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August 7, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11595-review.doc).

Title: Training Stem Cells for Treatment of Malignant Brain Tumors

Author: Shengwen Calvin Li; Mustafa H. Kabeer; Long T. Vu; Vic Keschrums; Hong Zhen Yin, Brent A. Dethlefs; Jiang F. Zhong; John H Weiss, William G. Loudon

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 11595 revision.

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

COMMENTS TO AUTHORS

Major issues: It is not quite clear that this is a review article. This should be made more clear in the beginning. Also, the title is misleading and not appropriate.

The article does not provide any data on how to train the stem cells to target tumor tissue more efficiently, rather it highlights the NEED to find ways of HOW to POTENTIALLY train them in future. The authors should therefore alter the title accordingly.

Response: We pointed out now – It is a review. We have clarified in revision about a need to “train” stem cells march toward tumors – We rethink that is a common term, which may convey our message – thus we would like to keep the word “training” in the title.

We reviewed the literature and pointed out that only a fraction number of stem cells are capable to migrating toward stem cells. That is the need to train stem cells to march toward tumors. We have provided data in Figures 5, 6, 7, 8, 9, showing we can train stem cells marching toward tumors in a uniform manner.

COMMENTS TO AUTHORS: It does not become evident why these strategies are "limited" to the treatment of pediatric brain tumors - this is an issue that regards brain tumors in general. So why focus on pediatric tumors?



Also, the authors do not address any pediatric brain tumor in detail, neither clinically, nor diagnostically.

Response: We agreed – Thank the reviewer for the insight – lack of information specifically for childhood cancer – even though medulloblastoma has been characterized recently by whole genome sequencing approach by both German and Canadian groups. We have incorporated the comment into the revision by removing those childhood cancer statements. In reality, we at Children’s Hospital treat only children patients and we have focused on childhood cancers.

COMMENTS TO AUTHORS: Also, the authors do not comment on recent molecular findings in brain tumors in general and in pediatric brain tumors specifically and their potential impact also on stem cell therapies (i.e. IDH1 mutations, H3F3A mutations in malignant pediatric gliomas, BRAF/fusion in pilocytic astrocytomas etc.). The authors should at least comment on that.

Response: We agreed. Thus, we have incorporated the new findings into a section entitled ‘genetic profiling.’

COMMENTS TO AUTHORS: Minor issues:

1. Typography should be changed to Arial or Times New Roman throughout the manuscript, as it is hard to read as it is now.

Response: We apologize for the inconvenience. We’ve changed from Papyrus typography to Times New Roman throughout the manuscript as you asked.

2. The authors should refrain from using military- derived vocabulary in an effort to illustrate their points of argument. Words like "intercontinental ballistic missile" are ethical questionable when we talk about life- saving strategies in the treatment of cancer. The authors should replace that image by a different more appropriate one. Also words like "army" should be avoided when we talk about therapies.

Response: We agreed. We have read documents and scientific publications using the military-derived vocabulary in an effort to illustrate the points of arguments to reaching out to the general public. For example, US President Richard Nixon used “War on cancer.” We read just now “A splicing magic bullet” by Luisa Vigevani and Juan Valcárcel. Science 8 August 2014: 624-625. (Drugs that modulate RNA splicing are potential therapeutics for spinal muscular atrophy [Also see Report by Naryshkin et al.]).

Nevertheless, we replaced the “intercontinental ballistic missile” with inter-organ movable vehicle as you advised.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Stem Cells*.

Sincerely,



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