Author's response to reviews

Title: Tetrathiomolybdate sensitizes ovarian cancer cells to anticancer drugs doxorubicin, fenretinide, 5-fluorouracil and mitomycin C

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Dear Editor,

Thank you for kindly considering our manuscript entitled “Tetrathiomolybdate sensitizes ovarian cancer cells to anticancer drugs doxorubicin, fenretinide, 5-fluorouracil and mitomycin C” for publication in BMC Cancer. We would like to thank the editorial board and reviewers for the thorough analysis of this manuscript and for providing helpful recommendations to improve it. Please find below our point-by-point description of the changes made as suggested by the reviewers. We hope that this manuscript is now acceptable for publication in BMC Cancer.

We greatly appreciate your help in this regard. If you have any further questions or concerns, please do not hesitate to contact me.

Sincerely yours,

Kyu Kwang Kim on behalf of the authors.

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Reviewer 1
Comment: Overall sound experimental techniques and assays used. Would recommend additional clarification on the choice of specific chemotherapeutic drugs
Response: The paragraph (page 4 and page 12) was revised as follows and the reference 19 and 20 were replaced;
Page 4 (first paragraph): The present study explores the ability of TM to potentiate the effect of doxorubicin and several other anticancer drugs including mitomycin C (MMC), fenretinide (4-HPR) and 5-fluorouracil (5-FU) in ovarian cancer cells. While these four drugs differ with respect to their application to treat ovarian cancer doxorubicin is used in recurrent disease, MMC showed activity in phase II trials, and 5-FU and 4-HPR showed positive responses in combination with platinum based drugs or as a single agent in phase II trials respectively [14-17]. These drugs were chosen for this study since they share one common target, the cellular oxidative defense system. Treatment with any of these drugs can lead to the elevation of oxidative stress promoting cell death in cancer cells [7,18-21]. Their efficacy may be improved if the oxidative balance in cancer cells is disrupted by agents that target cellular antioxidants such as TM.

Page 12 (second paragraph): 5-FU in these studies was well tolerated and can be used at relatively high concentrations without toxic side effects. The effects of anticancer drugs that are known to target DNA integrity or synthesis are often correlated to the induction of pro-apoptotic signaling and the generation of oxidative stress [7,20]. In the present report, the mild cytotoxicity displayed by 5-FU as a single agent was ROS independent while TM/5-FU combination treatment led to a significant ROS based reduction of ovarian cancer cell viability suggesting that expanded in vitro studies are needed to establish the parameters for the use of these two drugs in animal tumor models.