**Main R21 Application Feedback**

The below comments are also reflected in some of the comments in the provided documents, but are also provided here for clarity to emphasize what I see as some of the potentially largest points for revising the grant:

1. Aim 2 doesn’t really fit within the framework of your grant as written and feels disconnected. Obviously it is conceptually directly relevant to murine models of AD, but most of your text in the Innovation/Significance/ Background sections fails to set the stage for Aim 2 or to explain its importance. Therefore I suggest either removing this Aim to expand Aims 1+3, which are more related to the call for funding, incorporate it into Aim 1, or expand the background to better set the stage for its inclusion in your grant.
2. You will need to provide details for each aim on your expected outcomes, possible pitfalls, and alternative approaches. Given the variability of animal AD models, I would expect the discussion of alternative experimental systems to be important in this setting.
3. There is no need for a stand-alone Methods section at the end of the grant. It should end after Aim 3. I have revised the text for language and marked sections that can be entirely deleted. For the remainder, incorporate it into the corresponding Aims in the Research Strategy section.
4. Do mouse miRNAs always have human analogs? This is not something I am an expert in, but your grant reviewers will be so this is something important to take into consideration when writing your grant and suggesting your results are readily translatable, given that the NIH is ultimately focused on treating human disease.