Reviewer's report

Title: Endothelin Receptor B Antagonists Decrease Glioma Cell Viability Independently Of Their Cognate Receptor

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Reviewer: Marc Sanson

Reviewer's report:

The authors show that the two compounds, known as "specific" inhibitors of endothelin receptor B (ETRB), A-192621 and BQ788, reduce the number of viable cells in two glioma cell lines. The most potent, A-192621, inhibits proliferation with blockage at G2/M transition, induces apoptosis, and up-regulates DNA damage-inducible genes. However these effects appear independent of ETRB expression (and also ETRA) as shown by siRNA mediated inhibition of ETRB (and pharmacological inhibition of ETRA). Indeed one of the tumor cell lines SW1088 does not express ETRB and is still sensitive to these inhibitors of ETRB. In addition, the concentrations used here are much higher than the concentrations needed to displace ET-1 from ETRB.

Major Compulsory Revisions: my major criticism is that the effects of these "specific" ETRB do not involve ETRB inhibition: this points need to be discussed and clarified:

1- Taken together, these data suggest that these "specific" ETRB inhibitors are not so specific (at least at the concentrations used here). Is the effect shown here just a cytotoxic effect of the drugs, merely due to the high concentrations used and without any relation with endothelin/ETR inhibition? In this setting, upregulation of DNA damage-inducible genes is not surprising.

2- Or do the authors have any evidence that another mechanism of action, independent of ETRB, could be involved? This could be more interesting

3- These data (figure 1) suggests that a lower concentration of A-192621 and BQ788 -but still sufficient to inhibit efficiently ETRB- has no significant effect on the cells. In other words, they suggest that ETRB inhibition has no effect on growth tumor in vitro. If the authors confirm that point, they should mention it in the discussion.

4- In a pre-clinical perspective, it would be interesting to know whether such compounds (whatever the mechanism of action is) are suitable to be used in vivo at this concentration, or whether there is a lethal toxicity that limits definitely their use.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article of limited interest

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