Jin-Lei Wang
Science Editor
World Journal of Stem Cells

May 24, 2018

RE: **Manuscript 39577 "Murine models based on acute myeloid leukemia-initiating stem cells xenografting"** by Mambet C. et al.

Dear Editor,

Thank you and the reviewers for the careful evaluation of the above referenced manuscript. We are very grateful for your comments and suggestions, which were valuable in improving the quality of our manuscript. We have considered them carefully and addressed them in full in the revised manuscript. All the changes made in the revised manuscript are highlighted and explained in an itemized, point-by-point response to the **Reviewers Comments** (see enclosed).

We have checked and corrected the entire manuscript for language mistakes as suggested with the help of a native speaker of English.

We hope that the revised manuscript is now acceptable for publication in World Journal of Stem Cells.

We look forward to hearing from you.

Sincerely,

Mihaela Chivu-Economescu.

Response to Reviewers Comments:

Reviewer #02540473**:**

Comments: The manuscript is important in leukemia and the review is well-written.

Response: We are very grateful for your comments and appreciations.

Reviewer #02446101**:**

Comments: "The content of this manuscript is systemic and readable. I'm sure that it's helpful to the readers. So, acceptance should be recommended for this manuscript."

Response: We are grateful for your comments and appreciations.

Reviewer #02446280**:**

Comments:

1. *"In the Introduction section Authors state that "AML is one of the hematologic malignancies that fails to properly engraft into the existing strains of mice due to the lack of a proper BM niche, and absence of specific human growth factors and supporting stromal cells" however do not provide any experimental evidences for this.*

2. *"Even more, on the next pages Authors write: AML was among the first diseases in which the existence of cancer stem cells was documented using xenograft animal models". Indeed modern "engineered" animals provide better opportunity to study human malignancies although will never recapitulate variable human genetic background completely.*

3. *I would also consider that the section "Cell line derived xenografts" is out of the scope of murine models description but rather adapt human cells to the existing mouse strains."*

Response: Thank you for your comments and appreciations.

1. Through that specific phrase we intended to introduce the aim of the article. That statement have been fully supported by evidences and proper citations in the section "Murine models – which are the best choice?" (pages 9-10) were we explained that the limitations are due mainly to the differences between the murine and human biological systems. Moreover, in the section "Patient derived xenografts" (page 14) we presented and discussed the experiments of *Kennedy JA* et al. that showed a 66% engraftment failure when xenografting cells from a large cohort of acute myeloid leukemia (AML) patients in immunodeficient animal models. These data support also the statement from Introduction.

2. As we answer at the previous point, although all the percentage of failure is very high in engrafting AML cells, nevertheless AML was "one of the first diseases in which the

existence of cancer stem cells was documented using xenograft animal models" as reviewed in reference 10 by Pollyea DA, *et al*. As a support of this statement please see also the below seminal papers on the topic: Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. 1994;367(6464):645–8; Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997;3(7):730–7.

3. The sub-section "*Cell line derived xenografts"* is part of the section "Xenograft mouse models used for AML" that synthesizes all the methodologies that were successful in understanding oncogenesis process of acute myeloid leukemia by using xenograft mouse models. Using CD34+ cells transduced in cell lines with different fusion genes was an important strategy during the process of obtaining better mouse models of AML and we considered it was important for a complete analysis of the methodologies used for solving this particular problem. At the same time, we emphasized in this sub-section the disadvantage of this approach that do not reflect the behavior of the original cancer cells and the importance of obtaining patient derived xenografts (next sub-section).

Reviewer #00609434**:**

Comments: "I find it worthy of publication although English grammar should be thoroughly checked (I saw several errors) and also the consecutio temporum of the paragraphs should be fixed (for example in paragrah "3. Murine models – which are the best choice?" from the end of page 9 to the end of page 10)".

Response: We thank the reviewer for the comments and suggestions to our manuscript. We have checked and corrected the entire manuscript for English grammar as suggested.