Author's response to reviews

Title: Evaluation of bioactive sphingolipids in 4-HPR-resistant leukemia cells

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Author's response to reviews: see over
Dear BMC Cancer Editors,

Accompanying this file is our manuscript entitled "Evaluation of bioactive sphingolipids in 4-HPR-resistant leukemia cells" by Aintzane Apraiz García (aintzane.apraiz@ehu.es), Jolanta Idkowiak-Baldys (idkowiia@musc.edu), María Dolores Boyano (lola.boyano@ehu.es), Gorka Pérez-Yarza (gorka.perezyarza@ehu.es), Yusuf A Hannun (hannun@musc.edu) and Aintzane Asumendi (aintzane.asumendi@ehu.es) which we wish to submit for publication in the Research Paper section of BMC Cancer.

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The manuscript is an original work in which for the first time, a leukemia cell model resistant to 4-HPR has been developed in order to describe the role of main altered sphingolipids in observed resistance to the drug. Moreover, we have studied the possible crossresistance of 4-HPR-resistant leukemia cells to other sphingolipid-modulating agents. Acquired resistance to anticancer drugs is a common problem and an important source of failure in chemotherapy. Therefore, determination of resistance providing and non-providing alterations is crucial together with the development of resistance treatment.

Previous studies by our group and others described the capability of 4-HPR to profoundly alter endogenous (dihydro)ceramide levels that have been linked to the effectiveness of this chemotherapeutic drug for long time. On the other hand, drug-resistance has been associated with modifications in the sphingolipid metabolism. In the present study, we applied advance LC/MS
technology for sphingolipid analysis in order to obtain detailed data on endogenous sphingolipid profiles and sphingolipid metabolism in 4-HPR-sensitive vs. resistance leukemia cells. Our results indicate that resistance to 4-HPR may persist even in the absence of the characteristic sphingolipid alterations driven by this synthetic retinoid. Alternative antitumoral strategies have been also introduced including specific modifications of bioactive sphingolipid pathways.

We suggest the following experts in the field as possible reviewers:

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The nominees for reviewers have not conflict of interest with any of the authors of the paper being submitted.
Thank you for your consideration.

Sincerely,

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