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

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MODEL-AD
MODEL ORGANISM DEVELOPMENT AND EVALUATION FOR LATE-ONSET ALZHEIMER'S DISEASE

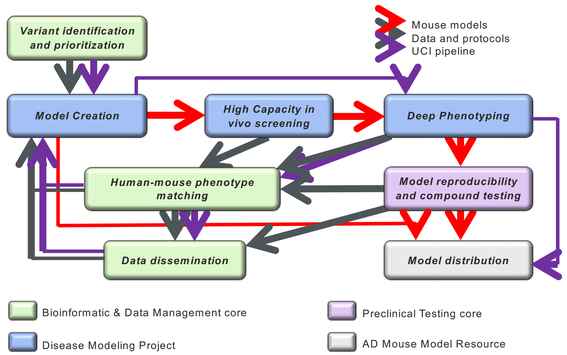
Abstract

Alzheimer's disease (AD) is the most common form of dementia, with no effective preventative strategies or treatments. A major obstacle when designing therapeutics to treat AD is the lack of predictive animal models in preclinical testing trials. One reason for this may be that existing models are based on familial mutations, which accounts for only 2-5% of all cases, while most AD cases are non-familial late-onset AD (LOAD). 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.

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. *APOE4* and *Trem2* alleles are the strongest genetic risk factors for LOAD; as such we have created a novel model expressing both human *APOE4* and the R47H allele of *Trem2*. This is 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. All data will be made available through the Sage-Synapse portal.

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 these LOAD variants; and to utilize these novel models in a preclinical testing paradigm. The *APOE4/Trem2* model as well as a humanized Aß mouse will serve as standard backgrounds as additional LOAD genetic variants are introduced at IU/JAX/ UCI
Conclusions: All models, protocols, and data sets will be made widely available. For more information see www.model-ad.org.

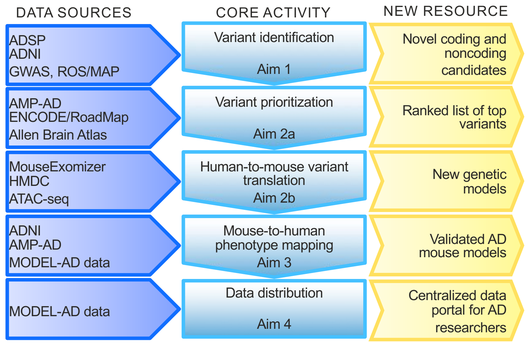
Model and Data Dissemination Pipeline



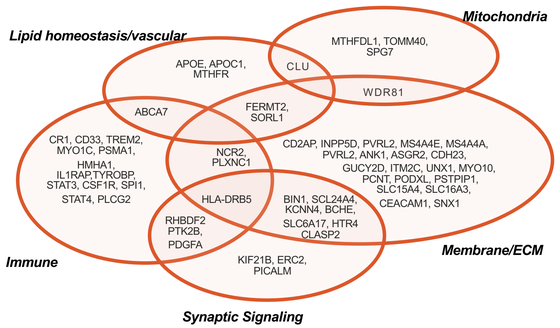
Bioinformatic and Data Management Core *BDMC*

AIM: To maximize human datasets to identify novel and putative variants, genes, and biomarkers for AD.

The BDMC 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 alignments, integrate external datasets for newly developed models, and present best practices for data analysis and preclinical model use.



Variant Prioritization



Disease Modeling Project *DMP*

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

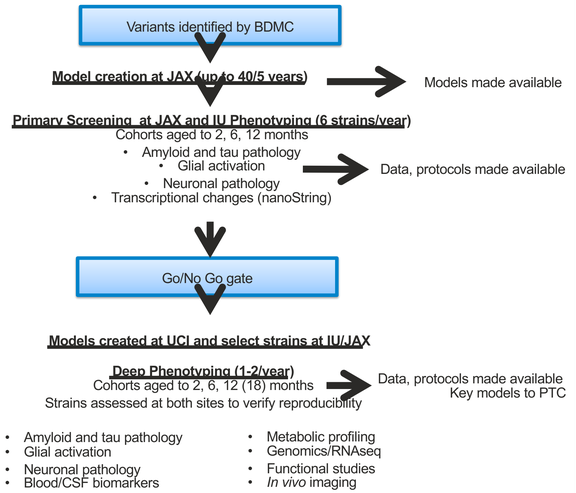
Model Creation

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 3xTg) will be used to determine the most informative measure. To further validate this pipeline, our newly developed APOE4/Trem2^{R47H} 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.

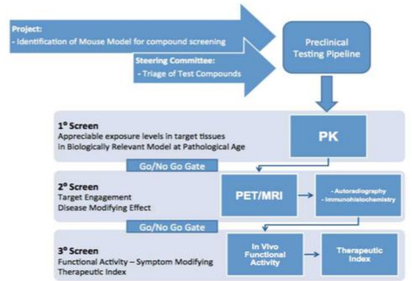
Primary screening phenotyping will determine the initial perturbations in these new strains. Those strains with promising LOAD relevant phenotypes will be moved onto the deep phenotyping phase of characterization. Deep phenotyping will include functional studies of memory/cognition, but also genomic/RNA-seq 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.



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). Pharmaco-kinetic (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.



Various, predetermined go/no-go criteria must be met before moving to the next phase of preclinical testing. Only models that have been validated by the DMP to have LOAD relevant endophenotypes will be selected to enter the primary screening phase of the PTC.

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 models will be made available from the JAX mouse repository, with no legal restrictions imposed by the MODEL-AD program.

Further Information

- MODEL AD: www.modelad.org
- AMP-AD Knowledge Portal: http://www.synapse.org/ampad
- JAX AD models: https://www.jax.org/alzheimers
- AlzForum research models: http://www.alzforum.org/research-models

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