Manuscript:

Title: Stem cell therapy for Alzheimer's disease

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We would like to thank all the reviewers for their explicit review and constructive comments. We have made all the changes as suggested, and incorporated them in the revised manuscript. Listed below are our point-by-point responses to their comments.

Response to Comments of Reviewer #1 (02445242):

Critique #1: *This is a concisely written article on the current status of stem cell therapy in Alzheimer's disease (AD). I had a few issues though, which I hope the authors could clarify. To begin with, could authors explain how their review adds to earlier ones, some of which appear to be quite recent (references 1-5 & 49). This is important because people may choose to read this review rather than the others, only if the current review has something new to add to the existing literature.*

Response: We are sorry we did not identify this clearly. We cited literatures inappropriately. We have now revised these references as suggested by the reviewer in **Introduction**.

Critique #2: *In the "Research progress in the pathogenesis of AD" - could the authors state a few lines on the debate on whether accumulation of tau proteins or of Aβ proteins is central to the pathogenesis of AD. Has this been settled either way & how does it impact the application of stem cell therapy to treat AD? This also has relevance for recent failures in medication trials for AD & could have an influence on stem cell therapy for AD in a similar way.*

Response: According to the reviewer，we have added some statements on whether accumulation of tau proteins or of Aβ proteins is central to the pathogenesis of AD，and the effects on the stem cell therapy for AD in **Research progress in the pathogenesis of AD** on page 8-9.

Critique #3: *In the section on "Mesenchymal stem cells" (page 9) the authors state that - " Previous studies on ucb-MSCs (mainly MSCs) have shown that ucb-MSCs*

can improve spatial learning and prevent memory decline." - In this section & some of the later sections it is not clear whether the authors are referring to animal or human studies. The references suggest that the studies being referred to are on murine models of AD, but it would be helpful if the authors could make this absolutely clear.

Response: We are sorry we did not identify this clearly. We have now described this sentence in detail as suggested by the reviewer in **Mesenchymal stem cells** and **Induced pluripotent stem cells** on page 11, and in **Neural stem cells** on page 13.

Critique #4*: The authors make certain statements about the current status of early diagnosis of AD. On pages 4-5 they state that - "Although cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers combined with some relatively new clinical standards can help diagnose alive patients, the diagnosis of AD requires post mortem assessment of brain tissue[4]." Again on page 18 they state that - " Due to the lack of effective biomarkers or reliable methods, early identification of AD with sufficient sensitivity is not feasible before symptoms appear, hindering early diagnosis." While this may be somewhat true, a flat statement such as this seems to discount much of the research on biomarkers to advance early diagnosis of AD. Perhaps the authors need to qualify these statements.*

Response: We have now qualified these statements as suggested by the reviewer in **Introduction** on page 5 and in **Discussion** on page 21.

Critique #5*: On page 18 the following is stated - "Conversely, in some studies, brain imaging showed that a few study participants did not have a trial treatment plan for amyloidosis, suggesting an urgent need for early detection technology. Given that the clinical trial lasted for several years, patients with dementia received several injections and went through some difficult follow-up procedures; some participants withdrew before the end of the trial, making it difficult to evaluate the results." It is not clear which trial or trials are the authors referring to. A clarification is required.*

Response: We have added trials clearly according to your suggestions in **Discussion** on page 21.

Critique #6*: One of the disadvantages of stem cell therapy appears to be the requirement for a neurosurgical procedure & immunosuppression. Could the authors comment on whether this is a problem with human trials with AD & how can it be overcome.*

Response: We have described disadvantages of stem cell therapy in detail according to your suggestions in **Future perspectives and challenges** on page

22-23.

Critique #7: *The main issue seems to be moving on to human trials. The authors have referred to the difficulties in conducting such trials in different parts of the manuscript. However, this issue has not been adequately elaborated or emphasized subsequently. For example, results from rodent models or from models using higher-order animals may not be sufficient to support the clinical use of stem cells in AD because of significant differences in neuronal function and anatomy in rodents and primates. Could this, perhaps, be more clearly stated.*

Response: We have adequately elaborated the issue of human trials according to your suggestions in **Future perspectives and challenges** on page 21.

Critique #8: *Moreover, could the authors provide some insights into specific issues relating to human trials in AD compared to clinical trials in other disorders such as Parkinson's disease or spinal cord injuries? It appears human trials in AD are at a more advanced stage than other neurological conditions. Could the authors clarify if this is indeed true?*

Response: We have added our statements on AD & PD clearly as suggested by the reviewer in **Clinical trials** on page 19-20.

Critique #9: *Finally, there has been a lot of discussion recently about the failure of medication trials for AD & subsequent withdrawal of industry support for research in this area. Many problems such as uncertainty about the amyloid hypothesis, differing objectives such as preventing progression from MCI to AD versus symptomatic treatment of established AD, methodological designs of the trials themselves have been mentioned. There is also the common misconception that stem cell therapy constitutes a cure for AD rather than being simply a treatment to halt decline or prevent progression. Could the authors discuss how these issues may impact stem cell therapy of AD?*

Response: We have now discussed these questions according to your suggestions in **Future perspectives and challenges** on page 23.

Response to Comments of Reviewer #2 (02519158):

Critique #1: *This is a very interesting piece of work which may be a valuable source of knowledge for all clinicians who in are interested in stem cell application in*

Alzheimer's disease treatment. The article is well designed and well written, clear and cogent. Therefore, I recommend this review for publication in World Journal of Stem Cells.

Response: Thanks for your review.