

Dear Editor,

Thanks again for considering our manuscript "**Update on Acute Myeloid Leukemia Stem cells: New discoveries and therapeutic opportunities**" for publication in *World Journal of stem cells*.

We carefully reviewed the comments of the 4 reviewers and we were able to integrate their suggestions and respond to their comments in our new version of the manuscript. You will find below a detailed, point by point, response to the reviews.

Best regards.

Maximilian Stahl
Amer Zeidan

Reviewer 1:

This review manuscript summarizes the current status of leukemia stem cells from biology to prognosis. Extensive literatures are cited and included figures and table are pretty good. The summary of clinical trials (table) must be very useful for physicians. I would like to list several comments below: Major comments

1. Page 6, "Symmetrical vs asymmetrical cell division" and "Quiescence" sections. I think that the descriptions in both sections are too short and somewhat insufficient. The authors can do much better job by doing a bit of homework. "Concise" but "sufficient enough" paragraphs needed. Regarding "Quiescence" and stem cell exhaustion — there are a few very important original research that the authors should cite.

The section on "symmetrical vs asymmetrical cell division" has been significantly expanded and include major studies expanding our knowledge of how dysregulation of the switch between symmetrical and asymmetrical cell division can lead to the expansion of cancer stem cells.

The paragraph describing stem cell quiescence and stem cell exhaustion has been completely reworked, now including important studies elucidating the impact stem cell exhaustion and quiescence have in aging and cancer development.

2. Page 7, "Key signaling pathways". Isn't Notch signaling also suggested in LSCs? **The Notch pathway (with appropriate reference) was added to the list of pathway. We thank the reviewer for noticing that this important pathway was missing on that list.**

3. General comment: I think descriptions in sub-sections under “3. Biology of leukemia stem cells” is superficial. A little bit more in-depth discussion would be appreciated. For example, “symmetrical vs asymmetrical cell division” quiescence” “key signaling pathways relevant for retaining stemness” may not be sufficient enough.

As detailed above, additional paragraphs describing the importance of symmetrical and asymmetrical stem cell division as well as stem cell exhaustion and quiescence have been added. The Notch pathway has been added to the pathways as suggested.

4. Page 24, line 6 “...human IgG4 monoclonal antibody against CXCR4...”. Is this really the correct information? I have never heard of IgG4.

Directly from the citation: “BMS-936564/MDX-1338 is a fully human IgG₄ monoclonal antibody that specifically recognizes human CXCR4”.

Minor comments 1. There are several minor grammatical errors. I attach the file (PDF) with correction instead of typing each here. I may miss additional minor errors as . The authors may want to carefully check the text again. 2. Minor polishing of English (just wording) would make the manuscript more attractive. There are also some (a bit) awkward phrasings. 3. Abbreviations. All should be spelled out at their first appearance. For example, "NPM-mutated...(page 8)". 4. Very minor formatting issues (such as font, DOI numbers in the reference section etc.). The authors should carefully check the submission guideline provided by the publisher. **Minor errors were corrected. We thank the reviewer for his/her attentiveness.**

Reviewer 2:

This is a well written and organized review article that updates the mechanistic insights into cancer stem cells in the pathogenesis and drug resistance of acute myeloid leukemia (AML). The authors primarily presented the signature of leukemia stem cells different from normal stem cells, focusing on the signaling pathways that regulate leukemia stem cell self-renewal and differentiation including surface markers, intracellular mediators, and oncogenes. Accordingly, a variety of therapeutic agents that are currently tested to target these individual molecules in clinical trials were clearly illustrated and summarized in a Figure and a Table. In general, the paper fits well the scope of this journal and will have great potential to help diagnose and treat the disease, given the most recent knowledge about cancer stem cells.

A minor concern should be addressed. The discussion of each drug is too long as such the paper appears imbalanced; thereof, a concise revision is highly recommended.

The section discussing the different drugs was shortened at several different sections. We also hope that Table II provides most of the concise information the reviewer is looking for.

Reviewer 3: Accept

This review is well organized. The topic on acute Myeloid Leukemia Stem cells is well discussed. But, the subtype of AML, such as M1-7, also should be covered. **Although the FAB classification of AML is not the latest classification system of AML (compared to the WHO classification system), specific reference was made to the different FAB subtypes in Table I**

Reviewer 4: Accept

This is an excellent revision on the topic of acute myeloid leukemias and cancer stem cells. The authors gave a comprehensive view in the main aspects of AML, focusing the attention on the translational implications of the knowledge gained through research. The style is clear and highly informative, and the list of references complete enough.

We thank the reviewer for his positive review of our work.

Editorial comments:

Please put the reference numbers in square brackets in **superscript**. Please check across the text.

All references were put in superscript.

Would you please provide the decomposable figure, whose parts are movable and words can be edited.

Powerpoint figure was provided, all parts in this powerpoint figure are movable and words can be edited.

Step 1. Please revise your manuscript according to the reviewers' comments.

All the reviewer's comments were addressed as detailed above

Step 2. Please update the manuscript according to the Guidelines and Requirements for Manuscript Revision-Review.

Manuscript was updated based on these guidelines

Step 3. Please provide an Audio Core Tip. In order to attract readers to read your full-text article, we request that the author make an audio file describing the final core tip of the manuscript. This audio file will be published online, along with your article. **Acceptable file formats** are .mp3, .wav, or .aiff.

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The authors do not have access to the *CrossCheck* software.

Step 5. Please provide the files related to academic rules and norms. The files related to academic rules and norms include the conflict-of-interest statement.

Conflict-of-interest statement was included

Step 6. Please provide the approved grant application form(s) or funding agency copy of any approval document(s)/letter(s).

No funding agency for this manuscript

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