

## **Response to reviewers' comments**

### **Title: Targeting head and neck tumoral stem cells: from biological aspects to therapeutic perspectives**

Dear reviewer,

Thank you for your insight and your constructive criticism on the above mentioned manuscript. Your comments and remarks have been taken into account in the finalization of our article. Responses to the referee comments are listed below, and appear in red color in the new version of the manuscript.

### **Reviewer 02928802**

#### **Major comments:**

*1. The abstract should be a summarization of the paper. However, the abstract in this article seems like an introduction of this paper. The abstract is poor designed. It is suggested to rewrite the abstract for clear understanding.*

Thank you for this suggestion. We entirely re-wrote the abstract in order to make it more clear.

“Radiotherapy is a cornerstone of anticancer treatment. However in spite of technical evolutions, important rates of failure and of toxicity are still reported. **Although numerous pre-clinical data have been published, we address the subject of radiotherapy-stem cells interaction from the clinical efficacy and toxicity perspective.** On one side, cancer stem cells (**CSCs**) have been recently evidenced in most of solid tumor primary locations and are thought to drive radio-resistance phenomena. **It is particularly suggested in glioblastoma, where CSCs were showed to be housed in the subventricular zone (SVZ). In recent retrospective studies, the radiation dose to SVZ was identified as an independent factor significantly influencing overall survival. On the other side, healthy tissue stem cells radio-destruction has been recently suggested to cause two of the most quality of life-impacting side effects of radiotherapy, namely memory disorders after brain radiotherapy, and xerostomia after head and neck radiotherapy. Recent publications studying the impact of a radiation dose decrease on healthy brain and salivary stem cells niches suggested significantly reduced long term toxicities. Stem cells comprehension should be a high priority for radiation oncologists, as this particular cell population seems able to widely modulate the efficacy/toxicity ratio of radiotherapy in real life patients.**”

2. The main structure of this paper only contains two sections: “Targeting CSC with radiation: Efficacy data” and “Sparing normal stem cells during radiotherapy: Toxicity data”. These two sections only discussed the advantages and disadvantages of targeting CSC with radiation. And it is difficult for the authors to get the points of this paper quickly. Therefore, more detailed contents and clear sections should be provided for brief understanding.

We thank the author for this suggestion. We added more sections and hope that the global understanding is now easier:

### 1. Targeting CSC with radiation: Efficacy data

*Clinical outcomes: the glioblastoma model*

*Properly imaging CSC through hypoxia: a necessary condition for an efficient radiotherapy?*

### 2. Sparing normal stem cells during radiotherapy: Toxicity data

*Clinical outcomes: the whole brain radiotherapy model*

*Clinical outcomes: the head and neck radiotherapy model*

3. There are numerous grammar errors in this article. The language must be rechecked! For example: Page 3, of “healty” tissue stem cells radiation-induced destruction in long term side effects of Page 5, CSC “are” defined by three main characteristics: they can initiate tumorigenesis and endlessly Page 7, NSC “were” showed to be physiologically housed in the subventricular zone (SVZ), .....

Thank you for this comment. The article has been spell-checked and grammar-checked another time by our native English speaker (AT Falk). We hope there are no mistakes anymore.

## **Reviewer 02446101**

### Major comments:

*Firstly, I don't think the abstract summarizes the whole manuscript well. An abstract should be a summary of a longer text, especially of an academic article. It is more like a introduction.*

We thank you for this comment. The abstract was entirely re-written accordingly to your suggestion (cf up above) to better reflect the manuscript content, rather than to introduce the subject.

*Secondly, there are several language mistakes. For example, the 'healthy' in the last line of page 3 was spelt wrongly as 'healty'. The language need to be rechecked.*

Thank you for this comment. The article has been spell-checked and grammar-checked another time by our native English speaker (AT Falk). We hope there are no mistakes anymore.

### **Reviewer 00504828**

#### *Major comments*

*1. Page 11, lines 5~8 “Thanks to the development of the intensity modulated rapiotherapy...”. I think it would be difficult for non-expert to follow exactly what IMRT is. I recommend inserting a short paragraph to introduce IMRT.*

We thank the reviewer for this suggestion. A short description of advantages of IMRT is now provided: “IMRT offers the possibility to spare areas that could not be spared with conventional radiotherapy indeed, thanks to highly conformal dose painting (Figure 2).”

And an explanatory figure (Figure 2) is provided.

*2. Introduction is excellent – however, I am disappointed a little bit that the authors do not discuss Wnt/?-catenin and Notch signaling later. I am just curious if there is any published research or clinical trials that examine the combination of Wnt/?-catenin or Notch signaling inhibitors and radiotherapy.*

We thank the reviewer for this comment. Yes, current phase 1 trials targeting Wnt/cathenin pathways are currently recruiting (that are summarized in “Jang et al. Cancer Research 2015”), but to our knowledge, nothing with radiotherapy.

*3. I am fine with this well-focused review discussing glioma and head and neck cancer. However – if the authors stick on these narrow topics – the current title does not reflect the contents well. I think the authors may consider revising the title. Otherwise, the review should be more comprehensive covering other cancers treated with radiotherapy.*

We totally understand this comment. However, the title of this invited manuscript was chosen and validated with the editor. We extensively reported all the results in the available literature and only the cancers we described are covered.

#### *Minor comments*

*1. There are several minor grammatical errors. I attach the file (PDF) with correction instead of typing each here (also yellow-highlighted). I may miss additional minor errors. The authors may want to carefully check the text again.*

We warmly thank the reviewer for his help, and corrected the manuscript accordingly.

**Reviewer 00503286**

*The paper "Targeting stem cells by radiation: from the biological angle to clinical aspects" should be published in World Journal of Stem Cells, after minor corrections with the editor. (I think: some figures or/and tables were welcome!)*

We thank the reviewer for this suggestion. Two figures have now been added.

Please, find enclosed the article modified according to your requirements. We hope that the changes that have been made will satisfy you.

Kind regards.