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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**ESPS manuscript NO:** 25972
**Title:** Immune checkpoint and inflammation as therapeutic targets in pancreatic carcinoma
**Reviewer's code:** 00068891
**Reviewer's country:** China
**Science editor:** Ya-Juan Ma
**Date sent for review:** 2016-03-27 14:08
**Date reviewed:** 2016-04-25 09:43

| 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 | [Y] 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 | [ ] Minor revision |
| [ ] Grade E: Poor | | [Y] No | [ ] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

The author reviewed the roles of immune checkpoint and inflammation in the pathogenesis , invasion and metastasis in pancreatic adenocarcinoma (PAC). The primary results so far seems to be encouraging and further studies are needed including large multicenter clinical trails worldwide to confirm the immune checkpoint and inflammation as potential targets in PAC patients.

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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**ESPS manuscript NO:** 25972
**Title:** Immune checkpoint and inflammation as therapeutic targets in pancreatic carcinoma
**Reviewer's code:** 02832523
**Reviewer's country:** United States
**Science editor:** Ya-Juan Ma
**Date sent for review:** 2016-03-27 14:08
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| 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

A review of immunotherapy approaches to pancreatic cancer is of interest to the WJG community. The article can be substantially improved though. The authors largely present a simple literature survey of immunotherapy trials in pancreatic cancer without critically evaluating the rationale behind such therapies, surmising the causes for failure and pointing out what approaches may work better. These factors are crucial for a good review paper. My recommendation to improve the manuscript is as follows: 1. The rationale for immune checkpoint use in various trials for PDA is not clear. Does PDA normally have a high infiltration of CTLs? This is a pre-requisite for CTLA4 to work normally. 2. Author states Tregs may contribute to PDL1 resistance, but at the same time mentions "a few effector T cells infiltrate into the tumor tissue". The next sentence seems contradictory to preceding two statements. 3. What is microsattelite instability? Why does it promote immune response? How does mismatch repair mirror underlying MSI? 4. How would combination therapy with cytotoxic regimens promote immunotherapy? What are the potential mechanisms that can be exploited – for example, has anyone looked at depletion of TAMs with paclitaxel? We encourage the

authors to look into pre-clinical studies looking into the mechanism. 5. What would be the underlying rationale for evaluating combination immunotherapy in PDA? That is, if either (CTLA4 or PD1 blockade) didn't work well by itself why would combination work better? 6. Radiation and thermal/cryo ablation are well known to promote antigen presentation and/or improve immune response. Has there been work looking into these mechanisms to improve immunotherapy in PDA? Include and discuss. 7. It is not clear how KRAS and p53 (tumor suppressor genes) contribute to inflammatory response – at least not directly. Further, how do these driver mutations affect immunotherapy? Melanoma which has shown most promise with immunotherapy has a high mutational load. Comparatively, KRAS and p53 mutant tumors (colorectal for example) do not have high mutational load. How does this affect antigen presentation in these tumors? Perhaps lack of immune response may be because of low mutational load/high self antigen recognition? 8. The contribution or research that combines CXCR2 and CXCL with immunotherapy is not discussed adequately. 9. The pathway to IL6 or NF-kB mediated response may involve cells that are involved in the secretion of these cytokines. The authors should discuss the role of such cells in the immune response and how this can be overcome.