OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-19-00212
Title: Early active immunization with Aβ3-10-KLH vaccine reduces tau phosphorylation in the hippocampus and protects cognition of 3xTg-AD mice
Reviewer's Name: Alain Buisson
Reviewer's country: France
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COMMENTS TO AUTHORS

This question is certainly important for the scientific communauty working in the field of AD therapy. However this is not what this work is about, as the authors did not compare different timing of the immunization strategy. This point should be changed in the abstract and in the introduction. Overall, this work is investigating the beneficial influence of immunization at early stages of the disease. The technical approaches are well chosen and the results obtained interesting there are still questions to answer:

Major concerns:

Page 2: the sentence "Ab has been shown to promote tau hyperphosphorylation through increasing glycogen synthase kinase-3 activity" is too definitive. They are many different kinases that might be implicated in the abnormal phosphorylation of tau in AD.

The sentence"tau hyperphosphorylation can promote Ab aggregation" deserve a reference. To my knowledge, this is not true.
Ab plaques (soluble oligomers)? Why are the authors mixing together the terms plaques and soluble oligomers?

Page 3: a phase 1 study in AD? This sentence is confusing. Phase 1 are usually corresponding to the Testing of drug on healthy volunteers for safety. There might be some confusion here with phase II.

Page 5: The sentence "The formation of Ab and tau is age and region dependent" deserves a reference and some re-writing to be understandable.
"At one month of age at which there was no Ab deposit": instead of deposit the authors should use plaque.
At the bottom of the page 5: "whther" should be corrected.
Page 6: "anti-oligomer antibody" how do the authors know which species of Ab the antibody is recognizing? This point should be clarified

Page 12: The figure 1 that is corresponding to this result section is not presenting the same value in the graph (118.808 vs 40). There is obviously a major mistake here.

Page 13: "no AT8 and AT 180 and HT-7 immunoreactive tau was detected". This result is surprising as there is certainly some tau in the mice brain tissue. How do the authors explain this result?

Page 15: "inhibit intracellular and extracellular Ab production". Do the authors have any proof of this reduction?
What do the authors mean by "the clearance of tau by Ab"?

Page 16: "p-tau expression" is not the adequate vocabulary for phosphorylation.
"Ab to aggravate nerve injury"…what do the authors means by "nerve injury"?

Figure 1 : how many samples have been used for this quantification? The number of samples used for the quantification should be indicated in the figure legend.