

**Name of Journal:** World Journal of Stem Cells

**Manuscript NO:** 35363

Dear Dr. Cao and dear Dr. Lee,

Thank you for your positive feedback and valuable comments by the editor and the reviewers. Enclosed please find the original copy of the revised manuscript.

I consider the editor's and referees' comments fair and very useful. I have revised the manuscript according to the provided proposals and I believe that I was able to answer all the questions to satisfy the reviewers.

Yours sincerely,

Dr. Ramin Radpour, MSc, PhD, MBA  
Tumor Immunology, Inselspital, Bern University Hospital,  
Department for BioMedical Research,  
University of Bern,  
Murtenstrasse 35,  
3010 Bern,  
Switzerland.  
Email: [ramin.radpour@dkf.unibe.ch](mailto:ramin.radpour@dkf.unibe.ch)

---

#### Reviewer's comments:

##### Comments:

This manuscript summarizes the novel methods of tracing CSCs and discusses the hallmarks of CSC identification influenced by the microenvironment or by having imperfect detection markers. In addition, explains the known molecular mechanisms of therapy resistance in CSCs.

While the problem is important and the work invested is significant, there are a few issues with the manuscript, as listed below.

##### Major points:

(1) "Chemo/radiotherapy resistance in tumor biology" section: This is an important section, which serves to remind readers of potentially importance of CSC on clinical chemo/radiotherapy resistance. However, the paragraph is vaguely described and unclear. The authors could consider presenting the precise cancer treatment, cancer types, the resistance caused by CSCs in a table.

Author: Thank you for the valuable comment. To be more specific, the main title of the section is changed to focus only on CSCs. In the part of "Molecular mechanisms of the therapy resistance of CSCs", the important signalings regulating CSC maintenance or proliferation is significantly updated and also a figure (assigned as Fig. 2) is added to illustrate the potential crosstalk between cancer- and CSC-related pathways. The section for "Targeting CSCs" is completely restructured.

(2) "High-throughput methods for the screening of CSCs" section: The authors could consider presenting the methods for the screening of CSCs in a table.

Author: Table 1 is added as a complementary to the "Methods for screening of CSCs" to summarize the potential hallmarks of using CSC-related markers.

(3) The "Targeting CSCs" section are vaguely described and unclear. Fig.2C showed four important approaches of CSC-targeted therapy. However, in the "Targeting CSCs" section, the author pay much attention to target key signaling pathways. Other three approaches should be precisely described. Additionally, please adjust the structure of this section properly in consistent with the four approaches of CSC-targeted therapy in Fig.2C, such that any reader can easily follow.

Author: the section of "Targeting CSCs" is completely revised and restructured to follow and address the points in Fig.3C.

Minor points:

1) Abstract sections: it should be "hallmarks", instead of "halmarks". In the second paragraph on page 8, it should be "Niclosamide", instead of "Nikosamide". Please check for potential typos in the rest of paragraphs.

Author: Typos are corrected accordingly and manuscript was re-polished!