Reviewer's report

Title: A novel copper complex induces ROS generation in doxorubicin resistant Ehrlich ascitis carcinoma cells and increases activity of antioxidant enzymes in vital organs.

Version: 1 Date: 28 August 2006

Reviewer: Zacharias Suntres

Reviewer's report:

The methods described are precise and provide sufficient information to replicate the study.

The conclusions are adequately supported by the data; however, the re-iteration of the results in the Discussion section should be deleted and some of the important findings presented in this manuscript warrant further discussion (please see revision sections).

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Although the levels of ROS were assessed in EAC/DOX cells ex vivo 24 h following in vivo CuNG treatment, the authors did not report the levels of copper and the antioxidant status in these cells. These data are important in the interpretation of the results regarding the prooxidant activity of CuNG. Were the ROS elevated because of an increased uptake of CuNG by EAC/DOX? What was the effect of CuNG on the antioxidant status of EAC or EAC/Dox cells? If CuNG conjugates with GSH to form GS-CuNG, how can CuNG elevate the production of ROS in the EAC/Dox cells?

In figures 2 and 3, the authors depict the effect of Ehrich ascites cells, with or without CuNG treatment, on several antioxidant enzymes and glutathione in vital organs. Generally, inoculation of mice with Ehrich ascites cells (EAC/DOX) significantly decreased the levels of tissue antioxidants, while treatment of these mice with CuNG increased the tissue antioxidant levels when compared to the EAC/DOX-bearing mice; however, in both cases the antioxidant status was still significantly lower when compared to the normal counterparts. The potential mechanism(s) of tissue antioxidant depletion observed following administration of EAC/DOX vs normals is an important finding and should be discussed.

Although an association between liver copper levels and hepatic GSH levels was made to ascertain the mechanism(s) of GSH depletion in the livers of animals, the copper levels in lung, kidney and heart were not reported. The relationship between copper and oxidant/antioxidant status in heart, kidney, and lung should be discussed?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

In the figures and table, the authors should depict the level of statistical significance.

In the Results section 3.1, the authors describe a set of experiments examining the effect of ROS on MRP1 expression but the data is not shown. I would recommend that the data be shown.

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Discretionary Revisions (which the author can choose to ignore)
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests