



PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46592

Title: Targeting cancer stem cells in drug discovery: Current state and future perspectives

Reviewer's code: 02566952

Reviewer's country: Romania

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-02 12:48

Reviewer performed review: 2019-04-02 13:46

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input 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 Grade E: Do not publish	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 checked="" type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input 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

The manuscript presents an interesting (and much needed) review about the controversial problem of cancer stem cells especially in the very practical purpose of conceiving improved therapies Several comments authors maybe wish to consider



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would add to an already well composed work Under the chapter CSC signaling and inhibitors there is a mention about these cells are deriving from normal cells. Maybe it would be useful for the reader to write a brief phrase about the hypothesis regarding their formation “The canonical Wnt signaling pathway may be involved in the development of benign or malignant breast cancer” breast cancer= malignant tumors, benign tumors are not cancer The display of pathways known to belong to CSC together with their inhibitors is interesting and for sure industry will greatly profit from reviewing them. Occasionally there is a text mention about adverse effects, however they are not as consequent as other (tabled) description This is an important topic and it would be good to insert the side effects (that are potentially a lot due to the fact these inhibitors interfere with pathways that are crucial for any tissue renewal mechanism Basicly we have here information about the existence of cancer stem cells (ascertain in some cancers but not in all) about the biochemical pathways active in such cells followed by a very thorough description of this pathway inhibition that could act as treatment A chapter about side effects is missing as well as a proof whatsoever this inhibitors actually DO target CSCs . Are the authors aware about studies reporting the precise targeting of CSCs using (at least some) of the molecules proposed? As it is a review about CSCs and not about potential pharmacological inhibitors, do authors are aware about other methods of targeting CSCs (such as hyperthermia, nanopartivcles, antibodies and so on). Even though it is obviously not within the authors field of interest their existence should be at least mentioned for making such review complete.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46592

Title: Targeting cancer stem cells in drug discovery: Current state and future perspectives

Reviewer's code: 02446215

Reviewer's country: Italy

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-26 09:30

Reviewer performed review: 2019-04-16 08:32

Review time: 20 Days and 23 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 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 checked="" 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 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

This is an interesting paper that summarize the therapeutic options related to cancer stem cells . Some suggestions are provided below to improve the manuscript: 1) I suggest to add a paragraph related to autophagy and cancer stem cells focus on



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therapeutic applications in this field 2) Please define acronymus the first time the term is used

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46592

Title: Targeting cancer stem cells in drug discovery: Current state and future perspectives

Reviewer's code: 02909322

Reviewer's country: China

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-15 03:29

Reviewer performed review: 2019-04-18 09:27

Review time: 3 Days and 5 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 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 type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" 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

This review aims to introduce the field of cancer stem cells and the important signaling pathways in cancer stem cells and to present the application of approved inhibitors in the clinical stage o patients. These are some issues should be concerned as below: 1)One



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main question : The review mainly discussed the targeting signaling pathway (including Wnt, Hedgehog, Notch, BMP, PI3K/Akt, etc) and related inhibitions in CSCs. However, these complex pathways have cross-talk to regulate the CSC phenotype. Moreover, non-CSC populations also exhibit overlapped signaling pathways. So, the authors have to discuss other issues about targeting CSCs ① Targeting surface markers expressed by CSCs (for example, CD47, ALDH1, CD44, etc), ② Targeting the CSC microenvironment (for example, CXCR4, CXCR1). 2)In recent years, the existence of CSCs in solid tumors including breast cancer, prostate cancer and pancreatic cancer, etc. In fact, according to head neck cancer, Wu A had indicated that aldehyde dehydrogenase 1(ALDH1) could be a functional marker for identifying cancer stem cells in human nasopharyngeal carcinoma (NPC).(Cancer Lett. 2013). The authors should add this finding in the Introduction section. 3)Regarding to Fig. 1. Targeting Wnt, Hedgehog, Notch, BMP, Bmi, PI3K/ Akt and STAT signaling pathways and the characteristics of cancer stem cells. The description of CSCs features is not somewhat correct. For example, "Apoptosis" should be rewritten as "Apoptosis resistance ". 4)What optimal time is for the use of a CSC-specific therapy ? before or soon after diagnosis, before or concurrently with neoadjuvant chemo/radiotherapy? The authors should discuss it in the Conclusion section.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46592

Title: Targeting cancer stem cells in drug discovery: Current state and future perspectives

Reviewer's code: 00007461

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-15 12:56

Reviewer performed review: 2019-04-20 21:38

Review time: 5 Days and 8 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:
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publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
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SPECIFIC COMMENTS TO AUTHORS

The manuscript/review is generally very well done and informative. An effort can be made to improve the review by including the most recent findings/most recent publications on these topics.



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