In the figure 1 A-B, I would suggest the Authors to show, at least, one representative picture of mice/tumor per condition in different week.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests