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ESPS Peer-review Report

Name of Journal: World Journal of Otorhinolaryngology

ESPS Manuscript NO: 3731

Title: Adenosine Amine Congener Ameliorates Cisplatin-Induced Hearing Loss

Reviewer code: 00503663

Science editor: Gou, Su-Xin

Date sent for review: 2013-05-17 12:32

Date reviewed: 2013-05-22 15:56

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	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"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This paper described protective effect of adenosine amine congener against cisplatin-induced hearing loss in rats. It is easy to read. Figures are beautiful. I recommend its prompt publication.



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ESPS Peer-review Report

Name of Journal: World Journal of Otorhinolaryngology

ESPS Manuscript NO: 3731

Title: Adenosine Amine Congener Ameliorates Cisplatin-Induced Hearing Loss

Reviewer code: 00503703

Science editor: Gou, Su-Xin

Date sent for review: 2013-05-17 12:32

Date reviewed: 2013-05-26 19:23

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	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"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The topic is interesting both from a scientific and a clinical point of view, the research is original and the methods are appropriate. In the "Discussion" section of the manuscript, given that the authors present no evidence on inflammatory mechanisms of inner ear damage and / or protection in their methods and / or results, we believe that a discussion on inner ear inflammation is less relevant within the framework of the present manuscript, and hence may rather be omitted from the present manuscript.



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ESPS Peer-review Report

Name of Journal: World Journal of Otorhinolaryngology

ESPS Manuscript NO: 3731

Title: Adenosine Amine Congener Ameliorates Cisplatin-Induced Hearing Loss

Reviewer code: 00503805

Science editor: Gou, Su-Xin

Date sent for review: 2013-05-17 12:32

Date reviewed: 2013-05-29 04:37

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

COMMENTS TO AUTHORS

ESPS Manuscript NO: 3731 Title: Adenosine Amine Congener Ameliorates Cisplatin-Induced Hearing Loss Authors: Niliksha Gunewardene, Cindy X. Guoa, Ann C.Y Wonga, Peter R. Thorne, Srdjan M. Vlajkovic The authors present compelling evidence supported by statistical analysis for the ability of a adenosine receptor agonist (adenosine amine congener, ADAC) to reduce loss of hearing function and loss of cochlear hair cells induced by cisplatin in Wistar rats, a recognized model of cisplatin ototoxicity. Descriptive data using TUNEL staining is consistent with a reduction of apoptosis in outer hair cells and stria marginal cells. These data are of particular interest due to the possibility of systemically treating humans undergoing cisplatin cancer therapy with reduced cardiovascular side effects of ADAC compared to other adenosine agonists. The authors correctly acknowledge the possibility of reduced cytotoxic effects of cisplatin toward tumor cells and caution readers that this possibility must be addressed in future studies. The manuscript is a welcome addition to our scant battery of otoprotective compounds and is suitable for publication with minor revisions by addressing the points raised below.

1. Introduction - The authors have misrepresented the literature in sentence "Cross-linking of DNA by cisplatin leads to apoptosis of the outer hair cells and the lateral wall tissues, the spiral ligament and stria vascularis[2]." Cross-linking of cochlear DNA by cisplatin was reviewed in reference 2, but reference 2 makes no claim that cisplatin-DNA adducts lead to apoptosis in the inner ear. Cisplatin cytotoxicity has been studied extensively in cancer cells where it can lead to apoptosis and necrosis like the inner ear. DNA adducts can definitely induce apoptotic pathways through p53 stabilization in cancer cells, but, even in cancer cells, oxidative damage can independently induce apoptosis and necrosis independent of DNA adduct formation. In cancer cells the relative importance of adduct formation and oxidative



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damage is still debated. In the inner ear we are a long way from establishing whether DNA-adducts are sufficient to induce apoptosis by themselves. This point is important to the authors' research program because it is integral to future experiments referred to in the last sentence of the abstract having to do with adenosine amine congener's potential for interference with antineoplastic effects. The problem can be rectified by stating the claim as a hypothesis or speculation and saying "Cross-linking of DNA and cisplatin may lead to p53-mediated apoptosis..." Evidence to support this hypothesis comes from experiments with cells derived from the organ of Corti (Devarajan et al, Hearing Res 174(1-2):45-54, 2002) with organotypic culture models (Zhang et al., Neuroscience 120(1):191-205, 2003), and live animal models (Jamesdaniel et al., J Proteome Res 7:3516-24, 2008). These studies are as important to the hypothesis as the DNA adduct studies cited, but author should still make it clear that DNA-adduct induced apoptosis is still a hypothesis for the cochlea. 2. The last sentence of the same paragraph mentions states that "A reduction in the endocochlear potential, probably resulting from a dysfunctional stria vascularis, appears to be one of the hallmarks of cisplatin ototoxicity[7]." Reference 7 does show that reduction of EP precedes outer hair cell loss in the acute model used. However, the placement of the sentence in the paragraph poses a problem of logical flow for the reader, especially since the authors have previously reported purinergic receptor effects as they relate to basal outer hair cells whose loss is still considered a hallmark of cisplatin ototoxicity. If the authors feel that it is important to talk about stria dysfunction at this point in the paragraph, it would be advised to consider including at least another mention of the hair cell so as not to lead the reader to expect mo