Dear editor,

Manuscript NO.: 46614

I thank you for your letter and comments concerning our manuscript. We very much appreciate the comments made by the reviewer, and we have addressed the raised issues. We have prepared a response to the reviewer's comments (below). Hereafter, you will find the revised text (the revised portions against reviewers' and editors' comments are denoted by red and blue fonts, respectively) of our manuscript attached.

We look forward to hearing from you concerning our manuscript.

On behalf of all the authors,

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Reviewer(s)' Comments to Author:

Reviewer 1:
Reviewer's code: 03947786

Comments to the Author
Comment: This mini review introduced a novel ischemia-induced stem cells-based therapy strategy for treating CNS diseases. Under the field of iNSPCs/iSCs derived from brain ischemic stroke, this paper proposed some hypotheses, mainly presented a lot of questions, such as the origin of iNSPCs? The relationship of brain pericytes and iNSPCs? The connection between iNSPCs and resident glia? The traits of brain multipotent stem cells (MSCs) or iNSPCs/iSCs? etc. Finally, they suggested two strategies of iNSPCs/iSCs application: exogenous iNSPCs/iSCs transplantation and endogenous iNSPCs/iSCs activation. However, there are much more problems about ischemia-induced stem cells need to be solved, for example whether they really exist, and what are the traits and potential mechanisms of iNSPCs/iSCs in brain.

Response to this comment: Thank you very much for the comment. Although the precise origin and traits of iNSPCs/iSCs remain unclear, our studies have shown that iNSPCs/iSCs, which likely originated from brain pericytes following ischemia (iPCs), were present within post-stroke areas of mouse and human brains. Similar to our previous studies, using a mouse model of cerebral infarction, other groups have shown that iPCs exhibit the potential to differentiate into multilineages (Gouveia, et al, Stem Cell Rep 9:1735–1744, 2017). This strongly indicates that iNSPCs/iSCs, which are presumably in part iPC derivatives, are indeed present within brains after stroke. We had added this description in the revised text. Moreover, we will continue the research regarding iNSPCs/iSCs and provide further evidence in our future studies.

Reviewer 2:
Reviewer's code: 03086928

Comments to the Author
The work by Nakagomi et al. is an extremely interesting work, well organized, fluent, logical and readable. This work summarized the most recent approaches in the field of neural regeneration, specifically in patients that have suffered a stroke and reflects the most recent

progresses in this field. Acceptance is recommended for the manuscript. However, there are some minor suggestions that, from this reviewer point of view, would improve the understanding of the manuscript for readers outside this very specific field.

Minor comments.

Comment 1: In the introduction the authors distinguish between mesenchymal stem cells and adipose-derived stem cells. Since adipose derived stem cells are as specific type of mesenchymal stem cells, these terms should be substituted by Bone marrow mesenchymal (BM-MSCs) stem cells and adipose tissue derived mesenchymal stem cells (AD-MSCs).

Response to 1: Thank you for the comment. In accordance with this reviewer's suggestion, we have corrected the aforementioned terms.

Comment 2: The authors state in the introduction that ¨lack of data (on whether the stem cell based therapies by NSPCs are clinically useful) may be due to the NSPCs being derived not from pathological but from normal conditions". The authors should explain the rationale of undergoing research in NSCPs in pathological conditions (iNSCPs) as an alternative of researching these cells in normal conditions (NSCPs).

Response to 2: Thank you for the comment. In accordance with this reviewer's suggestion, we have added the description in the revised text.

Comment 3: The authors mention the failure of a study using genetic mapping by the Cre-loxP system to demonstrate that pericytes (TBx18+) function as multipotent stem cells in vivo following mild injury. Is there any theory on why this method failed? Was it a question of homming, engraftment…? .The downsides of the Cre-LoxP approach should be mentioned briefly in the text, as it would help the reader to understand the context. A reference is not enough.

Response to 3: Thank you for the comment. In accordance with this reviewer's suggestion, we have added the description in the revised text.

Comment 4: As a general rule of thumb, words in latin (in vivo, in vitro) should appear in italics.

Response to 4: In accordance with this reviewer's suggestion, we have revised these terms in italic font.