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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 7345
Title: A Heme Oxygenase-1 Inhibitor, Zinc Protoporphyrin IX, Enhances the Chemotherapeutic Response of Liver Cancer Cells to Cisplatin
Reviewer code: 02492990
Science editor: Gou, Su-Xin
Date sent for review: 2013-11-15 09:41
Date reviewed: 2013-11-20 10:42

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
This manuscript reports the results of studying on the effect of zinc protoporphyrin IX, a HO-1 inhibitor, on the cellular sensitivity and susceptibility of liver cancer cell lines to cisplatin in vitro and in vivo. The findings are consistent with several related studies and do not provide further evidence for underlying mechanism. Moreover, some drawbacks as followings should be concerned. 1. All the experiments in this study should be reproducible at least three independently. Their n number and statistical analysis should be clearly described in each figure and legend. 2. The labels in the figures 1B and 4A are too small to identify specific cell lines and treatments. 3. The band density of the Western blot (Figs 1A and 2) should be quantified, normalized, and statistically analyzed. 4. Why does the xenograft experiment use female but not male mice? The tumor sizes for each group and treatment at different time points (before drug treatment) should be shown. Although the authors claim HepG2 cells have a higher HO-1 level and thus more resistant to cisplatin treatment than the others, the results of xenograft experiment seem not to show in Figure 7. Why? 5. The authors claim the resistance to apoptosis by upregulation of HO-1 is related to increased ROS level. The role of ROS in this mechanism should be evaluated in this study.

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ESPS Manuscript NO: 7345
Title: A Heme Oxygenase-1 Inhibitor, Zinc Protoporphyrin IX, Enhances the Chemotherapeutic Response of Liver Cancer Cells to Cisplatin
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Science editor: Gou, Su-Xin
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS
Reasoable conscept Well designed Appropriately written

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Name of Journal: World Journal of Gastroenterology
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS
Thank you for submitting the excellent manuscript,if some modification was made in disscuion, to close the topics,the paper may be more perfect.

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Name of Journal: World Journal of Gastroenterology
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
This manuscript shows that the inhibition of HO-1 was associated with increased cellular sensitivity and susceptibility of liver cancer to CDDP. However, there are several problems in this manuscript. Major points 1. The authors used three kind of human liver cancer cell lines; Hep G2, SMMC7721, and 97H. Could you show us clearly which cell line is the resistant cell to CDDP? The authors stated that the HepG2 cell line with the highest HO-1 expression was significantly more chemoresistance to cisplatin than the other cell lines with lower HO-1 expression ($P < 0.05$). Were there significant differences in several doses among three liver cancer cells? And the authors state that the levels of HO-1 protein were detected significantly higher in HEPG2 cell line than in other cell lines in Western blots. However, I think that there was no significant difference in the levels of HO-1 protein between HEPG2 and 97H. You should describe these data clearly. 2. How is the difference of HO-1 expression between the liver cancer cell and normal liver (hepatocyte, hepatic stellate cell or Kupffer cell)? 3. In vivo analysis, the authors showed the analysis of tumor weights. Could you show us the tumor size, tumor numbers and the morphology of tumors? Did you check the apoptosis of tumors by Tunel stain? 4. In FACS analysis, the authors showed almost same results between CDDP and CDDP+ZNPPIX, CDDP+Hemin. I do not understand the differences between CDDP+ZNPPIX and CDDP+Hemin. Please show us more clearly results. 5. In conclusion, the authors state that administration of HO-1 inhibitors may evolve new liver cancer treatment strategies. However, you did not describe the side effects of HO-1 inhibitors. You should describe the merit or demerits of HO-1 inhibitor. Therefore, you should investigate the effect of HO-1 inhibitor in normal liver or cirrhotic model in vitro and in vivo. In addition, is it possible to use ZnPP IX, HO-1 inhibitor as a

clinical trial in cirrhotic patients with HCC? Minor points 1. On page 5, line 1, the words "in vivo" should been changed to "in vitro". 2. The authors state that the over expression of HO-1 may be associated with chemoresistance to CDDP. In page 5, the authors state that the expression of HO-1 was significantly increased in all liver cancer cells with higher dose of CDDP. However, the high dose of CDDP inhibited all liver cell lines. You should explain the findings of these results. 3. On page 6, line 4, the authors state that ZnPP IX not only deceased HO-1 activity, but also decreased CDDP induced HO-1 activity ($P<0.05$). The authors show clearly us the difference in HO-1 activity among several groups. 4. On page 6, line, the sentence "In addition, hemin treatment significantly increased cell apoptosis induced by CDDP" should be changed to "In addition, hemin treatment significantly decreased cell apoptosis induced by CDDP". 5. On page 8, line 14, the sentence "but also increased CDDP (10 μg/ml) induced PROS in liver cancer cell lines" was not understood. Please show us clearly. 6. In Fig 6, the authors showed statistically significant differences. What did you compare? 7. On page 10, line 13, Fig 1 is a mistake.