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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 30174
Title: Pleiotrophin and N-syndecan promote perineural invasion and tumor progression in an in situ pancreatic cancer mouse model
Reviewer's code: 03086186
Reviewer's country: Taiwan
Science editor: Yuan Qi
Date sent for review: 2016-09-18 09:05
Date reviewed: 2016-09-19 15:54

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

COMMENTS TO AUTHORS

Dr. Yao and other authors investigated PTN and N-syndecan levels in patients with pancreatic cancer, and found that high expression of PTN and N-syndecan may contribute to increased PNI and poor prognosis in a previous study. In this study, they used an allograft model in nude mice to examine these proteins and PNI in pancreatic cancer tissues. The results showed that PTN and N-syndecan expressions were associated with PNI. High PTN expression was associated with large bloody ascites, liver metastases, and decreased survival time. N-syndecan expression was associated with tumor size. 1. No direct evidence from the study that PTN and N-syndecan promoted tumor progression and PNI. It is better to say that high PTN expression was closely associated with metastases, and poor prognosis. 2. The authors can provide pictures to support their observations that 1. PTN and N-syndecan protein levels were markedly increased in pancreatic cancer compared with normal pancreas. 2. PTN was highly expressed in pancreatic cancer cells. 3. PTN and N-syndecan expression levels in pancreatic cancers were significantly higher in nude mice with PNI than in those without PNI. 3. The authors should use software to quantify the intensity of protein expression and calculate

percent area of protein expression in the study.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 30174
Title: Pleiotrophin and N-syndecan promote perineural invasion and tumor progression in an in situ pancreatic cancer mouse model
Reviewer's code: 03087223
Reviewer's country: United States
Science editor: Yuan Qi
Date sent for review: 2016-09-18 09:05
Date reviewed: 2016-09-20 23:45

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

COMMENTS TO AUTHORS

General remarks In the current manuscript, the authors unravel the role of pleiotrophin (PTN), a heparin-binding growth factor and its receptor, N-syndecan in the occurrence of perineural invasion (PNI), a hallmark of pancreatic cancer progression and aggressiveness. The study is well designed, data interpretations are very insightful and accurate, and the conclusions are precisely compelling. However, a line of experiments needs to be addressed to substantiate the findings. Major points: 1. The positivity of N-Syndecan expression in the perineurium need to be further improved (Fig. 1D). The staining seems very weak and less convincing. The authors should consider using another antibody instead, or should provide more convincing images. 2. The staining in Fig. 1A and 1B seems compelling. However, a peptide competition assay needs to be performed to confirm the specificity of the staining. 3. How would the authors explain the discrepancy between the survival rate in Fig. 2A and the Fig. 2B, as PTN expression seems to correlate with that of N-syndecan, and considering the evidence the latter is the related-receptor? The authors need to provide further clarification. Minor points: 1. The authors should proofread this sentence: "Pleiotrophin (PTN) is a type of

neurotrophic factor, also known as neurite growth-promoting factor, found human, mouse, and rat". 2. "In addition, nude mice that were N-syndecan negative (n = 14) had a higher median survival time than those who were positive (n = 22); however, the difference was not significant (P > 0.05) (Figue 2B)." The authors should specify the median survival time as for PTN, although data seem less meaningful.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
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Title: Pleiotrophin and N-syndecan promote perineural invasion and tumor progression in an in situ pancreatic cancer mouse model
Reviewer's code: 03087211
Reviewer's country: India
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The work is interesting but I have the following suggestions. 1. English should be improved throughout the manuscript. 2. Quantitative information should be provided in the abstract 3. Introduction is not complete and a paragraph should be added on cancer scenario and natural products with the citation of the following references. -Heterocyclic Scaffolds: Centrality in Anticancer Drug Development, Curr. Drug Target, In Press (2015). -Glutamic acid and its derivatives: Candidates for rational design of anticancer drugs, Future Med. Chem., 5, 961-978 (2013). -Curcumin-I Knoevenagel's condensates and their Schiff's bases as anticancer agents: Synthesis, pharmacological and simulation studies, Bioorg. & Med. Chem., 21: 3808-3820 (2013). -Platinum Compounds: A hope for future cancer chemotherapy, Anti-Cancer Agents Med. Chem., 13: 296-306 (2013). -Thalidomide: A Banned Drug Resurged into Future Anticancer Drug, Current Drug Ther, 7: 13-23 (2012). -Cancer Scenario in India with Future Perspectives, Cancer Therapy, 8: 56-70 (2011). -Social aspects of cancer genesis, Can. Ther., 8: 6-14 (2011). - Nano anti-cancer drugs: Pros and cons and future perspectives, Current Cancer Drug Targets, 11, 131-134 (2011).

-Advances in nano drugs for cancer chemotherapy, Current Cancer Drug Targets, 11, 135-146 (2011).
-Natural Products: Human Friendly Anti-Cancer Medications, Egyp. Pharm. J., 9: 133-179 (2010). I WOULD LIKE TO SEE THE REVISED MANUSCRIPT.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 30174
Title: Pleiotrophin and N-syndecan promote perineural invasion and tumor progression in an in situ pancreatic cancer mouse model
Reviewer's code: 03089133
Reviewer's country: United States
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript entitled "Pleiotrophin and N-syndecan promote perineural invasion and tumor progression in an in situ pancreatic cancer mouse model by Yao et al focuses on the role of Pleiotrophin and N-syndecan in the pancreatic cancer mouse model. Authors have previously shown high expression of Pleiotrophin (PTN) and its receptor N-syndecan in human pancreatic cancer and correlated their expression with clinicopathological features. Authors suggested that higher expression of PTN and N-syndecan may promote increased PNI and poor prognosis of pancreatic cancer patients. In the present study authors injected pancreatic cancer cells into Fifty male athymic nude mice and analyzed the expression of PTN and N-syndecan proteins by immunohistochemistry. Perineural invasion (PNI) was assessed and scored by three investigators. Authors showed high expression of PTN and N-syndecan that was associated with large bloody ascites, liver metastases and decreased survival time. Suggesting role of PTN and N-syndecan in tumor progression and PNI formation in mouse model of pancreatic cancer. Specific comments: 1. What was the rationale of selecting MiaPaCa-2 line? 2. What was the rationale of selecting male

nude mice? Pancreatic cancer is about 30% more common in men than in women. Men are more likely than women to develop pancreatic Cancer. Authors should discuss if they anticipate any differences in the expression of PTN and N-syndecan and PNI invasion in male verses female. 3. In figure 1, it is very hard to appreciate the differences between moderate PTN expression and intense PTN expression. Authors should quantify the results or replace these images with other better representative images. Same is true for negative and positive N-syndecan expression in perineurium of nerves of pancreatic cancer. 4. In its present form this study is not adding any new information than what authors have shown previously. The study would benefit if there were some mechanistic studies or studies with some blockers showing how PTN and N-syndecan could be blocked to prevent PNI invasion.

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ESPS PEER-REVIEW REPORT

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ESPS manuscript NO: 30174
Title: Pleiotrophin and N-syndecan promote perineural invasion and tumor progression in an in situ pancreatic cancer mouse model
Reviewer's code: 03062291
Reviewer's country: Russia
Science editor: Yuan Qi
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[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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		[Y] No	

COMMENTS TO AUTHORS

It is a well written manuscript aiming to study correlation of N-syndecan and PTN expression in human pancreatic cancer with various parameters towards tumor progression. However, this study recapitulates authors previous findings and does not provide enough novelty. Authors claim that PTN and N-syndecan can stimulate PNI and promote tumorigenity but no supporting evidence is provided except that. Since expression of PTN correlates with the expression of N-syndecan I can hardly explain the difference in survival rates in Fig 2. Would be good to test the above expression by other methods. Also, I am curious if gender was considered as an influential factor in mice. If not, such model is not very much applicable to human subjects. Authors need to discuss this issue.