

## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 6460

**Title:** Pancreatic cancer organotypic cultures: preclinical, high throughput, bio-mimetic model for pharmacological agent evaluation.

**Reviewer code:** 00003652

**Science editor:** Cui, Xue-Mei

**Date sent for review:** 2013-10-22 08:54

**Date reviewed:** 2013-12-20 11:13

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 checked="" type="checkbox"/> Grade B (Very good)	<input checked="" 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

The concept that stromal tumour interactions play a critical role in cancer progression is being increasingly recognised in the field of oncology. Consequently, there is much interest in elucidating the molecular mechanisms mediating such interactions, so as to identify novel therapeutic targets for cancer. This is particularly important for cancers such as pancreatic cancer where chemotherapeutic agents targeting cancer cells alone have failed to significantly improve clinical outcome. Both in vitro and in vivo approaches are being used to characterise the mechanisms regulating stroma-tumour interactions and this review covers a relatively recently developed in vitro tool for such studies, namely 3D organotypic cell cultures. The review, from a group that has been at the forefront of studies using 3D cultures, is concise and generally well written. It adequately covers current knowledge in the field and would be useful to researchers interested in this particular area. I have the following comments : 1. Page 4, paragraph 1 : The sentence "Furthermore, matrix metalloproteinases .....invasion" appears to be incomplete. 2. Page 4, paragraph 1, last sentence : The authors state that "The net result is a unique tumour microenvironment inaccessible to chemotherapy....". I do not think that the microenvironment itself is inaccessible to chemotherapy. It is the cancer cells within the microenvironment that are inaccessible to chemotherapy. Please rewrite the sentence appropriately. 3. Page 5 : The authors mention the use of immortalised pancreatic stellate cell lines. There is some controversy in the literature about whether the available immortalised PSC lines closely represent the primary cells. A cautionary note should be inserted here to indicate that while immortalised PSC lines can certainly be used to provide proof of concept, it would be wise to ensure that the findings are subsequently confirmed using primary PSCs. 4. Page

6, paragraph 2 : In terms of hypoxic conditions in pancreatic cancer, it should be noted that this can differ significantly in different regions of the same tumour. Thus, while the central areas of the tumour with dense stroma can be hypoxic, the same may not be the case at the invading front of the tumour. 5. Page 10, paragraph 2 : Please clarify the sentence “Importantly, these results were..... resembling human PDAC”. How would ATRA lead to increased “histology resembling human PDAC”? 6. As the authors have noted, no single in vitro model can entirely replicate the in vivo system. In the Conclusion section, it may be useful to include the point that while 3D organotypic models are an important tool in elucidating molecular mechanisms of stroma-tumour interactions and are also useful for testing new treatment regimens, it remains critical that therapeutic approaches are subsequently tested in orthotopic or transgenic models of the disease, particularly because these animal models lend themselves to assessment of the effects of interventions on metastasis (a factor which the authors have acknowledged is the prime driver of the poor prognosis in pancreatic cancer).

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**Name of Journal:** World Journal of Gastroenterology

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**Title:** Pancreatic cancer organotypic cultures: preclinical, high throughput, bio-mimetic model for pharmacological agent evaluation.

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**Science editor:** Cui, Xue-Mei

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

## COMMENTS TO AUTHORS

Organotypic culture models are valuable tools for studying the mechanisms of pancreatic cancer, providing an easily manipulated system in which specific questions can be addressed, thus facilitating the translation of basic science to the clinic, especially for a good understanding of the fundamental molecular and cellular mechanisms governing tumour pathogenesis, metastasis. No in vitro models can perfectly replicate the ecosystem of pancreatic cancer. Thus the therapeutic importance of in vitro models should not be overestimated. In fact, comparing with animal model, it probably provides a poor contribution to investigate the preclinical drug and therapeutic discovery. Even the animal models are mostly can't well mimic the clinical ecosystem.