

Reply: Comment on 'Quiescence and γH2AX in neuroblastoma are regulated by ouabain/Na,K-ATPase': ouabain and cancer

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Sir,

We thank Dr López-Lázaro and co-workers for their interest in our work on quiescence and γH2AX in human neuroblastoma induced by ouabain/Na,K-ATPase (Hiyoshi *et al.*, 2012). They correctly point out that rodent cells are more resistant to ouabain than human cells and raise concerns about the effect of ouabain on human neuroblastoma-xenografts in nude mice. However, López-Lázaro and co-workers incorrectly claim that we, based on our results, are concluding that ouabain could be used in chemotherapies to suppress tumour growth and/or arrest cells to increase the therapeutic index in combination therapies. Moreover, López-Lázaro and co-workers are presenting data from viability experiments performed on various cell lines (none derived from the nervous system) treated with different concentrations of ouabain. From these results they are suggesting that the observed reduced neuroblastoma tumour growth reported in our study is due to cell death rather than quiescence. The fact that cells from different tissues have different Na,K-ATPase isoform expression patterns and consequently different ouabain-affinities is not mentioned by López-Lázaro and co-workers.

First, we would like to emphasise that the aim of our study was not to investigate the usage of ouabain as an anticancer treatment for neuroblastoma. We were performing a basic research study

demonstrating that 50 nM ouabain could trigger quiescence and γH2AX in a human neuroblastoma cell line. We also demonstrated that the applied concentration of ouabain did not induce significant cell death in neuroblastoma. In the last figure of the article we showed that similar results were obtained in an *in vivo* setting, when human neuroblastoma cells were xenografted into immune-deficient nude mice that were fed ouabain. Then we speculated in the discussion section that ouabain might be used in chemotherapies to suppress tumour growth and/or arrest cells to increase the therapeutic index in combination therapies.

To fully investigate if ouabain indeed could be used to treat neuroblastoma in the clinic, further comprehensive studies, in which all critical issues are addressed, will be needed. We look forward to these future studies before we jump to a conclusion on whether ouabain can have a role in treating neuroblastoma.

REFERENCE

- Hiyoshi H, Abdelhady S, Segerström L, Sveinbjörnsson B, Nuriya M, Lundgren TK, Desfrere L, Miyakawa A, Yasui M, Kogner P, Johnsen JI, Andäng M, Uhlén P (2012) Quiescence and γH2AX in neuroblastoma are regulated by ouabain/Na,K-ATPase. *Br J Cancer* **106**(11): 1807–1815.

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