Format for ANSWERING REVIEWERS

July 22, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 19954).

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

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Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 19954

The manuscript has been improved according to the suggestions of reviewers and We highlighted the changes made to the manuscript according to the peer-reviewers' comments as requested;

Reviewer #00110885

We thank the reviewer for the commentary and for the suggestions.

We added a paragraph describing the classic stochastic cancer evolution model and we introduced the suggested citations and the related discussions, respectively **(Introduction – highlighted yellow).**

We also introduced in the manuscript a paragraph related to EMT acquisition as important feature of CSCs and suggested citations **(Introduction – highlighted yellow).**

We agree with the reviewer regarding the identification of CSCs that must be performed on functional properties rather than cell surface phenotype. This has been stated in the original manuscript. We modified the respective paragraph in order to make it more

relevant **(CSCs: Definition, characteristics, markers – highlighted yellow).**

Regarding to CD133 expression, we agree with the reviewer comments and inserted one paragraph with experimental results showing that CD133- negative cells might also initiate tumors. Two examples are cited on colon and glioblastoma cancer cells (**Targeting surface markers – CD133 – highlighted yellow).**

Concerning the results on Notch targeting studies, we added two recent studies (2015), showing advances with two inhibitors BMS-906024 and OMP-59R5. Firs inhibitor is a γ-secretase inhibitor involved in Notch activation. Results for phase 1 clinical trial using BMS-906024, one of these γ-secretase inhibitors, for patients with relapsed T-cell acute lymphoblastic leukemia showed at least 50% reduction in BM blasts in 8 of the 25 patients (32%). Second one, is an antibody that inhibit Notch2 and Notch3 function, and was tested so far successfully only in animal models **(Targeting signal cascades – Notch – highlighted yellow).**

Regarding prostate studies, we actually did not intended to address each type of cancer specifically, and focused more on common mechanisms.

We have fixed the problems appeared in figure 1.

Reviewer #00204324

We thank the reviewer for the commentary and for the suggestions.

We agree with the reviewer about necessity to describe more markers for leukemia stem cells. Consequently, we introduced a new paragraph citing six additional surface markers that have been identified as highly expressed on leukemia stem cells: CD47, CLL-1, CD96, TIM3, CD32 and CD25 **(CSCs: Definition, characteristics, markers - highlighted green).**

Reviewer #00076088

We thank the reviewer for the commentary and for the suggestions.

We have checked and corrected the entire manuscript for language mistakes as suggested.

We have modified headings within the sections and now we hope that our manuscript is easier to follow.

Reviewer #02446114

We thank the reviewer for the commentary and appreciations.

Reviewer #00504335

We thank the reviewer for the commentary and for the suggestions.

Indeed the first author is only beginning her research career, and this is her's first review. However, she is a hard working scientist with a few publications in cancer and stem cell field (Dragu LD Researcher ID: I-3095-2015). Also, the other authors have a wide experience and relevant publications on this domain. (Thomson Reuters Researcher IDs: Mihaela Chivu-Economescu: B-4323-2011; Carmen C Diaconu: B-9119-2011; Laura G Necula: I-1668-2015).