Reviewer’s report

Title: Mechanisms of doxorubicin-induced drug resistance and drug resistant tumour growth in a murine breast tumour model

Version: 0 Date: 03 Jun 2019

Reviewer: Andrew Michael Rauth

Reviewer’s report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.


This is a clearly written and interesting paper in which Doxorubicin is interpreted to stimulate rather than inhibit tumor growth in a murine breast tumor model (E0771) in C57BL6 mice.

1. Please identify Acronyms on first appearance both in the abstract (e.g. MAPK, PI3K/Akt, ERK, EMT) and in the main text of the manuscript (e.g. GLOBOCAN, ANCOVA).

2. In the title do you mean (and would it be a more accurate title) if the title was changed to - "Mechanisms of doxorubicin-induced drug resistance and drug resistant tumor growth in a murine breast tumor model".

3. My main concern with this paper is the data shown in figure 1. In particular what happens at times later than 27, 29 days. I realize the tumor is reaching a half gram (500 mm^3) but the curves are still close. For what points in the growth curves are the TC, LD-DXR and HD-DXR significantly different from one another? Please indicate by asterisk. It is stated the ANCOVA was used to analyze the results but please state in the figure caption what the error bars indicate e.g. "Error bars indicate the standard error of the mean for N = ? experiments". It is stated the number of animals per group in figure 1 is 15-16. Was this in a single experiment or from pooled experiments? If pooled how many experiments? Why is there only one group at 29 days and only 2 groups at 27 days? Toxicity?

4. A lot of molecular biology was carried out based on the results in figure 1. I am concerned that in contrast to the proposed molecular explanation of the curve differences that a Matrigel/inflammation effect might be contributing to tumor volume measurements. Were tumor sections investigated after animal sacrifice? Can such competing effects be ruled out?
5. The E0771 tumor is triple negative and has been proposed for immunomodulatory studies. Any comments on the possible role of these factors on the results obtained?

6. If figure 1 is a single experiment have the results been reproduced?

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal