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

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MODEL-AD

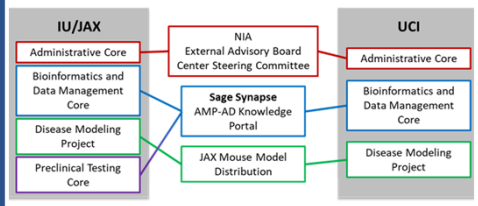
Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease

ABSTRACT

Alzheimer's disease (AD) is an irreversible, progressive brain disorder that slowly destroys memory and cognition, and eventually the ability to carry out the simplest tasks. In most people with Alzheimer's, symptoms first appear in their mid-60s. Estimates vary, but data suggest that more than 5 million Americans may have AD. Most of diagnosed cases (>95%) are late-onset AD (LOAD). One of the obstacles to developing compounds to treat AD may be that models currently used for preclinical testing are based on familial mutations, which account for less than 5% of all AD cases. 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 with the purpose of generating animal models of LOAD that can be used to develop therapeutics to prevent AD. Therefore, MODEL-AD aims to: identify and prioritize novel genetic variants, genes and biomarkers from AD patient data; generate and validate new animal models based on LOAD variants; and utilize these novel models in a preclinical testing paradigm.

The *APOE4/Trem2* model as well as a humanized Aß mouse are being considered as standard backgrounds as additional LOAD genetic variants are introduced at IU/JAX/ UCI.
Data from these models include: functional assays, neuropathology, amyloid and tau pathology, transcriptional and metabolic profiling, and *in vivo* imaging. All data will be made available through the Sage-Synapse portal.

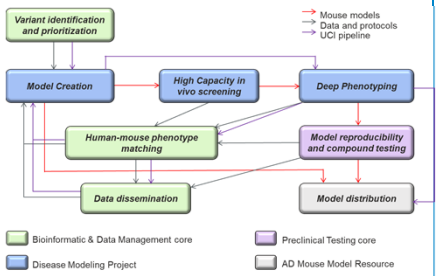
IU/JAX and UCI ORGANIZATIONAL STRUCTURE



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 to:

- Develop the next generation of *in vivo* AD models based on human data
- Institute a standardized and rigorous process for characterization of animal models
- 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

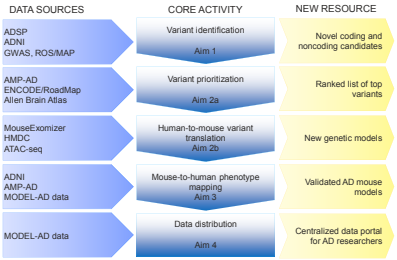
Model and Data Dissemination Pipeline



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.



Available Mouse Models

Common name	Genetic background	Strain Nomenclature	Availability	JAX #	Source
Familial AD models					
5XFAD	B6J	B6.Cg-Tg(APPSwFlLon,PSEN1*M146L*L286V)6799Vas/Mmjax	live	8730	Bob Vassar
APP/PS1	B6J	B6.Cg-Tg(APPswe,PSEN1dE9)85Dbo/Mmj	live	5864	Dave Borchelt
3XTg-AD	mixed B6; 129	B6;129-Tg(APPSwe,tauP301L)1Lfa $Psen1^{tm1Mpm}$/Mmjax	live	4807	Frank Laferla
3XTg-AD	B6J	B6.Cg-Tg(APPSwe,tauP301L)1Lfa $Psen1^{tm1Mpm}$/J	*Jan '19	8880	Frank Laferla
hTau	B6J	B6.Cg-$Mapt^{tm1(EGFP)Klt}$Tg(MAPTBc4dev)1/J	live	5491	Peter Davies
Late-onset AD-related models					
APOE models					
APOE4/Trem2* R47H	B6J	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$$Trem2^{tm1.1(R47H)Adiuj}$/J	live	28709	MODEL-AD
APOE4 KI	B6J	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$/J	live	27894	MODEL-AD
APOE3 KI	B6J	B6(SJL)-$Apoe^{tm1.1(APOE*3)Adiuj}$/J	live	29018	MODEL-AD
APOE2 KI	B6J	B6(SJL)-$Apoe^{tm1.1(APOE*2)Adiuj}$/J	*Feb '19	29017	MODEL-AD
APP models					
hAbeta-loxP-KI	mixed B6J; B6N	B6(SJL)-$App^{tm1.1(hAbeta)Adiuj}$	*March '19	30898	MODEL-AD
hAbeta-loxP-KI	B6NJ	B6N(CB)-$App^{tm1.1(hAbeta)Adiuj}$/J	tbd	32013	MODEL-AD
hAbeta KI	B6J-APOE4/Trem2*R47H	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$$App^{tm1.1(hAbeta)Adiuj}$ $Trem2^{tm1.1(R47H)Adiuj}$/J	*Feb '19	30070	MODEL-AD
App KO	B6J-APOE4/Trem2*R47H	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$$App^{tm1.1(KO)Adiuj}$ $Trem2^{tm1.1(R47H)Adiuj}$/J	cryo	31722	MODEL-AD
Trem2 models					
Trem2*R47H	B6J	C57BL/6J-$Trem2^{tm1.1(R47H)Adiuj}$/J	live	27918	MODEL-AD
Trem2*R47HC	B6J	C57BL/6J-$Trem2^{tm1.2(R47HC)Adiuj}$/J	cryo	29725	MODEL-AD
Trem2 KO	B6J	C57BL/6J-$Trem2^{tm1.1(KO)Adiuj}$/J	live	27197	MODEL-AD
floxed Trem2	B6J	B6(CB)-$Trem2^{tm1.1(R47HFL)Adiuj}$/J(Adiuj)	live	29853	MODEL-AD
AD GWAS LOAD variant models					
Abca7*V1527G SNP	B6J-APOE4/Trem2*R47H	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$$Abca7^{tm4.1Adiuj}$ $Trem2^{tm1.1(R47H)Adiuj}$/J	*Jan '19	30283	MODEL-AD
Abca7 KO	B6J-APOE4/Trem2*R47H	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$$Abca7^{tm1.1(KO)Adiuj}$ $Trem2^{tm1.1(R47H)Adiuj}$/J	*Jan '19	30320	MODEL-AD
Cescam1 KO	B6J-APOE4/Trem2*R47H	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$$Cexcam1^{tm1.1Adiuj}$ $Trem2^{tm1.1(R47H)Adiuj}$/J	*Jan '19	30673	MODEL-AD
Clnp2 I163F SNP	B6J-APOE4/Trem2*R47H	B6(SJL)-$Apoe^{tm1.1(APOE*4)Adiuj}$$Clnp2^{tm1.1(I163F)Adiuj}$ $Trem2^{tm1.1(R47H)Adiuj}$/J	2019	31944	MODEL-AD

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

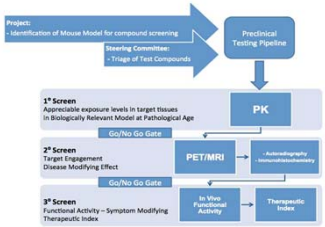
To develop effective testing pipelines, familial AD models (5xFAD, hTau, and 3xTg) will be used to determine the most informative measure. To further validate this pipeline, our newly developed APOE4/Trem2^{R47H} strain will be subject to the same testing paradigm as the familial models. This will enable us to ensure robust and rigorous results, along with comparing data generate at multiple institutions on the same strains of mice.

Primary 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.

Preclinical Testing Core PTC

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

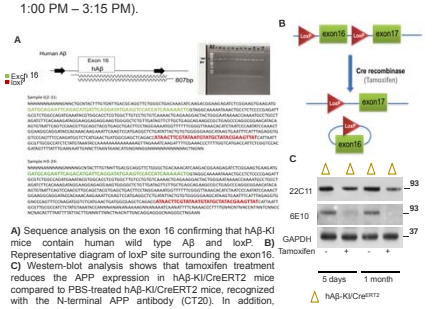
The PTC aims to establish best practice pipelines for novel compound testing in animal models for LOAD. To develop the pipeline, compounds that have been (BACE inhibitor, Verubecestat), or are being evaluated (Levetiracetam), in clinical trials will be used with a familial model of AD (5xFAD). Pharmaco-kinetic (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.

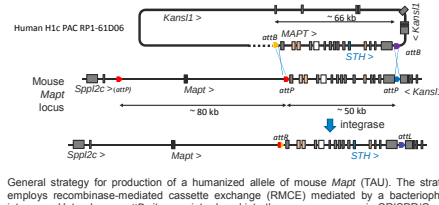
Humanized Aβ and Tau models

The generated knock-in mice expressing human wildtype Aβ that show age dependent amyloid accumulation, cognitive and electrophysiological deficits, and altered metabolic and neuroplasticity gene expression. This model may serve as a basis to study sporadic AD and lead to better translational concordance, which represents a critical new direction for the field. For further information please visit poster #467.02 and nanosymposium 713.04 (Wednesday, Nov 7, 1:00 PM – 3:15 PM).



A) Sequence analysis on the exon 16 confirming that hAβ-KI mice contain human wild type Aβ and loxP. **B)** Representative diagram of loxP site surrounding the exon16. **C)** Western-blot analysis shows that tamoxifen treatment reduces the APP expression in hAβ-KI/CreERT2 mice compared to PBS-treated hAβ-KI/CreERT2 mice, recognized with the N-terminal APP antibody (CT20). In addition, absence of signal is observed by using 6E10 antibody.

hTau-KI mice - humanization of mouse *Mapt* via RMCE



General strategy for production of a humanized allele of mouse *Mapt* (TAU). The strategy employs recombinase-mediated cassette exchange (RMCE) mediated by a bacteriophage integrase. Heterologous *attP* sites are introduced into the mouse genome via CRISPR/Cas9 in the indicated locations, and corresponding *attB* sites are introduced into a H1c haplotype PAC clone using recombineering in *E.coli*. The RMCE is mediated by injecting fertilized oocytes from a mouse strain that contains the appropriate *attP* landing-pad sites with the recombineered PAC clone along with mRNA encoding the integrase.

CONCLUSIONS

- All models, protocols, and data sets will be made widely available to researchers. We seek input and collaborations from research and pharma/biotech communities. For more information see www.model-ad.org.

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

ACKNOWLEDGEMENT

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NIH National Institute on Aging