Reviewer’s report

Title: Obatoclax is a Direct and Potent Antagonist of Membrane-restricted Mcl-1 and is Synthetic Lethal with Treatment that Induces Bim

Version: 2  Date: 1 May 2015

Reviewer: Eric Solary

Reviewer’s report:

In this manuscript, Mai Nguyen et al demonstrate that the hydrophobic molecule Obatoclax partitions into lipid bi-layers, and is able to target the anti-apoptotic protein Mcl-1, which is constitutively associated with the mitochondrial outer membrane, but not Bcl-XL.

Obatoclax shows some efficacy in in vivo mouse models of grafted lymphoma cells and is demonstrated to synergize with dexamethasone that induces Bim expression to kill a myeloma cell line, providing a rationale for testing such a combination.

Overall, the work represents a sound study of the properties of Obatoclax and its ability to act specifically on Bak/Mcl-1 axis. In addition, the manuscript is clearly written and well-balanced.

More specific comments are as follows.

Major comments

• The conclusions of the abstract discuss off-target effects of the drugs that are not explored in the study, even though they are discussed in the conclusions. This sentence should be removed from the abstract, which otherwise clearly reflects the content of the manuscript.

• The way tumor-free survival was measured in mice injected with Eµ-Myc/(myr)Akt lymphoma cells remains unclear. The notion of “palpable” tumor, complete response and relapse is poorly defined. Please clarify.

• What is the statistical significance of the differences between IC50s in Fig. 6D. Indicate SD of IC50 measured in repeated experiments.

Minor points

• In Fig. 1A, left panel, obatoclax is shown as OBX but its presence does not fit with the comments made in the figure legend.

• In all the figure legends, there are no or few indications on the number of experiments performed to generate each panel

• The order of figure citation in the text is confusing, with Fig. 4A appearing between 2B and 2C and 6B between 3C and 4A

• Fig 6D is labelled as Fig 6B page 14, line 417
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests