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Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8141

Title: Clinical significance of nerve growth factor and TrkA signaling pathway in intrahepatic cholangiocarcinoma

Reviewer code: 02545385

Science editor: Ma, Ya-Juan

Date sent for review: 2013-12-18 17:23

Date reviewed: 2014-01-06 16:30

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input 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

The manuscript investigated the expression of NGF and TRKA in 83 cases of IHCC by immunohistochemistry staining, correlation of the expression with clinicopathology and survival, and the involvement of NGF-TRKA signaling pathway in IHCC progression. The manuscript gave the conclusion that NGF-TrkA double positivity is an independent prognostic factor in IHCC, and NGF-TrkA signaling pathway involved in IHCC progression. The results are interesting and provide some new information on biomarker of IHCC. The study was well designed and the methods applied were appropriately performed. The manuscript was well written, and the results are reliable and reasonable. However, several points need to be addressed before being considered for acceptance. Major points: 1. Discussion is quite rough and superficial, and also is not sufficient. Discussion is not a repeat of Results. Author should discuss some results in detail, such as 1) other publication on NFG-TRKA as a biomarker or prognostic factor in other cancers, 2) on involving proliferation and invasion, the potential mechanism involved, based on present results. 3) Basic knowledge on NFG, TRKA and NFG-TRAKA signal pathway, their multiple functions, potential links with tumorigenesis, and significance of present results..... 2. Results should be precise and easy to follow. Some description in Results can be in Materials and Methods, and some in Results can be in Discussion. Author should reconsider the writing structure in both Results and Discussion 3. Author gave a conclusion that both high expression of NGF and TRKA could be an independent prognostic factor of IHCC. According to author's grouping way, high expression of NGF is 38% and high TRKA expression is 28%. How many percent in both high expression of NGF and TRKA ? (At least less than 28%), and what is the significance as a prognosis factor in the low percent of high

expression of NGF-TRKA? 4. In Fig 2C, it seems the result is obtained from multivariate analysis of NGF+TRKA+(both high) vs NGF-TRKA-(both low). There should be four situations: both high expression, both low expression, only NGF high, only TRKA high. Author should provide these data and show how to analyze with multivariate analysis, such as, both high expression vs all others. 5. Figure 3 showed the results on AKT and ERK, but less description in manuscript. Author should include the information on the results in Introduction, Results and Discussion, especially the significance in involvement in IHCC progression through NGF-TRKA signal pathway Minor points . 1. Page 7, first line: The description "The samples were divided into positive and negative groups according to the average score" is not suitable. If author insists in grouping based on average score, "> average score and < average score" or "high expression and low expression" 2. Similar in page 9, "NGF was observed positively expressed in 38.3%(28/60) IHCC samples while TrkA was overexpressed in 28.3%(17/60) samples", it should be revised, such as, "The NGF expression more than average score was observed in" 3. It is necessary to describe the results precisely and in detail. For example, in page 9, "From table1, we can see that NGF was significantly associated with differentiation (P=0.024)." From Table 1, well differentiation has more case with high expression and poor differentiation has less case with high expression. Author should give precise description on the results. 4. In page 10, in the result on multivariate analysis, please give a RESULT of the analysis.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8141

Title: Clinical significance of nerve growth factor and TrkA signaling pathway in intrahepatic cholangiocarcinoma

Reviewer code: 02537303

Science editor: Ma, Ya-Juan

Date sent for review: 2013-12-18 17:23

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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	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

Dear Authors, thank you for submission of this highly interesting manuscript. Especially the high quality in many parts supports acceptance of this paper. Just a minor comment: Please move 4 Sentences from results (Correlation between NGF, TrkA and overall survival rates) to method section of the manuscript: The relationship between.... (following 2 sentences) and In addition, multivariate analysis... (following two sentences). Instead you can summerice the results related to Tab 3 in ashort paragraph. Congratulations! Sincerely Reviewer



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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8141

Title: Clinical significance of nerve growth factor and TrkA signaling pathway in intrahepatic cholangiocarcinoma

Reviewer code: 02545518

Science editor: Ma, Ya-Juan

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Date reviewed: 2014-01-30 03:41

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input 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
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		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This article is original and while the Nerve growth factor has been studied in relation to other types of cancers, cholangiocarcinoma data is sparse. Since we live in the age of molecular biology, studies like that of the present paper are of considerable importance for the development of new therapies. Nevertheless, there must be some corrections. Minor comments: (i) In the Introduction the authors state that "the relation between NGF and CCA has not been reported in clinical study? although in 2010, Xu LB et al. in their article "Nerve growth factor-beta expression is associated with lymph node metastasis and nerve infiltration in human hilar cholangiocarcinoma" (World J Surg 2010; 34:1039-45), they report that Nerve growth factor-beta was investigated by immunohistochemistry in samples from 28 cases of hilar cholangiocarcinoma and they found that Nerve growth factor-beta might promote lymph node metastasis and nerve infiltration in human hilar cholangiocarcinoma. The authors must comment on this article in their discussion section. (ii)

Below the horizontal line of Fig. 2, they must include patients at risk, in 10 months follow up interval.