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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Stem Cells
ESPS manuscript NO: 12696
Title: Identification and Targeting Leukemia Stem Cells: the Path to the Cure for Acute Myeloid Leukemia
Reviewer code: 00572825
Science editor: Ling-Ling Wen
Date sent for review: 2014-07-23 17:31
Date reviewed: 2014-07-30 21:40

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The manuscript submitted by Jianbiao Zhou and Wee-Joo Chng provides an overview of the origin of leukemic stem cells with emphasis on the differences of the surface immunophenotype of LSCs. The differences between LSC and HSC surface antigen expression may constitute the base for attractive therapeutic targets for AML and therefore an outstandingly exciting field. The review focuses on the identification and separation of LSC by cell surface and functional markers relevant to the phenotype of LSC, preceded by a historical perspective on the definition of LSC. Finally, a short section of conclusions and perspectives of developing new treatment strategies are included. The manuscript is well organized, clearly written with minor language errors. In general this review highlights recent findings in the leukemic stem cell field and discusses new directions for therapy, aspects that will attract a broad audience both in basic and clinical research. Therefore, I recommend this manuscript for publication in the World Journal of Stem Cells.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Stem Cells
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Title: Identification and Targeting Leukemia Stem Cells: the Path to the Cure for Acute Myeloid Leukemia
Reviewer code: 01021289
Science editor: Ling-Ling Wen
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The manuscript summarizes the recent findings in identifying AML stem cells and the potential therapeutic strategies based on the surface molecules that are specifically expressed on the AML stem cells. Overall, the manuscript is well written and educational for the hematologists and basic scientists pursuing leukemia research. minor point: In the 11th lines of 2.2.6, it is said "on" engraftment was detected...", but this should be "no" engraftment was detected.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Stem Cells
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Science editor: Ling-Ling Wen
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

There are a few minor errors in the manuscript that need to edit and correct. Several minor points are as follows: 1. There are some sentences in the manuscript that are not clear or not convincing. For example: (1) Page 4, the authors described that "Elegant studies tracking clonal evolution from diagnosis to relapse revealed the greater clonal heterogeneity in AML than we previously estimated [1-3]. Some clones either founding clone (major clone) or subclones (minor clone) at diagnosis, can survive chemotherapy. These survival clones may gain a small number of cooperating mutations, eventually leading to a relapse [1-3]." -- Please make it clear in the text the effects of the pivot gene mutation(s) on the development and clonal evolution of AML. (2) Page 7, the authors described that "Higher level of spontaneous signal transducer and activator of transcription 5 (STAT5) activity is another factor contributing to the proliferative advantage and resistance to apoptosis of AML blasts with elevated CD123 [24]. It is well documented that enhanced STAT pathway activity confers drug resistance in AML [25].". -- What is the author interpretation? Please state clearly. (3) Page 8, "The utility of CD123 as a LSC marker has been convincingly confirmed by many other studies. A flow cytometric analysis of CD123 expression of diagnostic blasts from 111 de novo AML patients younger than 65 years old shows the presence of more than 1% population of CD34(+)CD38(low/-)CD123(+) cells adversely affected the disease-free-survival and over-all survival [26]. Notably, not only the percentage of CD123+ cells, but also the expression level of CD123+ predicts clinical outcome.". --

Please confirm that the original meaning has been maintained in the text. (4) Page 8, "Antibody therapy specifically targeting CD123 has been advanced to clinical development over a short 5-year period since the first report of in vivo preclinical study [30]. Anti-CD123 monoclonal antibody 7G3 has been shown to completely inhibit bone marrow engraftment by ex vivo treatment and partially impede bone marrow engraftment in a pre-established disease model in mice.". -- Please verify that the original meaning was maintained. (5) Page 9, "It was previously reported CD47 expressed on red blood cells (RBC) as a marker of self and interaction of CD47 and SIRP? on phagocytic cells delivered a "do not eat me" message, limiting clearance of circulating RBC by the means of phagocytosis [39]. ------ "Secondly, transgenic mice expressing SIRPα variants with differential ability to bind human CD47 demonstrates that the engraftment of AML LSCs depends on the interaction of CD47 with SIRP? and AML LSCs are eliminated by macrophage-mediated phagocytosis in the absence of SIRP? signaling.". -- What is the author interpretation? Please state clearly. 2. References should be cited in the text. For example: (1) Page 6, CD90, also known as Thy-1, is a small glycosylphosphatidylinositol (GPI)-anchored protein (25–37 kDa) regulating multiple signaling cascades which control cellular survival, proliferation, adhesion and response to cytokines. (2) Page 7, CD123 is also known as interleukin 3 receptor, alpha (IL-3R?). IL3R is a heterodimeric cytokine receptor comprised of the alpha unit and beta unit, which is activated by the ligand binding and necessary of IL-3 activity. IL-3 is one of the prominent cytokines that controls proliferation, growth and differentiation of hematopoietic cells. Compared to all other cell surface antigens as potential LSC markers, the studies on CD123 have been investigated into much more details and targeting CD123 is now in clinical trials. (3) Page 8, The utility of CD123 as a LSC marker has been convincingly confirmed by many other studies. ---------- Both FLT3 and c-Kit are important RTKs for the survival of hematopoietic stem/progenitor cells. N-Cadherin and Tie2 play a pivotal role in regulation of interaction between LSCs and their niche