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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 19954

Title: Therapies targeting cancer stem cells: Current trends and future challenges

Reviewer's code: 00504335

Reviewer's country: Czech Republic

Science editor: Yue-Li Tian

Date sent for review: 2015-05-28 15:31

Date reviewed: 2015-06-01 17:03

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<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"/> Duplicate publication	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is well prepared compilation of data published by other authors on cancer stem cells (CSC) and on possibilities to target these cells for cancer therapy. The existence of CSC is still questionable. This should be stressed in the manuscript. Nevertheless, such review should be prepared by a researcher publishing in the field of CSC and having the experience with CSC and their therapy. Otherwise, it looks like an attempt to publish introduction to diploma or PhD thesis.



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 19954

Title: Therapies targeting cancer stem cells: Current trends and future challenges

Reviewer's code: 00204324

Reviewer's country: France

Science editor: Yue-Li Tian

Date sent for review: 2015-05-28 15:31

Date reviewed: 2015-06-07 23:17

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

* The subject of this review is a bit too wide and could be more limited. Some mechanisms that are here described do not involved specifically stem cells (ex.: targeting signal cascades, targeting ABC cassette)and could be not extensively developed. * English should be checked all along the manuscript. * MDR1 modulators did not really show benefit in hematological malignancies and should not be extensively developed. * It is stated that CD34+CD38- cells possess stem cell capacities. However, this population is not the only one. Other hypotheses should be mentioned.



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 19954

Title: Therapies targeting cancer stem cells: Current trends and future challenges

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Reviewer's country: Taiwan

Science editor: Yue-Li Tian

Date sent for review: 2015-05-28 15:31

Date reviewed: 2015-06-29 11:19

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	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"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This manuscript is a well-prepared review paper, although the existence of cancer stem cell is controversial. I suggest the content could be focus and limited. Finally, I believe this review paper can attract the readers in the field of stem cell research.



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 19954

Title: Therapies targeting cancer stem cells: Current trends and future challenges

Reviewer's code: 00110885

Reviewer's country: United States

Science editor: Yue-Li Tian

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

In their review "Therapies targeting cancer stem cells: current trends and future challenges" Dragu and colleagues discuss approaches to targeting CSC. The CSC paradigm has emerged based on the notion that only a subset of tumor cells have the potential, following prospective isolation, to re-capitulate the phenotypic diversity of the original tumor in primary and secondary recipients, thus defining CSC as multipotent self-renewing progenitors. To confirm the cell population as CSC, the gold standard in the field is serial mouse transplantation assays to determine if it re-creates other populations found in the tumor. Dragu et al. discuss approaches to targeting surface biomarkers and signaling pathways that regulate CSC self-renewal and differentiation, drug-efflux pumps involved in apoptosis resistance, microenvironment signals that sustain CSC growth, manipulation of miRNA expression, and induction of CSC apoptosis and differentiation, aiming at suppressing cancer. The importance of the research area discussed is very significant and the subject is cutting-edge. The presentation and clarity of the manuscript is satisfactory. It is suggested that the manuscript is carefully checked by a professional native English speaking editor. Also, statements about the CSC role in tumor formation, metastasis, cancer relapse, as well as the capacity of CSC function targeting



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to hamper these attributes of cancer progression, are not well backed up with references. To my knowledge, these strides are mainly wishful thinking, and the authors should contain these speculations to Discussion only. The same relates to the discussion of therapy resistance in cases where the references do not have solid data showing that CSCs are responsible. As is, in most cases papers cited measure only tumor growth upon treatment, which in no way addresses the possibility of CSC involvement. Please describe the classic stochastic cancer evolution model alternative to the CSC theory. The authors take the existence of CSCs for granted. However they should make it more clear in the Introduction that the presence and function of CSCs in human cancers is largely speculative at this point. Some tumor cells being more resistant than others does not make them stem cells. Identification of CSCs must be based on functional properties rather than cell surface phenotype. In most papers cited there is no evidence that the cell population studied is tumor-forming and serially transplantable. And even in vivo clonogenicity assays are a matter of the xenotransplantation model used. Studies demonstrating this, such as PN Kelly et al. Science, 2007 and Quintana et al. Nature 456, 593-598(2008) showing tumor formation by random single human cancer cells must be cited. EMT is only casually mentioned. Yet, Robert Weinberg's group has used EMT acquisition upon E-cadherin loss as the fundamental feature of CSC. Cite the original paper and the one on CSC generation through E-cadherin inhibition: Cell. 2009 Aug 21;138(4):645-59. Gupta PB, et al. and Lander ES. The authors should add 'cautionary' notes to each paragraph to make it clear that the conclusions on the targeting of / role of CSC are tentative and explain why and what the caveats are. None of the markers of pathways discussed are CSC-specific or even cancer cell-specific. For example, CD133 expression is not restricted to stem cells, and both CD133+ and CD133-metastatic colon cancer cells can initiate tumors. (Shmelkov, S.V., et al. J. Clin. Invest. 2008;118:2111-2120). What are the results of experimental Notch targeting studies? Notch is expressed in stoma rather than epithelium in prostate cancer. Prostate CSC studies are not adequately covered in the review. Cite the paper by Y. Zhang et al., Stem Cell Research, 2013 demonstrating malignant cells with CSC properties and a phenotype resembling benign adipose stem cells in human liposarcomas. The Figure should be fixed so that the circles / labels



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 19954

Title: Therapies targeting cancer stem cells: Current trends and future challenges

Reviewer's code: 00076088

Reviewer's country: Hungary

Science editor: Yue-Li Tian

Date sent for review: 2015-05-28 15:31

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	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"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a nice and informative review discussing many aspects of cancer stem cells. 1. The paper would need some language polishing, I indicated some of these problems in the manuscript. 2. Within the sections an indication (e.g by underline or italic) of the different aspects could improve reading.