



PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 41000

Title: Pancreatic cancer stem cells: Perspectives on potential therapeutic approaches of pancreatic ductal adenocarcinoma

Reviewer's code: 03370303

Reviewer's country: Japan

Science editor: Fang-Fang Ji

Date sent for review: 2018-07-19

Date reviewed: 2018-07-20

Review time: 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This review is interesting providing a large amount of information regarding the strategy for targeting pancreatic cancer stem cells (PCSC). This review will improve the general understanding of the characteristics of PCSCs, which may contribute to the



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development of new protocols for the treatment of pancreatic tumors in future. Although the manuscript is written in a high-level English, there is only one concern. I hope that authors would rewrite the sentence before the publication in WJSC. A minor concern The first sentence in the second paragraph of Introduction “Diagnosis followed by surgery and chemo or radiation therapy is the main treatment approach, however it doesn’t present satisfactory results [2].” is hard to be understood. It should be rewritten in a clearer expression, for example, “Currently, surgery coupled with chemo or radiation therapy is the main treatment approach although it doesn’t present satisfactory results [2].”.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 41000

Title: Pancreatic cancer stem cells: Perspectives on potential therapeutic approaches of pancreatic ductal adenocarcinoma

Reviewer's code: 03670299

Reviewer's country: Italy

Science editor: Fang-Fang Ji

Date sent for review: 2018-07-19

Date reviewed: 2018-07-27

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this manuscript the author describe the potential use of Pancreatic cancer stem cells in the treatment of pancreas cancer. According to the manuscript description that indicates fundamentally as pancreatic cancer the pancreatic ductal adenocarcinoma (PDAC), it



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should be more appropriate change the title of the manuscript describing in the specific the treatment of PDAC. The manuscript is interesting even if recently Ercan et al., 2017 published a similar manuscript entitled Pancreatic Cancer Stem Cells and Therapeutic Approaches, *Anticancer Research*, 2017, 37, 2761-2775. The manuscript should be revised in its complex organization. The authors should add more recent literature regarding different themes treated in the manuscript. in addition, the characteristics of pancreatic ductal adenocarcinoma in the introduction should be described in more detail. Moreover a recently reference should added: Gallmeier E and Gress TM. Pancreatic ductal adenocarcinoma. *Internist (Berl)*. 2018 Aug;59(8):805-822. doi: 10.1007/s00108-018-0460-z. Regarding the chapter relative to PANCREATIC CANCER STEM CELLS CHARACTERISTICS the authors should clarify the possible interaction between pancreatic cancer stem cells (PCSCs) and parental cells. A recently paper describe with clarity this interaction describing that “high local invasion of parenchymal cells into the CSC-derived vascular network suggests that a symbiotic relationship between the parenchymal cells and the CSCs underlies the initiation and maintenance of early PDAC infiltration and metastasis” (Biondani G. et al., *FEBS Journal* 285 (2018) 2104–2124). Regarding the paragraph on Chemoresistance related to EMT process, other interesting references should be added (Renz et al., 2017, Repurposing Established Compounds to Target Pancreatic Cancer Stem Cells (CSCs), *Med. Sci.* 2017, 5, 14; doi:10.3390). Moreover, some interesting data from Meidhof et al. demonstrated that the class I HDAC inhibitor mocetinostat acts as an epigenetic drug and interferes with Zeb1 function, restores miR-203 expression, and thereby represses EMT and stemness properties in PDAC and prostate cancer (Meidhof, S.; Brabletz, S.; Lehmann, W.; Preca, B.T.; Mock, K.; Ruh, M.; Schuler, J.; Berthold, M.; Weber, A.; Burk, U.; et al. ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC inhibitor mocetinostat. *EMBO Mol. Med.* 2015, 7, 831–847). Another interesting paper not cited by



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authors is: Zheng, X. et al., Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature* 2015, 527, 525–530. Other the chapter on nanoparticles the authors should give results on the possible use of phytochemicals to targeting PCSCs (see references Aliebrahimi et al., 2018, *Biomedicine & Pharmacotherapy* 106 (2018) 1527–1536; Suvroma Gupta and Dipankar Pramanik. *Phytochemicals and Cancer Stem Cells: A Pancreatic Cancer Overview*, *Current Chemical Biology*, 10.2174/2212796810666160419152309).

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 41000

Title: Pancreatic cancer stem cells: Perspectives on potential therapeutic approaches of pancreatic ductal adenocarcinoma

Reviewer's code: 03811054

Reviewer's country: Egypt

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-13

Date reviewed: 2018-08-16

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Minor Revision 1- There are some spelling/grammar/formatting errors in the current version of the manuscript. Please correct them carefully. 2- Abbreviations need to be described at first time in the text.



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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 41000

Title: Pancreatic cancer stem cells: Perspectives on potential therapeutic approaches of pancreatic ductal adenocarcinoma

Reviewer's code: 03197771

Reviewer's country: Spain

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-13

Date reviewed: 2018-08-17

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
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			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
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SPECIFIC COMMENTS TO AUTHORS

In the manuscript entitled "Pancreatic cancer stem cells: perspectives on potential therapeutic approaches of pancreatic cancer" Di Carlo et al., review the literature to identify compounds with inhibitory effects on cancer stem cells which are non-cancer



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drugs and therefore could be tested as pancreatic stem cells (PCSCs) inhibitors; or compounds that target proteins or pathways deregulated on PCSCs and have not yet been used in the clinic for the treatment of pancreatic ductal adenocarcinoma and thus offer potential novel therapeutic options. Although the authors made an effort to tabulate the information, the fact that some compounds overlap both sections, together with the lack of an explanation of the mechanisms or levels of action of non-cancer drugs hinders an integrated understanding of the proposed novel therapies for pancreatic cancer to be explored and the justification behind these proposals. A summary figure is recommended. The following previous related reviews should be included: Ishiwata T, Matsuda Y, Yoshimura H, Sasaki N, Ishiwata S, Ishikawa N, Takubo K, Arai T, Aida J. Pancreatic cancer stem cells: features and detection methods. *Pathol Oncol Res.* 2018 Jun 8. doi: 10.1007/s12253-018-0420-x. Valle S, Martin-Hijano L, Alcalá S, Alonso-Nocelo M, Sainz B Jr. The Ever-Evolving Concept of the Cancer Stem Cell in Pancreatic Cancer. *Cancers(Basel).* 2018 Jan 26;10(2). pii: E33. doi: 10.3390/cancers10020033. Testing of novel approaches should highlight how new treatments are expected to surpass conventional current treatments, if so, stating their possible limitations. This part is not clearly presented in the manuscript. Specific comments: The information provided in the abstract should be carefully chosen as it is limited in length. It has been noted a redundancy on the second sentence “Unfortunately, up to date the clinical efforts to fight this cancer have not yet resulted in improved long-term survival”, which does not add any new information to the first. Page 4, lines 124 and following: “..other pathways such as autophagy”, autophagy is a cellular process, not a pathway. Authors should review statements that lack references in the whole manuscript, for example: Page 4, lines 94 and following: “Recently, it has been demonstrated that cancer stem cells play critical roles in anticancer treatment resistance and are responsible for metastasis in several human malignancies, including PDAC” ; Page 8, lines 250 and following: “. In



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particular, Crocetin acid decreases the number and size of the spheroids in a dose-dependent manner, and suppressed the expression of DclK1, a PCSCs surface marker.”; Page 9, lines 264 and following: “This compound targets PCSCs by decreasing the expression of: Notch 1–4 receptors, their ligands Jagged1, Jagged2, DLL1, DLL3, DLL4, the downstream protein Hes-1, as well as of γ -secretase complex (required for Notch activation).” Etc Page 12, lines 358 and following: it is not clear how NP approach could be integrated in pancreatic cancer prevention. Page 6, the sentence: “This observation suggests that it should be further investigated to verify if it is also effective for targeting PCSCs” should be relocated as the authors continue to describe additional antibiotics that impact CSCs. Authors should elaborate Figure 1 legend further. Extensive English language correction is needed. Examples are: Page 2, lines 35 and following: “Recent reports..” is fragmented, should be rewritten. Page 3, line 71: “..the major of patients..” Avoid subjective vague adjectives such as “the most conventional...” (How is this measured?); “only few months..” (Indicate range, otherwise the information provided is limited/incomplete); “very resistant..” ; “the most mature...” etc In general, the manuscript text needs to be edited to avoid unneeded terms or sentences. Explain acronyms in its first appearance, example: “GEMM model..” “Canadensis” should appear in lower case.

INITIAL REVIEW OF THE MANUSCRIPT

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