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

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Reviewer: Akira Yoshida

Reviewer's report:

In this study, Nguyen et al. characterize the dynamic interactions of obatoclax with lipid bilayers. Employing Mcl-1 and Bak constitutively anchored to reconstituted proteoliposomes, authors show for the first time that obatoclax is a direct and potent inhibitor of Mcl-1, overcoming Mcl-1’s ability to restrain tBid-induced activation of Bak. In an Akt-lymphoma mouse model, the anti-tumor effects of obatoclax synergized with doxorubicin. Finally, treatment of the multiple myeloma KMS11 cell model (dependent on Mcl-1 for survival) with dexamethasone induced Bim and Bim-dependent lethality. As predicted for an Mcl-1 antagonist, obatoclax and dexamethasone were synergistic in this model. These data are interesting.

However, reviewer would like to point out following problems.

1.- Authors claimed that obatoclax and dexamethasone were synergistic in KMS11 cells.
In Fig 6a. the changes of IC50 values were observed after combination treatment with obatoclax and dexamethasone. However, based on this figure, it is not reasonable to conclude “synergistic”. Authors should perform additional experiment, for example, using the Chou-Talalay method, in order to clarify the effect of this combination (obatoclax and dexamethasone), just additive or synergistic.

2.- In Background on page 4, author described, “Additionally, obatoclax is shown to cooperate with the induction of Bim as a synthetic lethal partner to drive cell death”. Authors assumed that obatoclax may kill myeloma KMS11 cells by the induction of Bim. However, reviewer cannot find such a data in this paper. Authors should present data that up-regulation of BIM protein occurs after treatment of KMS11 cells with obatoclax and dexamethasone.

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:
No competing interests