MODEL-AD: Late-Onset Alzheimer’s Disease Models

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Abstract

Alzheimer’s disease (AD) is the most common form of dementia, with no effective preventative strategies or treatments. A major challenge is determining the role of selective preventive and therapeutic targets. The MODEL-AD consortium aims to generate and develop new animal models of LOAD with the goal of identifying biomarkers and developing therapeutics to prevent AD. The Model Organism Development and Evaluation Center (MODEC) at the Jackson Laboratory has established an Alzheimer’s Disease Modeling Project (DMP) to develop new mouse models. The MODEC aims to identify and prioritize novel LOAD variants, analyze data generated by high capacity and deep phenotyping pipelines, create analytical pipelines for human-mouse phenotyping integrations, and develop preclinical testing models and best practices for data dissemination and analytical protocol use.

Biometric and Data Management Core BDMC

Aim 1: To maximize human datasets to identify novel and positive variants, genes, and biomarkers for AD.

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Disease Modeling Project DMP

Aim 2: To generate and characterize new mouse models of LOAD.

Model Creation

Over the period of this grant the MODEL-AD consortium aims to generate at least 50 new mouse models of LOAD. In phase 1, 20 models will be characterized at a high capacity level, with the most promising models being further phenotyped in the deep phenotyping pipeline. All studies will use male and female mice to determine the variation that may occur due to sex.

Phenotyping Pipelines

To develop effective testing pipelines, familial AD models (5xFAD, T652A, and 3xTg) will be used to determine the most informative measure. To further validate this pipeline, our newly developed non-human primate (THY1-TgR47H) model will be subject to the same testing paradigm as the familial models. This will enable us to ensure robust and rigorous results, along with comparing data generated at multiple locations on the same strain.

Primary screening phenotyping will determine the initial perturbations in these new strains. These strains with promising LOAD relevant phenotypes will be moved on to the deep-phenotyping phase of characterization. Deep-phenotyping will include functional studies of memory/cognition, but also genomic/RNAseq, blood and CSF biomarkers, and in vivo imaging. Some strains will be assessed at multiple sites using standardized protocols to ensure reproducibility. Models developed at UCI will undergo the same testing paradigm as IU/JAX to further corroborate data generated at IU/JAX.

Conclusion

The goal of the MODEL-AD program is to develop and distribute new animal models of LOAD that will serve as predictive models in preclinical screening. All protocols, data, and best practices for preclinical model use will be made freely available. All assays will be made available through the JAX mouse repository, with no legal restrictions imposed by the MODEL-AD program.

Further Information

• MODEL-AD: www.model-adt.org
• AMP-AD Knowledge Portal: http://www.exeprize.org/ampad
• JAX models: https://www.jax.org/resources
• AlzForum research models: http://www.alzforum.org/research

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