Model Organism Development and Evaluation for Late-onset Alzheimer’s Disease (MODEL-AD) Consortium

Translational Infrastructure for Next-Gen Animal Models Development and Rigorous Preclinical Efficacy Testing: Overview of MODEL-AD Capabilities

Bruce Lamb  Frank M. LaFerla
Alzheimer’s Disease Is Defined by Distinctive Brain Pathology

✦ **Senile Plaques**
  ✓ Extracellular Deposition of Fibrillar β-Amyloid (Aβ) Peptide

✦ **Neurofibrillary Tangles (NFTs)**
  ✓ Intracellular Accumulation of Hyperphosphorylated MAPT Protein
  ✓ Also Observed in Other Neurodegenerative Diseases (FTDP, PSP, etc.)
Alzheimer’s Disease Genetics

AD
- Familial
  - Trisomy 21
    - Early-Onset (30s-50s)
  - APP Dup.
    - Late-Onset (60s-70s)
    - Sporadic (80s)

Genes/Loci
- APOE (HC19)
- ????
- APP (HC21)
- PSEN1 (HC14)
- PSEN2 (HC1)
- ????
Alzheimer’s Disease Mouse Models: Aβ Deposition

5xFAD
(Familial Alzheimer’s Disease)

APPSS1

radde et al., embo rep., 7:940-946, 2006
Alzheimer’s Disease Mouse Models: Tau Pathology

Therapies Developed in Mouse Models of AD

- Anti-Amyloid Therapies
  - Antibodies
  - Secretase Inhibitors
  - Aggregation Inhibitors

- Anti-Tau Therapies
  - Antibodies
  - Kinase Inhibitors
  - Aggregation Inhibitors

99.6% fail on clinical trials

Cummings et al., 2014
Reasons for Clinical Trials Failure?

01. Stage of Disease Targeted (Current Phase III Clinical Trials)

02. Mechanism of Delivery

03. Suitability of the Patient Population

04. Effective Target Engagement; Off-Target Effects; Suitability of the Target

05. Face and Construct Validity of the Animal Models
Concerns with Existing Animal Models

Models Do Not Develop Robust Neurodegeneration
Largely Focused on Early-Onset AD Mechanisms
Appropriate Species?
Reproducibility of Findings in Models and Relating to Human-Relevant Biomarkers
Difficulties in Relating Behavioral Deficits Observed in Mouse Models to Human AD
Many Models Generated/Maintained on Hybrid Genetic Backgrounds
Toxic Effects of Overexpression of Transgenes
Legal Restrictions for Some Models
Recommendations from 2015 AD Summit

- Develop the next generation of *in vivo* models based on human data to explore Alzheimer’s and related dementia
- Establish a standardized and rigorous process for the development and characterization of animal models, and ensuring their maximal and rapid availability to all researchers for preclinical drug development
- Align the pathophysiological features of AD animal models with the corresponding stages of clinical disease using translatable biomarkers
- Establish guidelines for rigorous preclinical testing in animal models and reporting of both positive and negative findings

NIA Funding Initiative RFA AG16-04

**MODEL-AD Consortium**

Model Organism Development and Evaluation for Late-onset Alzheimer’s Disease

U54 AG054345 (IU/JAX), U54 AG054349 (UCI)

Expand animal model resources for basic research and preclinical testing of candidate therapeutics with 50 new mouse models of AD and AD pathology.
MODEL-AD Consortium

IU/JAX
- Administrative Core
- Bioinformatics and Data Management Core
- Disease Modeling Project
- Preclinical Testing Core

U54 AG054345

NIA
- External Advisory Board Center Steering Committee

Sage Synapse
- AMP-AD Knowledge Portal

JAX Mouse Model Distribution

UCI
- Administrative Core
- Bioinformatics and Data Management Core
- Disease Modeling Project

U54 AG054349

MODEL-AD
INFORMATION ON ORGANIZATION/DEPARTMENT/PROGRAM FOR LATE-ONSET ALZHEIMER'S DISEASE
INDIANA UNIVERSITY
The Jackson Laboratory
University of California, Irvine
Sage
Overall MODEL-AD Goals

- Prioritize LOAD variants for animal modeling
- Create new mouse models with CRISPR (piloting rat models)
- High-capacity screening of all models, deep phenotyping of promising models
- Alignment of mouse and human phenotypes (neuropath, ’omics, imaging)
- Preclinical testing of the most promising models and therapeutics
- Broad, unrestricted distribution of all data and models
Leveraging the AD Data Universe

MODEL-AD

Genetics
case/control, imaging, ‘omics

‘Omics
transcriptomes, proteomes, metabolomes
brain, serum, CSF

Imaging
brain MRI, PET

Cognition
MMSE, mood

ADSP

AMP-AD

ADNI

ROS/MAP

IGAP

M²OVE-AD

Resilience-AD

ACT

MODEL-AD

INDIANA UNIVERSITY

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UCI University of California, Irvine
IU/JAX: Variant Prioritization

- Significance in multiple studies
- Predicted effect on function

- Human-mouse sequence conservation
- Differential expression in AD
IU/JAX: Model Creation and Dissemination

Now available:

- Humanized *APP* (hAβ KI)
- *APOE* allele series (ε2, ε3, ε4)
- *TREM2* variants: R47H, Y38C, KO, floxed
- *APOE*ε4/ε4 *Trem2*R47H/R47H

Additional variants to CRISPR:

- 8 variants per year for 5 years
  - New models now available:
    - *Abca7* (KO and A1527G)
    - *Ceacam1* (KO)
    - *Ilarap* (KO)
    - *Plcg2* (KO and M28L)
- Combinations of variants for broad pathology

CRISPR/Cas9 enabled

ET Liu et al. EMBO Rep. 2017
IU/JAX: Model Characterization

Neuropathology

Blood biomarkers

Neurodegeneration

RNA-seq

in vivo imaging

T2W MRI

18F-FDG PET

18F-FDG PET/MRI

18F-FDG Autorad

neurogenesis $3 \times 10^{-19}$

neuron differentiation $9 \times 10^{-15}$

long-term potentiation $3 \times 10^{-5}$

nervous system development $1 \times 10^{-6}$

Jak-STAT signaling pathway $3 \times 10^{-4}$

MODEL-AD

INDIANA UNIVERSITY

The Jackson Laboratory

Sage

University of California, Irvine
IU/JAX: Preclinical Testing

- Efficacy determined by primary and secondary markers specific to the compound
- Standardization of protocols, strains, and outcome measures shared via AMP-AD Knowledge Portal
- Develop drug prioritization criteria/schema
- Compounds nominated by scientific community and External Advisory Board
- One strain, 1-2 compounds per year over five years

**New Model**
- genetic model with associated molecular pathology

**Pharmacokinetics (PK)**
- dose-response
- blood, CSF, and tissue analysis biomarker assays

**Pharmacodynamics (PD)**
- PET, MRI imaging
- molecular signatures ('Omics)
- histopathology
- functional/behavioral tests
IU/JAX MODEL-AD Supplements

• **PTC Supplement (2017):** These supplemental funds will be used to develop and validate a preclinical testing pipeline for assessing candidate compounds in Alzheimer’s disease rodent models.

• **Rat F344 (2017):** These supplemental funds are being used to characterize and Stage the F344 rat model of Early Onset Alzheimer Disease.

• **Metabolomics (2017):** These studies will directly complement ongoing studies in AMP-AD led by Dr. Rima Kaddurah-Daouk at Duke University, with whom we will collaborate to allow seamless comparison between the model and clinical metabolomes. Animal models used in this study: 5xFAD, APOE4;Trem2R47H; B6.

• **Nanostring (2018):** Using AMP-AD data, we propose here to work with NanoString to develop an AD-specific panel to evaluate mouse models of AD.

• **Drug Selection Criteria (2018):** We will develop a front end web portal that will allow users to nominate compounds for the PTC pipeline.
IU/JAX MODEL-AD Presentations at AAIC

**Sunday July 22**

Poster P1-130

MODEL-AD: Characterization of Familial AD Models (5xFAD, APP/PS1, hTau, 3xTg-AD)

Poster P1-131

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

**Monday July 23**

8:00-8:20AM
S2-02-01
Room 183

*New In Vivo Models for Alzheimer’s Disease – MODEL-AD*

Poster P2-045

The MODEL-AD Consortium Preclinical Testing Pipeline: Pharmacokinetics and Pharmacodynamics of Prophylactic Treatment with Leviteracetam in the 5XFAD Mouse Model of Alzheimer’s Disease
IU/JAX MODEL-AD Presentations at AAIC

Wednesday July 25
9:15-9:30
O4-01-06
Room 185

Whole-Exome Analysis of Late-Onset Alzheimer’s Disease Reveals Novel Candidate Genes Involved in Cognitive Function

Poster P4-028
Characterizing the APOE4/Trem2*R47H Mouse Model for Late Onset Alzheimer’s Disease

Poster P4-031
Novel Models of Late-Onset Alzheimer’s Disease Based on GWAS

Poster P4-045
Biological Pathways and Related Protein Biomarkers of Clinical Progression in Early Alzheimer’s Disease
UCI: Overview of Preclinical Model Development for LOAD

**Human Data**
Maximize human data to identify relevant variants

**Other Variants**
Introduce tau and other variants

**Aβ**
Use hAβ mice as platform

**Environmental & Diet**
Introduce risk factors

**Validate and Share**
UCI: Goals for the Next Generation Models

- Physiological levels of AD relevant protein such as Aβ or tau (no ectopic or over-expression).
- Better concordance with human pathology.
- Identification of potential targets for therapeutic intervention.
- Analysis of risk factors (i.e., genetic, environmental, co-morbid conditions, etc).
UCI: Rationale for Humanizing Aβ in Mice

01
Aβ | human v. rodent
Rodent Aβ doesn’t aggregate as readily
(3 amino acid differences: position 5, 10, 13)

02
Wild-type human Aβ KI
Regardless of pathway causing s-AD, a mouse
with human Aβ will be required

03
Physiological expression
Mice express physiological levels of APP under the
endogenous promoter

04
Cre/loxP
Engineered loxP sites for option to determine if
pathways are Aβ-dependent

05
Platform
hAβ KI: used as a platform to introduce other
relevant AD genes
(e.g., tau, ApoE, TREM2, GWAS)
UCI: Key Challenges Modeling in Late Onset Alzheimer’s

**KEY CHALLENGES**

- **Humanize mouse genes**
  - Likely require the “humanization” of several key AD related genes

- **Aging/environment**
  - Pathology should ensue from aging/environmental factors vs. overexpression or FAD mutations

- **Multiple Pathologies**
  - Not all human pathologies may occur in a single mouse model

- **Mouse Background**
  - Mouse genetic background may have a profound impact on phenotype.
UCI: Strategy of Animal Model Development

GWAS variants
1. Spi1/PU.1
2. Clusterin

Platform
Humanized Aβ and Tau

Crosses
1. hAβ-KIxTrem2
2. hAβ-KIxApoE
3. hAβ-KIxTrem2xApoE

Additional variants in development
- Humanized MAPT (TAU) via substitution of mouse Mapt locus with human H1c MAPT.
- Humanized CLU via substitution of mouse Clu locus with human CLU.
- GWAS variants of SPI1 (PU.1) via CRISPR.
UCI: Phenotypic Evaluation

Neuropathology and Neurodegeneration

Aβ-plaques  Intracellular Tangles

Network analysis: Molecular Profiling (RNA-Seq)

Behavioral and Cognitive Phenotyping

ThioS-iba1  ThioS-GFAP

WT-22mo  hAβ-KI 22mo

Behavioral and Cognitive Phenotyping

A  Elevated Plus Maze

B  Contextual Fear Conditioning

ThioS-iba1  ThioS-GFAP

WT-22mo  hAβ-KI 22mo

Behavioral and Cognitive Phenotyping

ThioS-iba1  ThioS-GFAP

WT-22mo  hAβ-KI 22mo

Behavioral and Cognitive Phenotyping

ThioS-iba1  ThioS-GFAP

WT-22mo  hAβ-KI 22mo
UCI Supplements

Quantify hTau
Mice that express human TAU (hTAU) at physiological levels, with equivalent expression of the 3R and 4R hTAU isoforms, are being generated.

Behavior
Harmonize with data generated by IU/Jax and extend the LTP and cognitive phenotype

Neuroimaging
Combine approaches in standard use in human imaging with novel ultrahigh resolution in vivo and ex vivo imaging aimed at histopathological validation, including plaque imaging using MRI.

Single-cell RNA-seq
Guide human-mouse analyses and selection of mouse targets.
Now available:

- Mouse *App* expressing humanized Aβ (floxed).
Resource Sharing
Enabling researchers to find the right model

Data
• Mouse genetic information: variant(s), strain background
• Mouse phenotype data: RNA-seq, imaging, etc.
• Preclinical data: standards, protocols, results
• Preclinical results searchable on AlzPED

Mice
• Available from JAX mouse repository without restrictions
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

Recent Posts
- MODEL-AD presentations at AAIC 2018
- MODEL-AD presentations at ICMN
- Indiana U, Alzheimer's symposium
- New method for identifying candidate loci for late-onset Alzheimer's disease published
- Workshop on the use of mouse models to study neurodegenerative disease

Quick Links
- AMP-AD Knowledge Portal
- JAX AD Models
The MODEL-AD Consortium

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