Reviewer's report

**Title:** ABT-737 increases treatment efficiency of paclitaxel against hepatoblastoma

**Version:** 1  **Date:** 12 May 2011

**Reviewer:** Antoine Galmiche

**Reviewer's report:**

Hepatoblastoma is a pediatric liver tumour that is treated by surgical resection, usually after neoadjuvant chemotherapy. Improving the efficacy of chemotherapy is an important aim of actual cancer research. In a previous report, Lieber et al. reported the synergistic pro-apoptotic efficacy of the combination ABT-737 / paclitaxel in two hepatoblastoma cell lines. In the present study, Lieber et al. apply this knowledge to an animal model using xenografted tumors. I find the topic interesting and worth pursuing, but I have the following comments on the manuscript.

Major Compulsory revisions

1. The observations reported in Fig. 1, showing a pro-apoptotic synergy between ABT-737 and paclitaxel in vitro, largely overlap those presented in a previous report by Lieber et al. (see Fig. 3 from Lieber et al. Pediatr Blood Cancer 2010; 55: 1089-95). I suggest that the authors introduce a different assay to probe the viability of cancer cells, so as not to publish the same observations several times. Clonogenicity assays are usually considered to be the most reliable way to estimate the impact of anti-cancer drugs, and could be used here.

2. The major problem of the current report is that the authors do not observe a statistically significant increase in efficacy of the combination of ABT-737 + paclitaxel compared to paclitaxel alone when they compare the volume of tumours (experiments presented in Fig. 2B). The authors should increase the number of mice used in this experiment in order to reach significance, considering that this is a key point of the manuscript. Without this, the authors cannot state that “ABT-737 increases treatment efficiency of paclitaxel”, as they do in the title of their manuscript.

3. The paper is merely descriptive, and does not provide any explanation for the observations that are presented.

There is no explanation for the synergistic effect between ABT-737 and paclitaxel in hepatoblastoma. This is a pity considering that recent studies point to BCL2 proteins as regulators of cancer cell susceptibility to taxanes (see for example Wertz et al., Nature 2011; 471: 110-4 or Craik et al. Oncogene 2010; 29: 5381-91). I think that a survey of the expression of BCL2 proteins in hepatoblastoma cells / tumours exposed to paclitaxel and / or ABT-737 is...
required.
Similarly, it would be important to explain how ABT-737 increases the toxicity of paclitaxel on mice. To the best of my knowledge, a well documented side effect of ABT-737 consists of a reduction in platelet levels (Mason et al. Cell 2007; 128: 1173-86; Zhang et al. Cell Death Differ 2007; 14: 943-51). The authors should explore this parameter to explain the high lethality reported with ABT-737.

Minor essential revisions

4. I disagree with the citation on page 4, line 8 that “ABT-737 has shown cytotoxic potential as a single agent against many solid tumours”… Oltersdorf et al. in fact report that ABT-737 as a single agent is poorly efficient in most solid tumours, with the noticeable exception of small cell lung carcinoma.

Discretionary revisions / recommendations for improvement

5. Control experiments using the inactive enantiomer of ABT-737 should be included, as the authors did in their previous manuscript.

6. I think that the title of the manuscript should be expanded to improve its readability. ABT-737 could be introduced as a BH3-mimetic or as an inhibitor of BCL2 / BCL-XL.

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