Author’s response to reviews

Title: ApoE4: an emerging therapeutic target for Alzheimer’s disease

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Author’s response to reviews:

response to editorial comments:

1. Author Amos Korczyn still needs to confirm authorship for this manuscript, an email in this regard

An email was sent to the journal in this regard.

2. Please add a full list of declarations to the manuscript.

An email was sent to the journal in this regard.

3. Please add a list of abbreviations.

The requested list of abbreviation was added to the text and is also attached as a separate file.

4. Please separate the figures and upload them as individual files.

The figures have been uploaded in a separate file as requested.

Response to reviewer #1: G. William Rebeck. We thank Dr. Rebeck for his compliments and for the valuable comments.

1. In the portion of Section 2 devoted to Aβ interactions, there should be more of the original citations regarding the effects of ApoE genotype and Aβ aggregation, deposition and clearance. It is a large research area.
The requested references were added to the manuscript. See section (2.1) on page 6.

2. The portion related to tau phosphorylation could focus more on the relationship between Tau hyperphosphorylation and ApoE genotype (most of this section is directed to more general aspects of tau in AD).

As recommended, additional information regarding the mechanisms underlying the relationship between tau hyperphosphorylation and apoE genotype and how they differentially regulate tau phosphorylation was added to the revised manuscript (see section 2.2 on page 7).

3. In the neuroinflammation portion, there could be consideration of interactions between ApoE genotype and NSAID treatment in humans.

The requested additional information regarding the interaction between apoE genotype and NSAID treatment was added to the manuscript (see section 2.6 on page 9).

4. In this section, there is discussion of ApoE genotype and miRNA146a levels is difficult to follow. The relevant section (2.6 on page 9) has been clarified.

5. In the vascular integrity/function portion, there could be a reiteration of the effects of ApoE genotype on the integrity of the blood brain barrier. There are mentions of this effect in other parts of the review, but it is logical to include it here.

AS recommended, the effects of the apoE genotypes of the integrity and functionality of the BBB are now discussed in the revised manuscript. (see section 2.7 page 20).

6. At the end of Section 2, it would be interesting to include a paragraph on how the information on different mechanisms may integrate. Figure 1 would be more interesting if the upstream or better-supported effects of ApoE were highlighted somehow.

The requested information regarding the links between apoE to AD and the limitations of these studies has now been added to the manuscript (see page 11).

7. In the ApoE receptor-related approach, the authors conclude that this is not a promising venue for therapeutic target. It would be more useful then to reduce this section and perhaps expand the "ApoE mimetics" section. There is a rich and comprehensive body of literature regarding ApoE mimetics.

The discussion of apoE mimetics and their mechanism of action have been expanded on as requested and are presented in section (3.3.iii) on pages 16.
8. The subtitle related to ApoE2 should be changed to reflect the type of therapy that is required to deliver ApoE2, since that is the therapeutic approach proposed here.

The subtitle was changed to: "ApoE2-focused therapeutic approach" as recommended (see section 3.4 page 16)

9. ApoE4 is mentioned as a potential transcription factor, but there is no indication of how that could be translated into a potential therapeutic target for AD. This section could be moved or eliminated.

Recent findings point at the possibility that apoE4 has transcription factor activity. We therefore opted to leave this information in the manuscript and to expand the discussion of the therapeutic potential of this findings. (See section 3.7 on page 17).

10. Finally, as a general comment, there are a few places where the sentences went for 5-6 lines, and those sentences are difficult to follow.

We edited the manuscript and shortened the sentences in several places. (eg see line 9-11 page 3; line 24-27 page 6; line 30-34 page 8; line 25-28 page 10)

Response to reviewer #2: Takahisa Kanekiyo: we thank Dr. Takahisa Kanekiyo for his helpful comments which were addressed as follows:

1. Recent findings have suggested that ApoE4 is predominantly involved in Aβ aggregation stage in accelerating amyloid pathology (DOI: 10.1016/j.neuron.2017.11.014; DOI: 10.1016/j.neuron.2017.11.013), which should be discussed. For ApoE4-targeted therapy in AD, the timing of treatment might be critical to be effective.

An additional section was added as the end of part 2 (section2.10 plus additional refs in section 2.1.page 6) which discuss the contribution of Aβ/ apoE4 interactions to AD pathology.

2. APOE4’s effects may be different depending on sex, which should be considered in designing ApoE4-targeted therapy.

The contribution of gender and sex-related issues to the pathological effects of apoE4 in AD is now discussed as suggested (See section 2.10).

3. While ApoE4 is likely associated with the risk for DLB and synucleinopathy, there is no discussion of this point. The contribution of APOE genotype to tauopathy should be also discussed more comprehensively.
The link between DLB and apoE4 and between apoE4 and taupathies has now been addressed as recommended. See section 1.2.

4. There is a controversy regarding whether ApoE4 really functions as a transcription factor. Authors need to describe this section with more balanced view.

As requested the possible function of spoE4 as a transcription factor is now discussed with a more balanced view. (see 3.7 on page 17).

5. CRISPR is a strong tool to investigate ApoE4 function in vitro and to generate animal models. However, there is a substantial technical limitation to edit APOE gene using current CRISPR techniques in adult human.

The current technical limitations in applying CRISPR in vivo to animal models and to humans have been expanded on and are now discussed in section 3.1 on page 12.

6. Whenever ApoE genes are indicated, all letters should be italicized in upper-case.

APOE is now used consistently for the gene whereas the corresponding protein is denoted by apoE.

7. To be an unbiased review, only published studies should be cited. Thus, the last sentence in page 13 should be removed.

The article addressed has now been accepted for publication and is cited accordingly.

Response to reviewer #3: Huaxi Xu We thank Dr. Huaxi Xu for his compliments and valuable comments.

1. The conclusion focuses on the second part of the review, regarding experimental approaches for targeting ApoE4, but does not summarize the pathological effects discussed in the first section of the review. A more effective conclusion would address or summarize the most relevant effects of ApoE4 as discussed in sections 1.1 through 2.8.

The requested conclusion was added at the end of section 2 in a subsection 2.10.