MODELS OF LATE ONSET ALZHEIMER’S DISEASE: THE MODEL-AD CONSORTIUM

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Abstract
Objectives: The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) Center has been established as a consortium consisting of Indiana University, The Jackson Laboratory, University of California-Irvine and Sage Bionetworks to create new animal models of LOAD with the end goal of identifying biomarkers and developing therapeutics to prevent AD.

Methods: The Bioinformatics and Data Management Core (BDMC) prioritizes novel sequence variants, creating analytical pipelines for human-mouse phenotype comparisons, and analyzing phenotypic data. The Disease Modeling Project (DMP) creates new mouse models based on variants identified by the BDMC. New mouse models are being phenotypically characterized using functional assays, neurodegeneration, amyloid and tau pathology, transcriptional and metabolic profiling, and in vivo imaging. The Preclinical Testing Core (PTC) evaluates novel compounds in new models with an AD-like phenotype based on a tertiary screening pipeline with predetermined go/no go criteria. These criteria include exposure levels in target tissues, target engagement, disease modifying effect, and in vivo functional activity and therapeutic index.

Results: The Center goals are: to identify and prioritize novel genetic variants, genes and biomarkers from AD patient data; to generate and validate new animal models based on LOAD variants; and to utilize these novel models in a preclinical testing paradigm. The APOE4/Trem2 model as well as a humanized Aβ mouse will serve as standard backgrounds as additional LOAD genetic variants are introduced at IU/JAX/UCI.

IU/JAX and UCI Organizational Structure

The MODEL-AD consortium consisting of a Center at Indiana University, The Jackson Laboratory, and Sage Bionetworks and a Center at the University of California Irvine has been established by the National Institute on Aging (NIH).

- Develop the next generation of in vivo AD models based on human data
- Institute a standardized and rigorous process for characterization of animal model
- Align the pathophysiological features of AD models with corresponding stages of clinical disease using translatable biomarkers
- Establish guidelines for rigorous preclinical testing in animal models
- Ensure rapid availability of animal models, protocols and validation data to all researchers for preclinical drug development

Model and Data Dissemination Pipeline

Preclinical Testing Core PTC

AIM: To validate the next generation of mouse models of LOAD and develop a best practice preclinical testing pipeline.

The PTC aims to establish best practice pipelines for novel compound testing in animal models for LOAD. To develop the pipeline, compounds that have been (BACE inhibitor, Verubecestat), or are being evaluated (Levetiracetam), in clinical trials will be used with a familial model of AD (5xFAD). Pharmacokinetic (PK)/dynamic (PD) studies will be carried out in males and females to determine sex specific dosing differences, whether the compound is penetrant, and the efficacy of the compound.

Available Mouse Models

IU/JAX and UCI Venn Diagram

Disease Modeling Project DMP

AIM: To generate and characterize the next generation of mouse models for LOAD.

Model Production

Over the period of this grant the MODEL-AD consortium aims to generate at least 50 new mouse models for LOAD. Of these, 24 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 assess the variation that may occur due to sex.

Phenotyping Pipelines

To develop effective testing pipelines, familial AD models (5xFAD, hTau, and 3×Tg) will be used to determine the most informative measure. To further validate this pipeline, our newly developed APOE4/Trem2 model strain 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 generate at multiple institutions on the same strains of mice.

Primary high capacity phenotyping will determine the initial perturbations in these new strains. Those strains with promising LOAD relevant phenotypes will be moved onto the deep phenotyping phase of characterization. Deep phenotyping will include functional studies (behavior and electrophysiology) of memory/cognition, but also genomic/RNA-seq data, 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 experimental reproducibility.

FURTHER INFORMATION
MODEL AD: modelad.org
AMP-AD knowledge portal: ampadportal.org
AlzForum research models: alzforum.org/research-models

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