Manuscript 516 review response

**A mouse model of naturally occurring age-related cognitive impairment**

We thank the reviewers for their time and effort. We have addressed their comments and suggestions in the following points.

**Reviewer 1.**

1. The abstract should be amended by some numerical values.

*Response. We respectfully disagree with the need for numerical values in the abstract for this type of manuscript. The manuscript is not a scientific report, it is a description of an animal model and therefore designed to be a summary overview of the model.*

*2.* Gender and weight of animals and ethical approval details are needed.

*Response. We agree and thank the reviewer for pointing this out. We have added the gender (males) of the four age groups of mice in Figure 1. We had already described that both sexes were included in the 20-month-old mice in Figures 2 and 3*. *We respectfully disagree with the need to provide body weights as the mice were present only a short period of time and the lack of any differences in body weights within each gender group would provide no added value to the manuscript. We do thank the reviewer for pointing out our failure to add an ethical use and approval statement, which has now been added in the text in red font.*

3. Were animals naïve or trained before behavior testing?

*Response. We are confused by this question. There was no training of mice before behavioral testing. The reviewer may have been confused by the term “acclimation”. This simply describes the waiting period from the time they arrive at our facility from being shipped to us, until they recover from the shipping stress and acclimate to the new environment and return to physiological homeostasis so we can do the behavior testing.*

4. Figure 3 should contain the statistical analysis procedure.

*Response. Thank you for pointing this out. It has been added.*

**Reviewer 2.**

1. Each mouse was acclimated for 3 weeks. Did the authors consider the time during analysis?

*Response. We are confused by this question. The 3-week acclimation period was to allow the mice to recover from the stress of shipping and introduction to a new housing environment. We have been working with mice for many years and know that reliable data cannot be obtained from mice under these conditions until they have returned to normal physiological homeostasis. Therefore, no testing was done on any mouse until three weeks after their arrival at our facility.*

2. Figure 1 performance of 12 and 20 month old mice is confusing.

*Response. Figure 1 represents real data with no legend errors or incorrect descriptions. The difference between 12 and 20 month old mice is not as robust, but still represents a trend such that with the additional ages, the evidence that cognitive impairment increases with increasing age is very clear.*

3. Why choose neuroinflammation?

*Response. The manuscript describes an animal model. It is not a scientific report. Therefore, we include neuroinflammation as a robust prototype observation to illustrate the power of the model. We do have additional data on other pathways, which will be included in a future manuscript in preparation.*

4. Anomalies in rotarod and grip performance could be due to motor nerve dysfunction. Please include an explanation.

*Response. We respectfully disagree with the suggestion that there are anomalies in grip and rotarod performance data. We have performed these tests in mice for many years and have extensive experience interpreting the data and including this type of data in peer reviewed publications. The data show that there are no differences in physical performance between ARCI-resistant mice and ARCI-sensitive mice thereby providing evidence that the behavioral tests represent cognitive ability and not musculoskeletal dysfunction. The sex differences within each group simply represent different physical abilities between males and females for the respective test.*