

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**ESPS manuscript NO:** 20178

**Title:** Role of copper transporters in platinum resistance

**Reviewer's code:** 00055078

**Reviewer's country:** Italy

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2015-05-31 17:16

**Date reviewed:** 2015-06-27 21:48

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

### COMMENTS TO AUTHORS

The manuscript presents a clear and comprehensive review of the role of copper transporters in the resistance to platinum drugs. Molecular aspects of the topic are thoroughly considered and discussed on the basis of the available experimental findings and linked to possible clinical aspects for improving cancer therapy. The topic has been widely considered in the literature and surely it deserves wide further debate, also following the future results from ongoing clinical trials. In this view the references quoted are appropriate. However, I would suggest to consider also the following ones, if believed of interest by Authors: Liang et al., Regulation of the high-affinity copper transporter (hCtr1) expression by cisplatin and heavy metals, *J Biol Inorg Chem*. 19(1): 17-27, 2014. doi: 10.1007/s00775-013-1051-z [which focuses on the regulation of hCTR1 expression by Pt and other heavy metal ions through Sp1]. Also the paper by Ivy & Kaplan (A Re-Evaluation of the Role of hCTR1, the Human High-Affinity Copper Transporter, in Platinum-Drug Entry into Human Cells, *Mol Pharmacol* 83:1237-1246, 2013. doi: 10.1124/mol.113.085068) might be quoted, since it considers data on the fact that hCTR1 is not the main route for entry of Pt drugs; moreover, the copper transporter is not internalized in response to extracellular drug, indicating that hCTR1 mechanism



## BAISHIDENG PUBLISHING GROUP INC

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

<http://www.wjgnet.com>

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is not saturable and not protein-mediated. Regarding the pharmacological modulation of CTR1 a very recent paper showed that also compounds of natural origin could be useful [Wang X, Jiang P, Wang P, Yang CS, Wang X, Feng Q (2015) EGCG Enhances Cisplatin Sensitivity by Regulating Expression of the Copper and Cisplatin Influx Transporter CTR1 in Ovary Cancer. PLoS ONE 10(4): 0125402. doi:10.1371/journal.pone.0125402] and therefore may deserve quotation in order to widen the spectrum of intervention. Also, a new paper has considered the contemporary modulation of CTR1 and ATP7A targets by D-penicillamine, in order to improve the therapeutic efficacy of Pt drugs in oxaliplatin-resistant tumors: Chen SJ et al., Mechanistic basis of a combination D-penicillamine and platinum drugs synergistically inhibits tumor growth in oxaliplatin-resistant human cervical cancer cells in vitro and in vivo. *Biochem Pharmacol.* 95(1):28-37, 2015. doi: 10.1016/j.bcp.2015.03.006. As a mere suggestion, and if believed appropriate, the Authors might consider to present a scheme of the main molecular mechanisms here discussed. Minor points: Introduction, page 3, line 6: "Escherichia coli" must appear as italics Page 10, line 5, 11, 16; page 11 line 8: "Pt-based" Page 12 line 8: "Copper" Page 12 line 23: "penicillamine"

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Oncology

**ESPS manuscript NO:** 20178

**Title:** Role of copper transporters in platinum resistance

**Reviewer's code:** 00066723

**Reviewer's country:** Netherlands

**Science editor:** Fang-Fang Ji

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

### COMMENTS TO AUTHORS

The manuscript reviews the literature on the role of copper transporters in platinum resistance. The manuscript is interesting and well written giving a concise overview of the topic. The manuscript could benefit from a figure indicating the cellular location of the discussed copper related transporters, this is particularly illuminating as ATP7A and ATP7B are not located in the plasma membrane but in the trans-Golgi network. Some comments need to be addressed before this manuscript is acceptable for publication. Major comments 1. Page 4, line 25: A more recent paper than refs 17 and 18 that describes influx and efflux transporters related to Pt compounds is Burger et al. (Drug Resist Updat. 2011 Feb;14(1):22-34). 2. Page 5, line 20: It is stated that Pt has a long half-life in human tissue. How long exactly and how does this tissue half-life relates to its pharmacokinetics (half-life in plasma)? 3. Page 6, III. Copper transporters, line 17: it is not true that none of the pumps and transporters implicated in Pt transport is well-characterized (see again Burger et al. Drug Resist Updat. 2011 Feb;14(1):22-34). For example SLC22A2 is well characterized as Pt. influx transporter. 4. Page 7, line 1: It is stated that "Higher CTR2 levels correlated with Pt resistance in ovarian cancer cell lines" is this correct, if so I do not understand as CTR2 activity may lead to increased influx of Pt



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8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

<http://www.wjgnet.com>

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compounds. Please explain /more clearly address this discrepancy. 5. Page 7, line 10-11: As ATP7B is not located in the plasma membrane one could say that in addition to efflux also sequestration (in Golgi network and/or vesicles) may play a role in resistance. 6. Page7, line 14-15: It is stated that "ATP7B silencing results in enhanced cisplatin sensitivity and increased DNA adducts formation in cisplatin-resistant cells" I do not understand you would expect less DNA adducts in cisplatin-resistant cells not more adducts! Please check. 7. In the context of this review a critical question would be whether Pt compounds are taken up by transporters (e.g. CTR1) or diffusion. This may be different for the various Pt compounds. Please discuss. Minor comments 1. Give in the text - at least once - the official gene names for the transporters that are discussed e.g. CTR1 = SLC31A1 2. Page 3, I. introduction, line 15-16: The main adverse event related to oxaliplatin is actually neurotoxicity. Please mention this. 3. Page 3, I. introduction, third paragraph: I miss the referral to ovarian cancer as the standard treatment for this cancer is a combi of carboplatin and paclitaxel. Moreover experiments relating to ovarian cancer are discussed several times throughout the manuscript. 4. Page 4, line 9: "...with up to an 80 percent response rates..." remove "an" 5. Page 4, line 23: "infux" should be "influx" 6. Page 6, line 23: "These transporters possess..." I guess with transporters you mean ATP7A and ATP7B? 7. Page 7, line 8: Note that the KB-3-1 was recently identified as a derivative of HELA (cervix carcinoma). 8. Page 7 and page 8: There are two chapters IV. 9. Page 11: Chapter VII is missing. 10. Page 10, line 11: what is meant by Pt-based doublet chemotherapy? 11. Page 11, line 15: What is meant by "different rs10981694 genetic polymorphisms"? 12. Reference 29: please give year in which this ASCO abstract was published 13. Reference 57: remove capitals