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

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

INDIANA UNIVERSITY

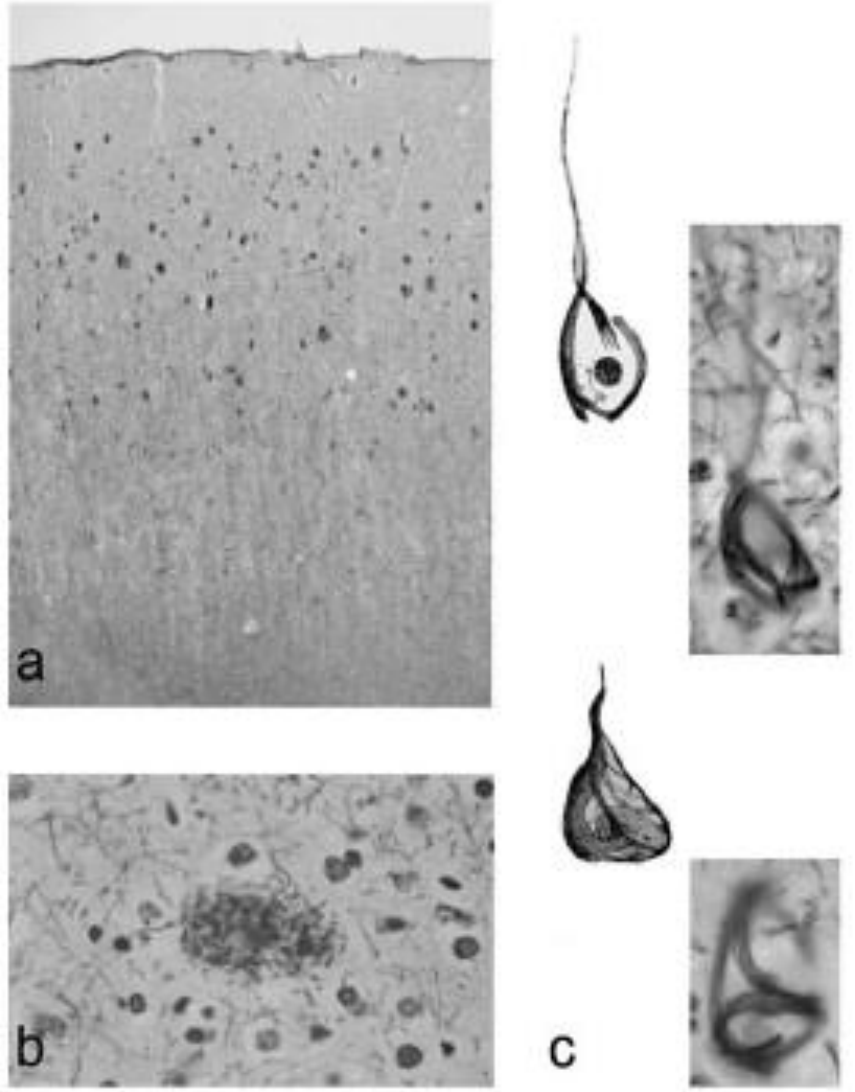
The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

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.)



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

INDIANA UNIVERSITY

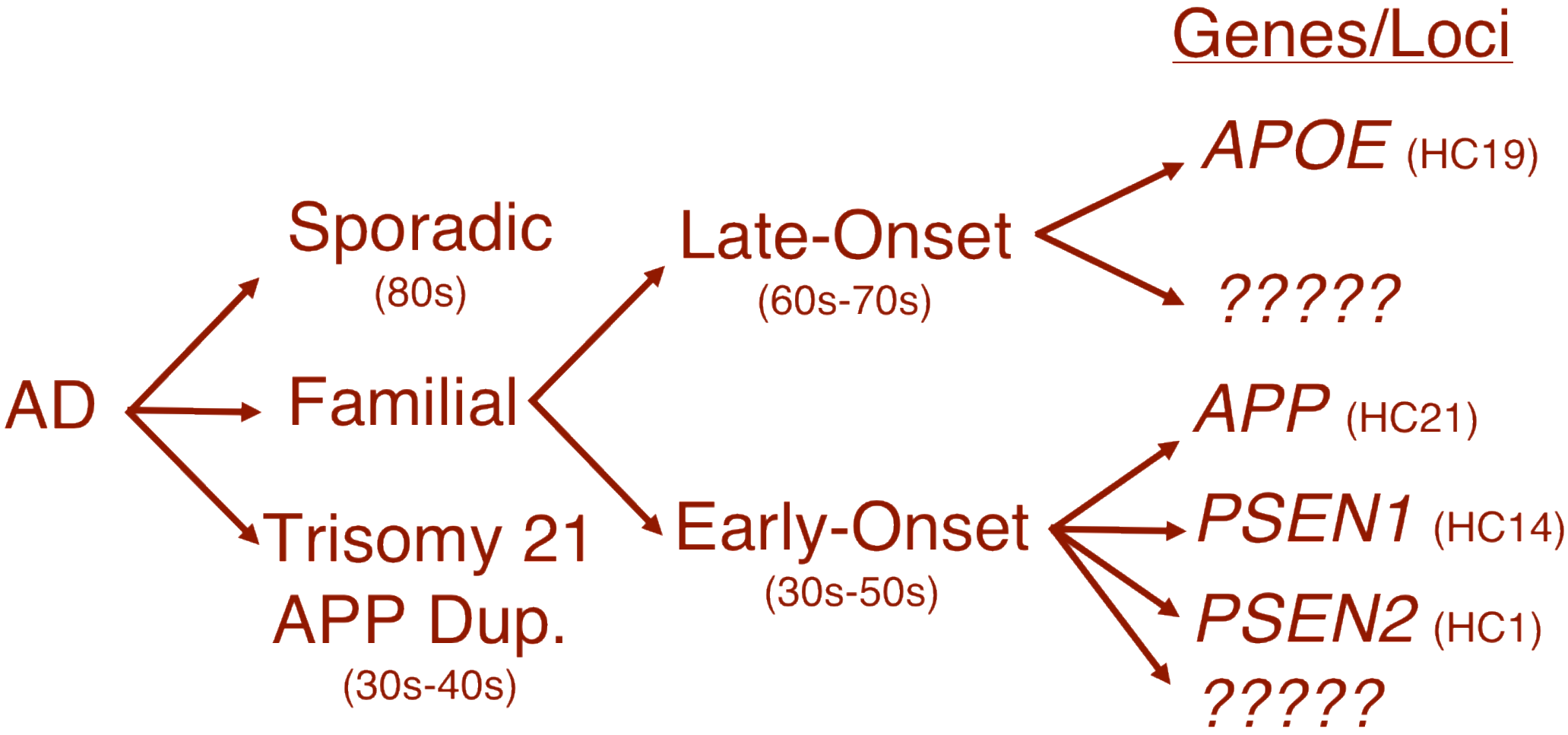
The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

Graeber and Mehraein, *Eur. Arch. Psychiatry Clin. Neurosci.*, **249**:S10-S13, 1999

Alzheimer's Disease Genetics



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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

Alzheimer's Disease Mouse Models: Aβ Deposition

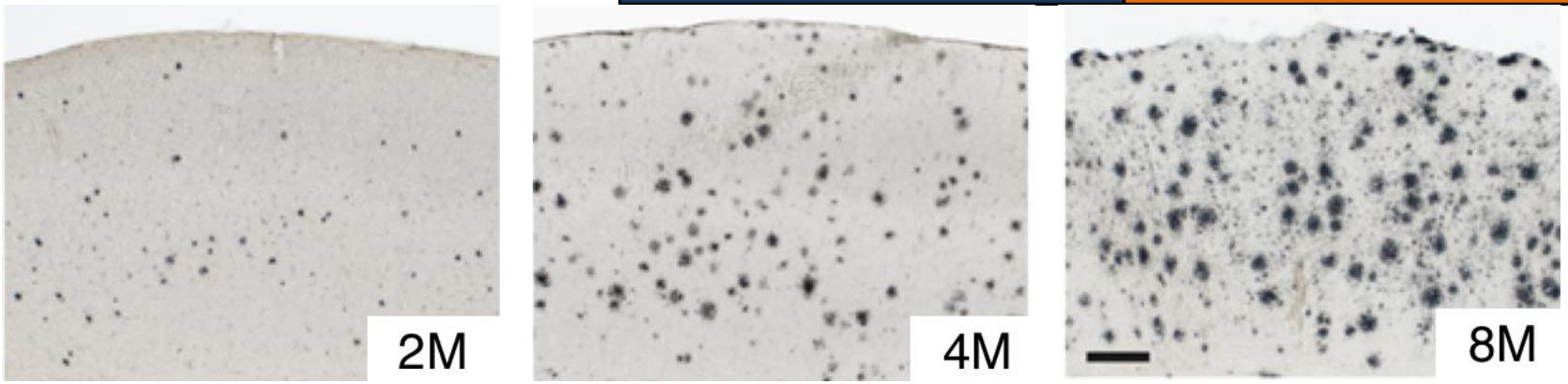
5xFAD

(Familial Alzheimer's Disease)

+

APPPS1

+



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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

Radde et al., *EMBO Rep.*, **7**:940-946, 2006

Alzheimer's Disease Mouse Models: Tau Pathology

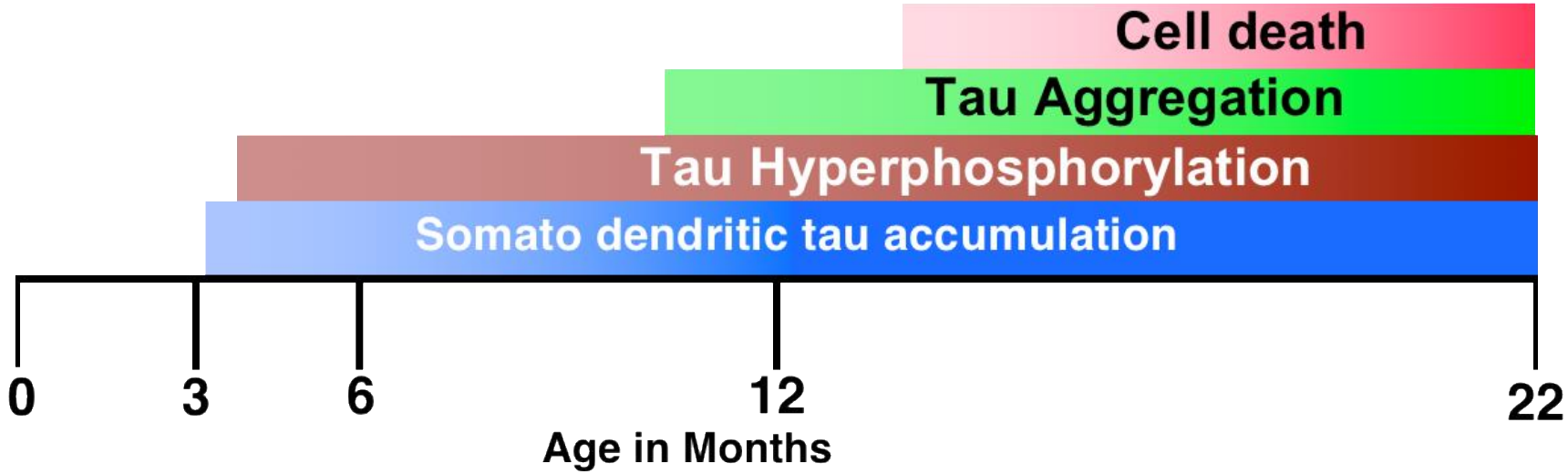
Human Tau Promoter

Wild-Type Human Tau

Genomic Models

hTau

hMAPT$^{+/-}$;Mapt$^{-/-}$



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

INDIANA UNIVERSITY

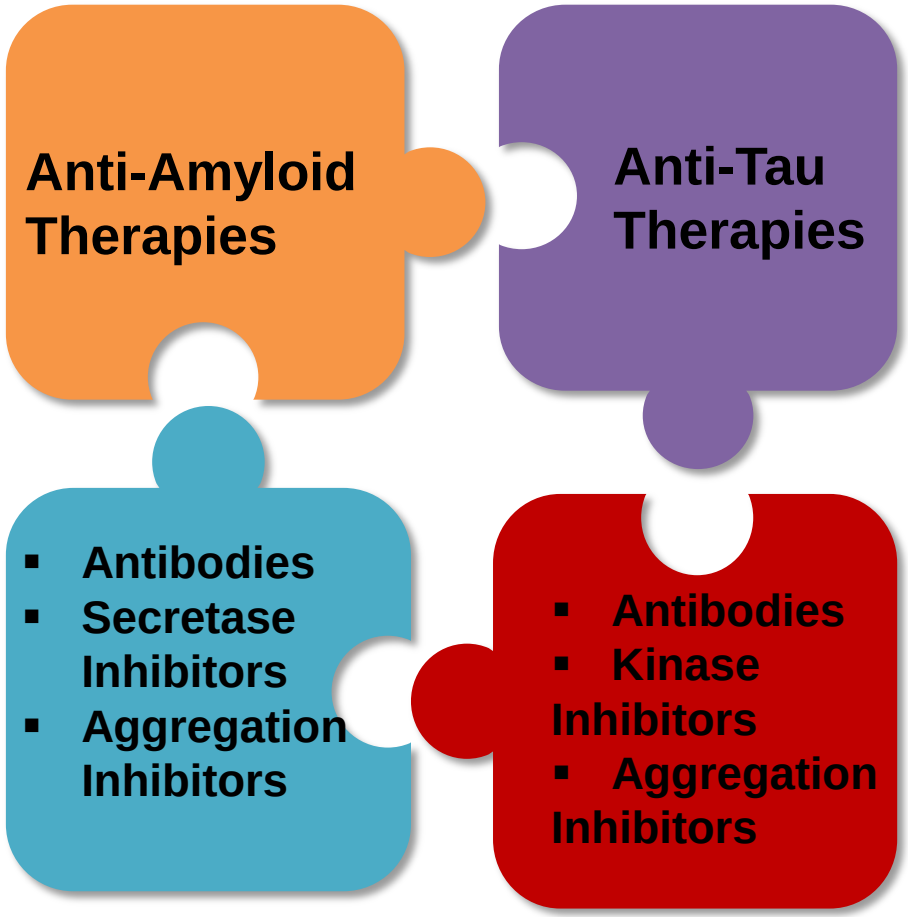
The Jackson Laboratory

Sage BIONETWORKS

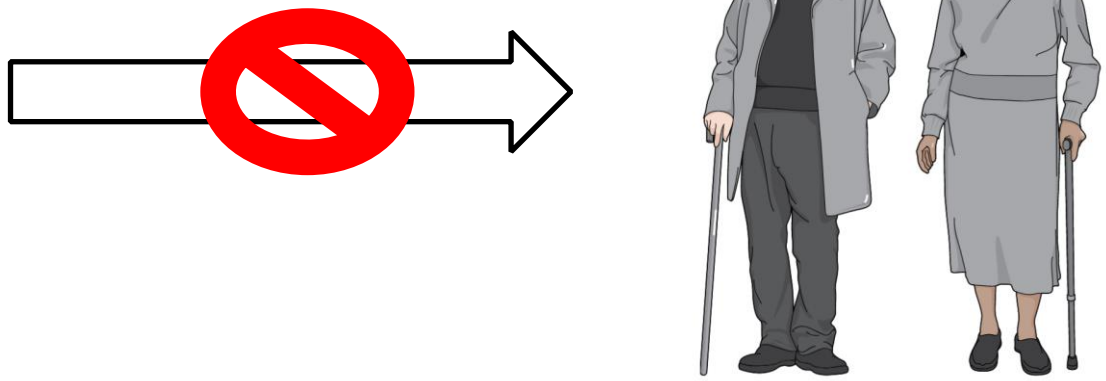
UCI University of California, Irvine

Andorfer et al., *J. Neurochem.*, **86**:582-590, 2003; Andorfer et al., *J. Neurosci.*. **25**:5446-5454, 2005

Therapies Developed in Mouse Models of AD



99.6% fail on clinical trials



Cummings et al., 2014

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

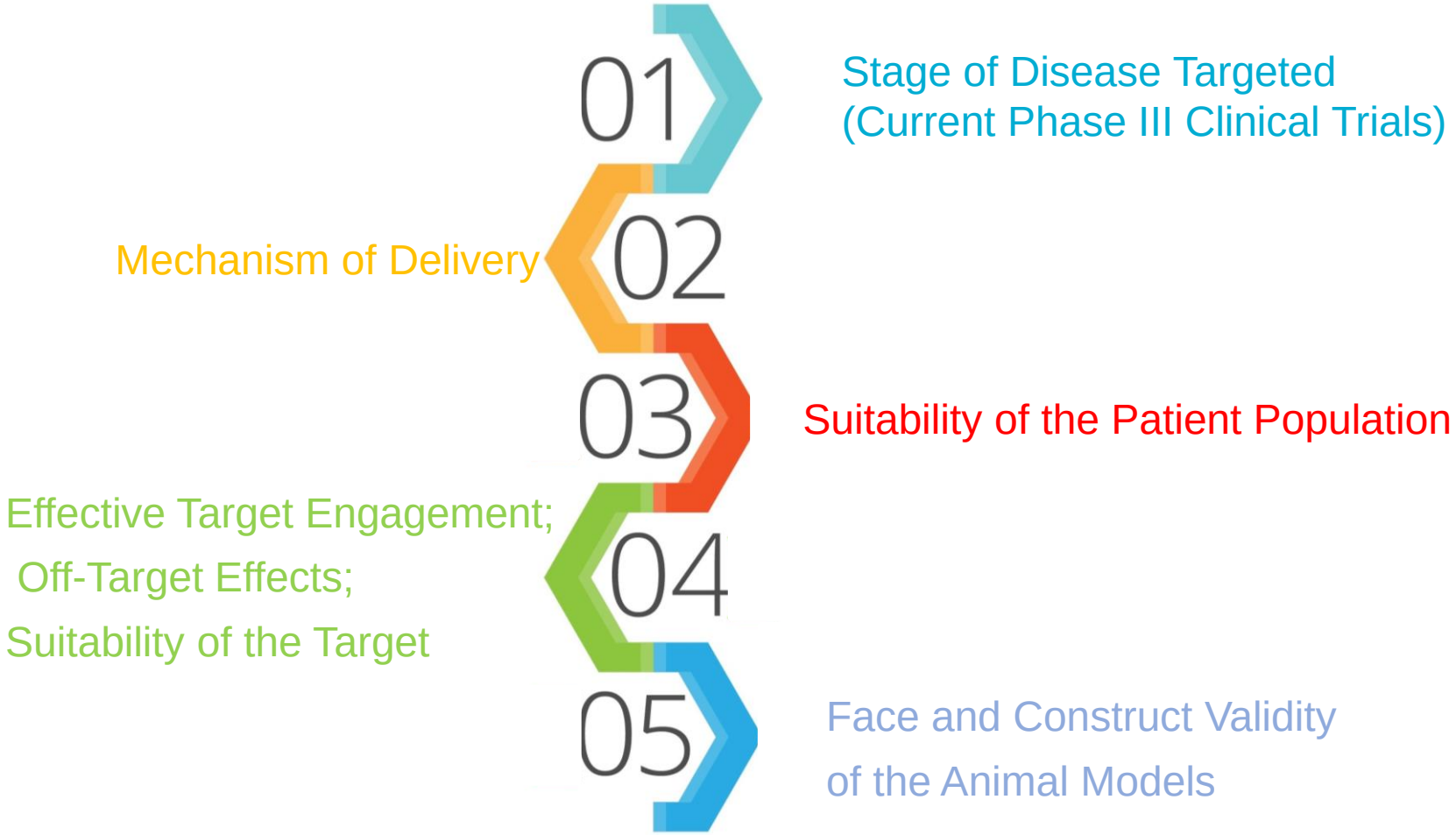
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

Reasons for Clinical Trials Failure?



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

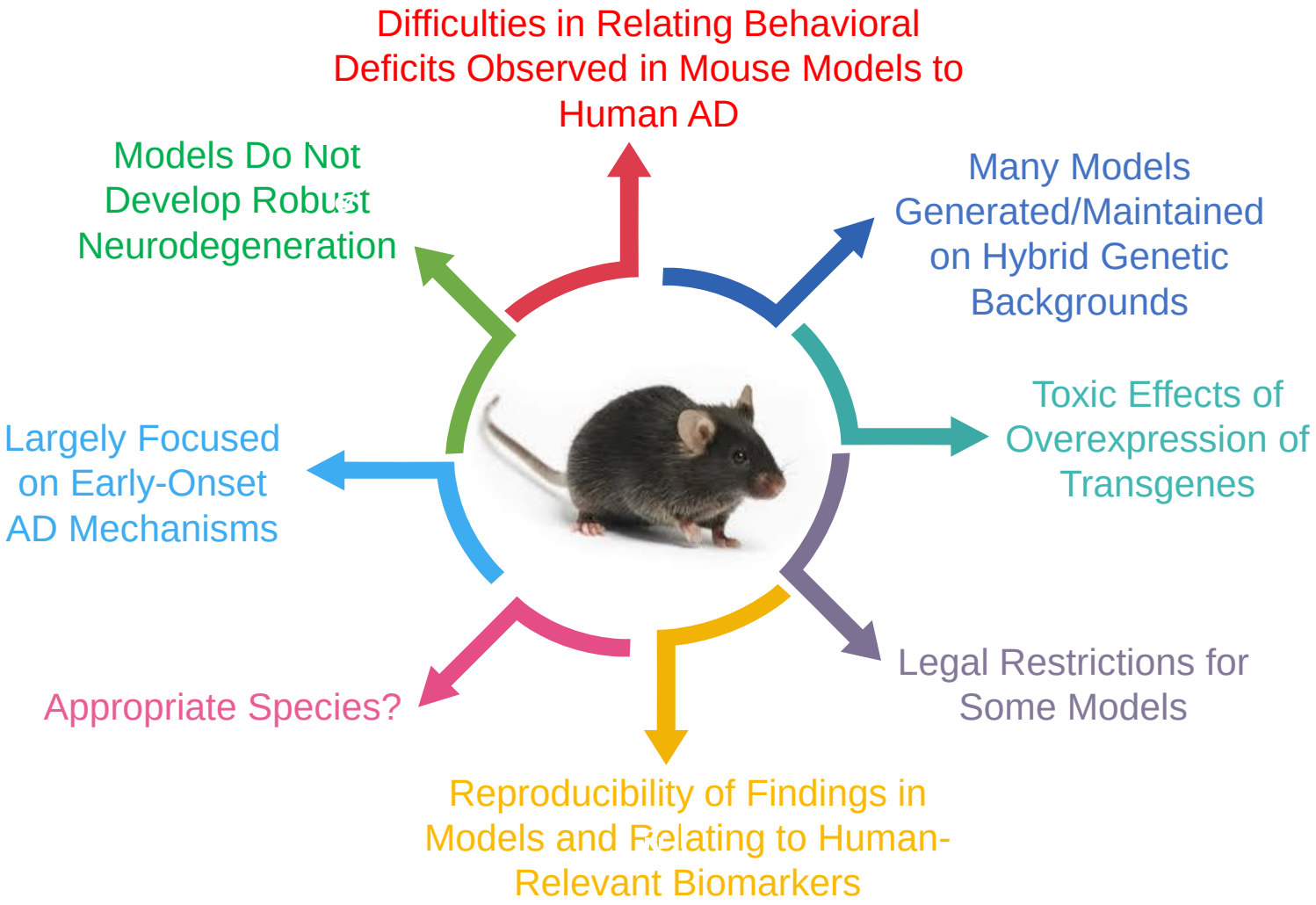
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

Concerns with Existing Animal Models



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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

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 **O**rganism **D**evelopment and **E**valuation for
Late-onset **A**lzheimer's **D**isease

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

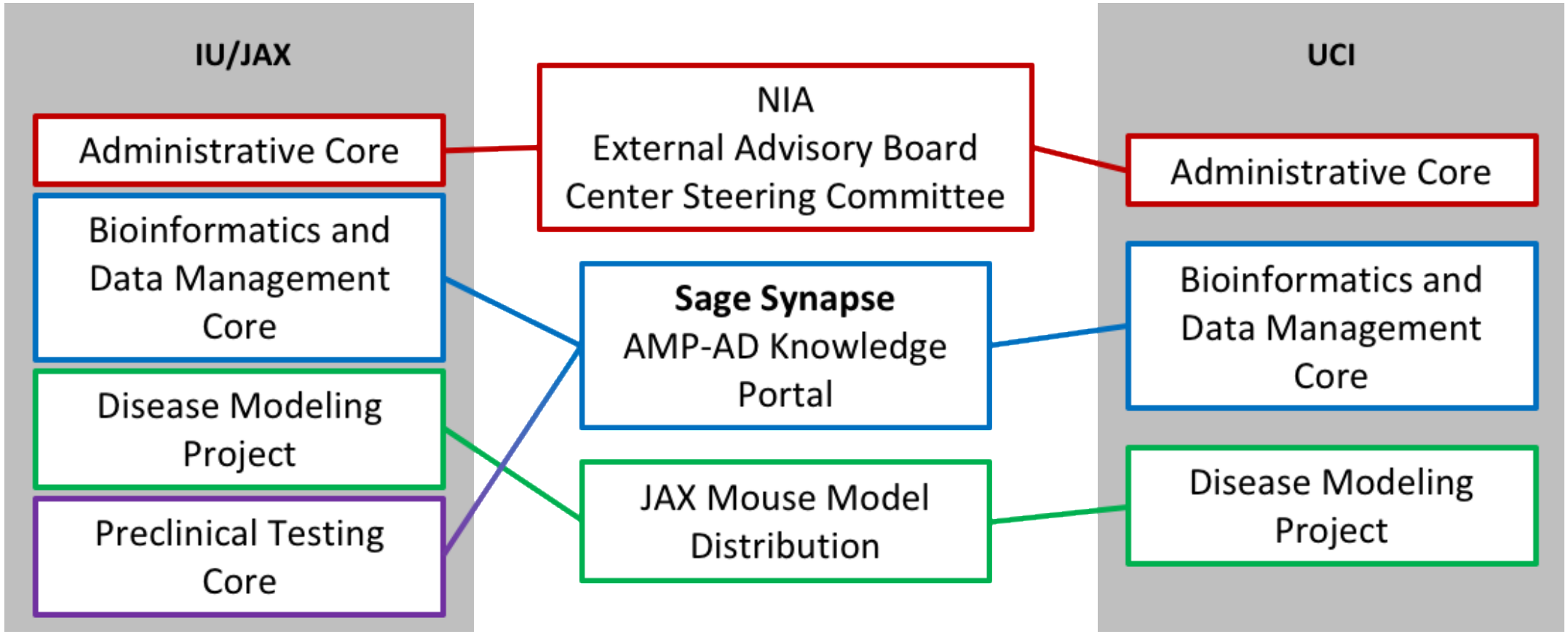
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

MODEL-AD Consortium



U54 AG054345

U54 AG054349

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

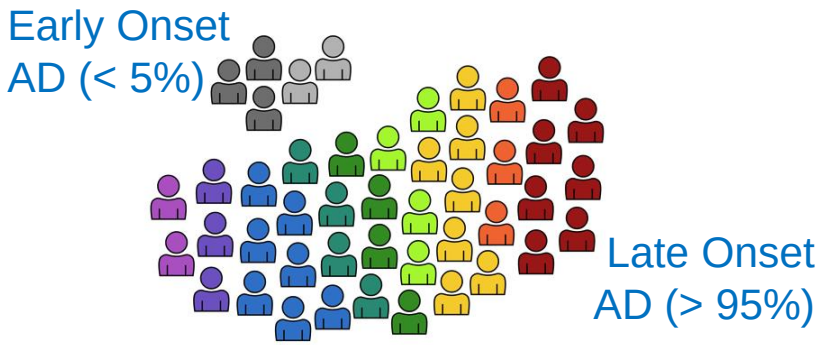
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

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

Bioinformatics and Data Management Core
The Jackson Lab Sage Bionetworks
Indiana U UC Irvine

Disease Modeling Project
The Jackson Lab
Indiana U UC Irvine

Preclinical Testing Core
Indiana U The Jackson Lab
Sage Bionetworks

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

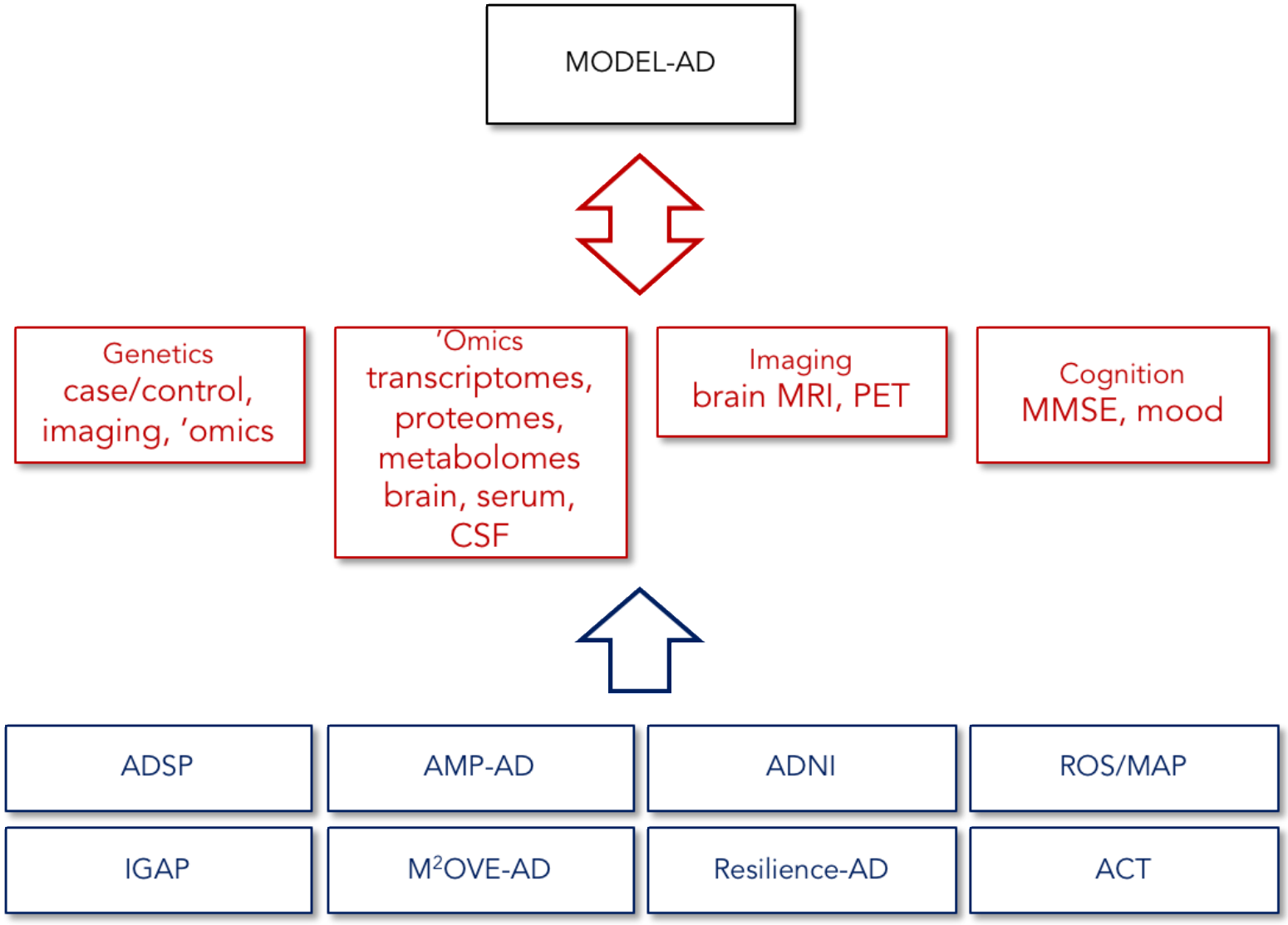
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

Leveraging the AD Data Universe



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

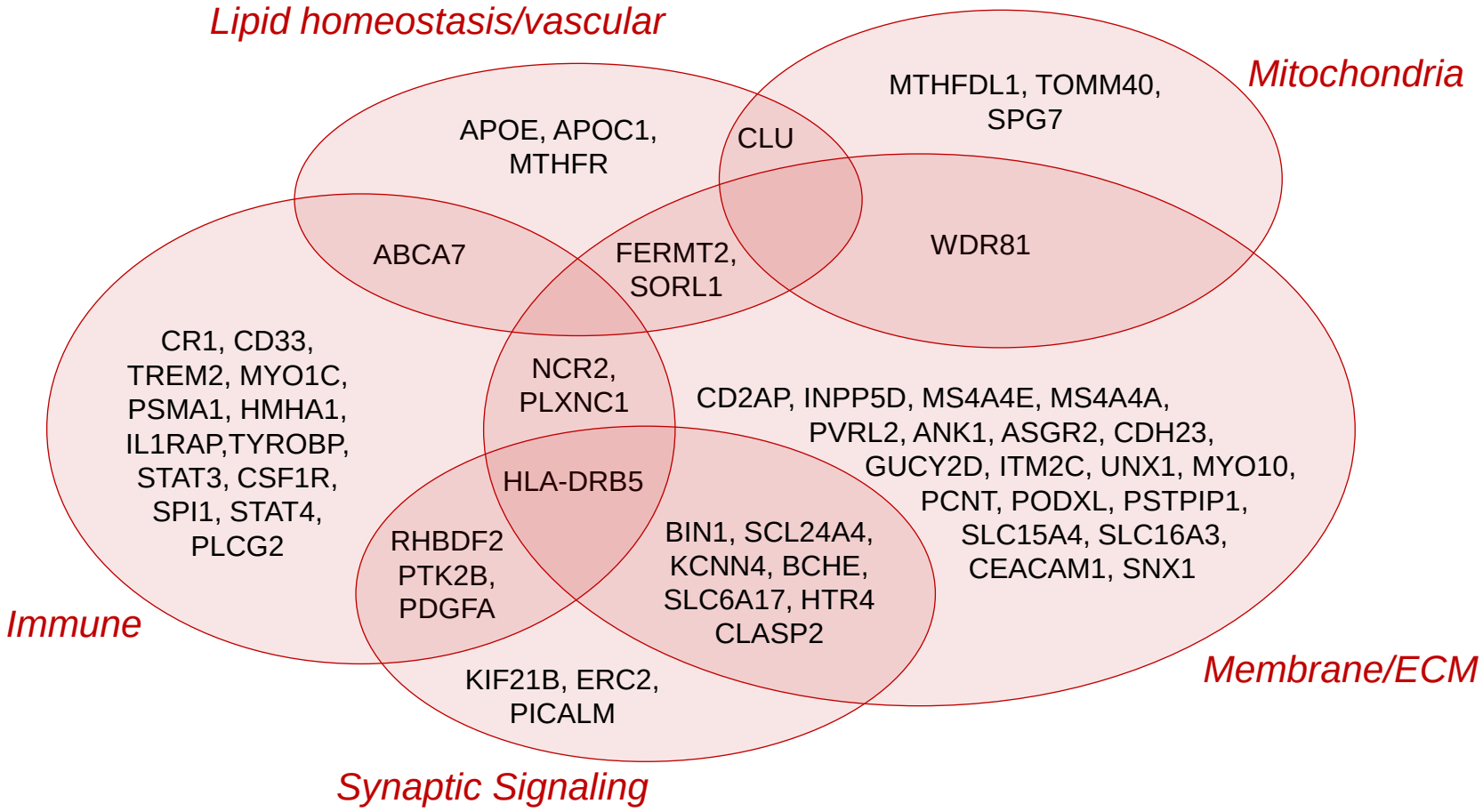
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

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

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

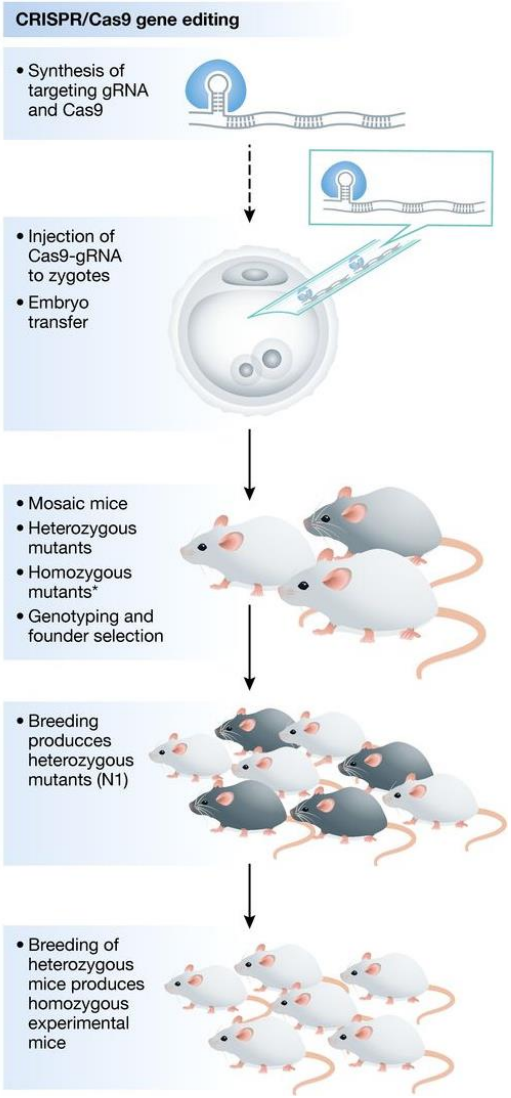
IU/JAX: Model Creation and Dissemination

Now available:

- Humanized *APP* (hAβ KI)
- *APOE* allele series (ε2, ε3, ε4)
- *TREM2* variants: *R47H*, *Y38C*, KO, floxed
- $APOE^{\varepsilon4/\varepsilon4}Trem2^{R47H/R47H}$

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

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

INDIANA UNIVERSITY

The Jackson Laboratory

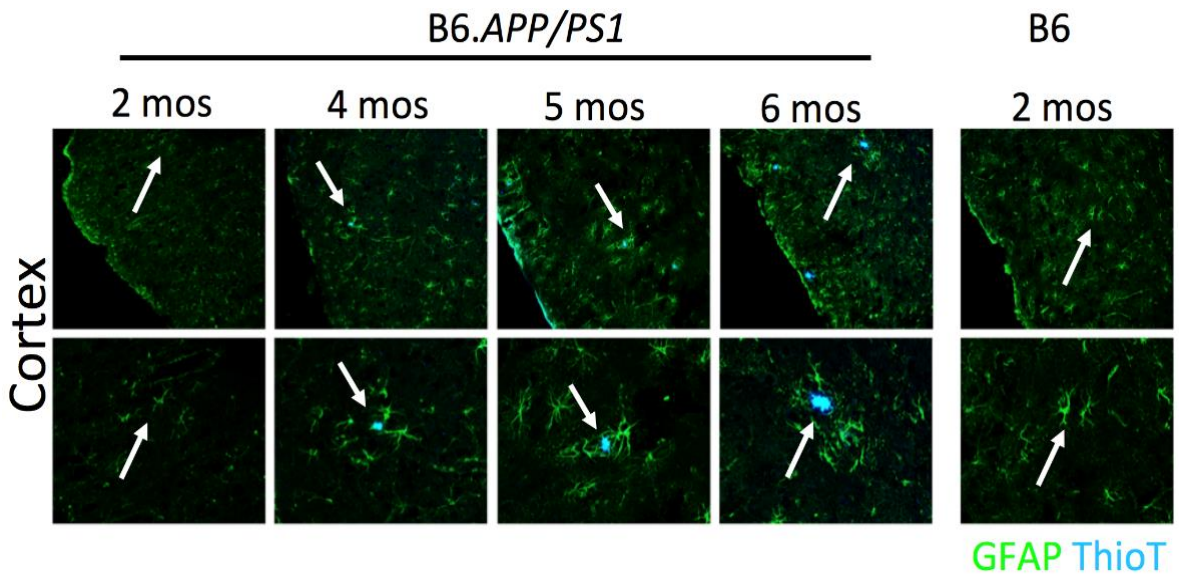
Sage BIONETWORKS

UCI University of California, Irvine

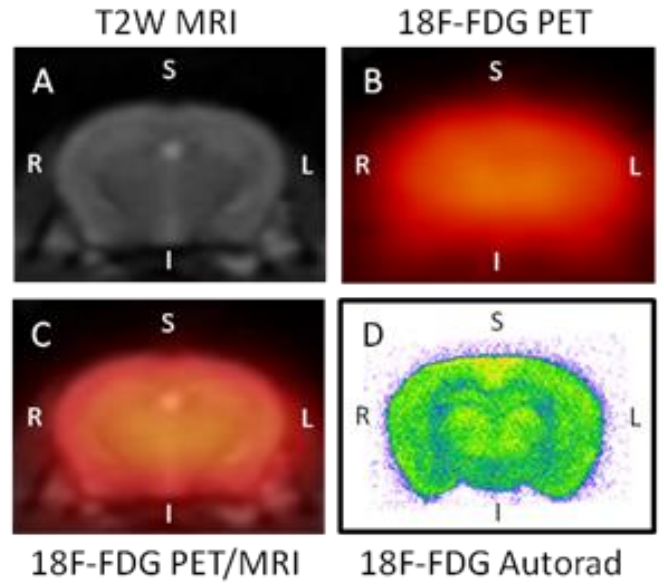
ET Liu *et al*. EMBO Rep. 2017

IU/JAX: Model Characterization

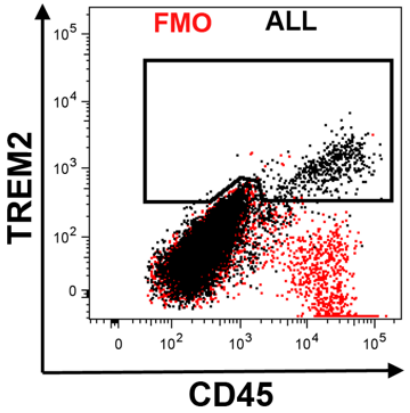
Neuro-pathology



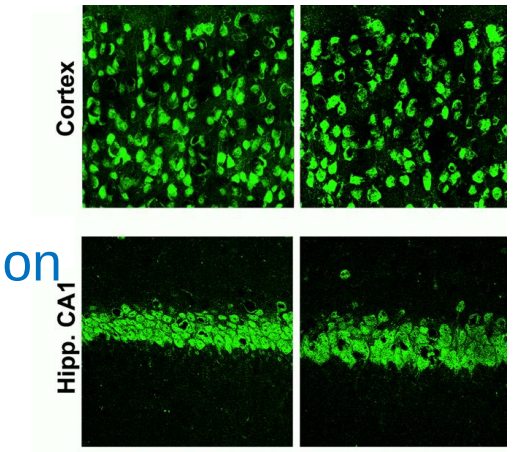
in vivo imaging



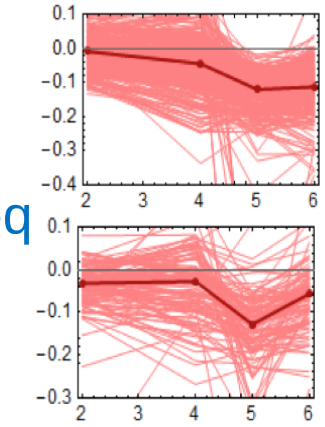
blood biomarkers



Neuro-degeneration



RNA-seq



neurogenesis	3 x 10^{-19}
neuron differentiation	9 x 10^{-19}
long-term potentiation	3 x 10^{-5}

nervous system development	1 x 10^{-6}
Jak-STAT signaling pathway	**3 x 10^{-4}**

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

INDIANA UNIVERSITY

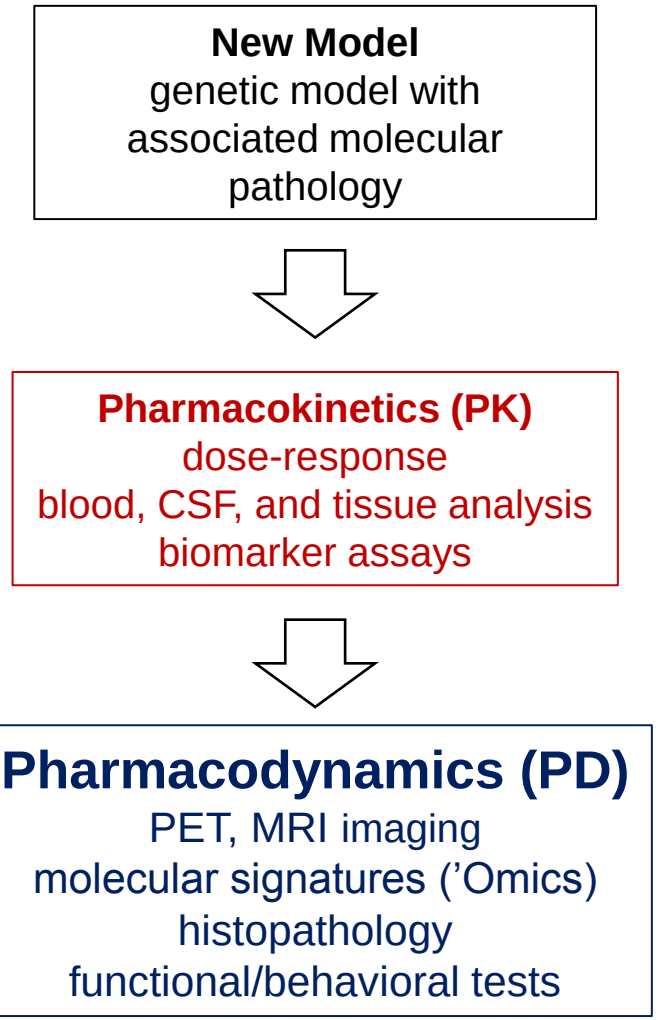
The Jackson Laboratory

Sage BIONETWORKS

UCI 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



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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

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.

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

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

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

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

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

UCI: Overview of Preclinical Model Development for LOAD

Human Data
Maximize human data to identify relevant variants

Other Variants
Introduce tau and other variants

Validate and Share

Aß
Use hAß mice as platform

Environmental & Diet
Introduce risk factors

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

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)

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

UCI: Rationale for Humanizing Aβ in Mice

Aß | human v. rodent

Rodent Aß doesn't aggregate as readily
(3 amino acid differences: position 5, 10, 13)

Wild-type human Aß KI

Regardless of pathway causing s-AD, a mouse with human Aß will be required

Physiological expression

Mice express physiological levels of APP under the endogenous promoter

Cre/loxP

Engineered loxP sites for option to determine if pathways are Aß-dependent

Platform

hAß KI: used as a platform to introduce other relevant AD genes
(*e.g.*, tau, ApoE, TREM2, GWAS)

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

UCI: Key Challenges Modeling in Late Onset Alzheimer's

Likely require the "humanization" of several key AD related genes

Not all human pathologies may occur in a single mouse model

Pathology should ensue from aging/ environmental factors vs. overexpression or FAD mutations

Mouse genetic background may have a profound impact on phenotype.

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

INDIANA UNIVERSITY

The Jackson Laboratory

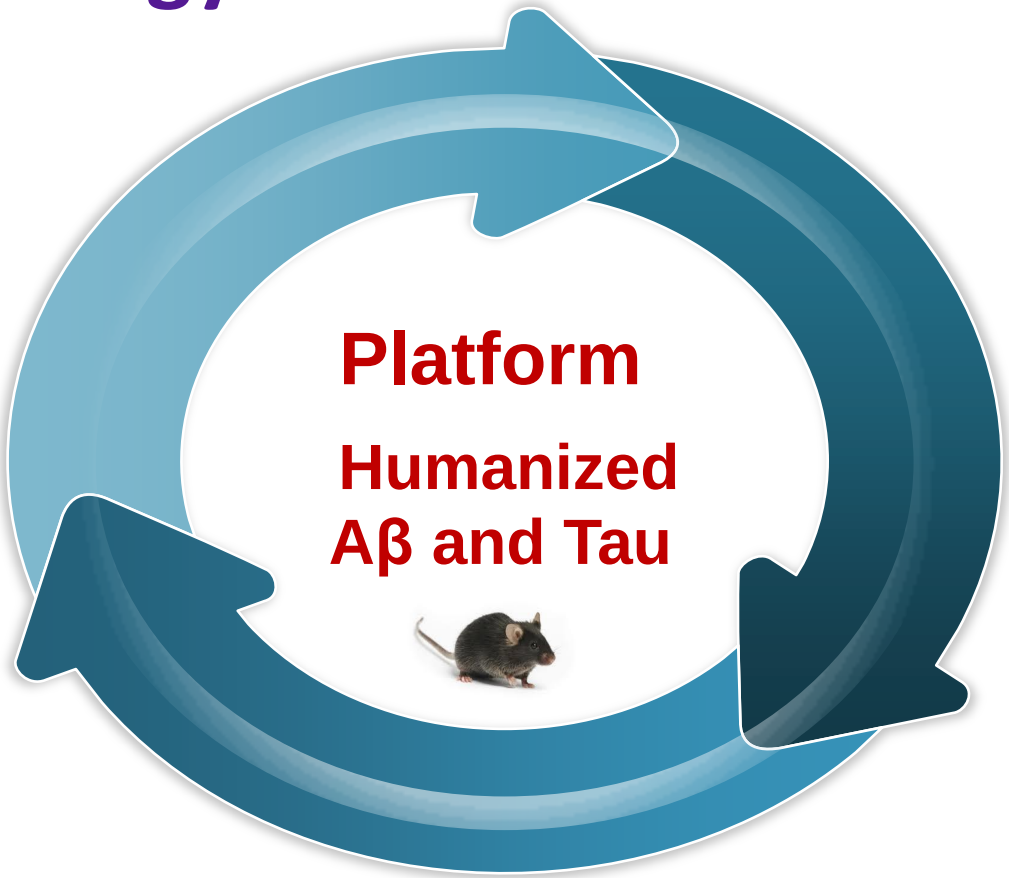
Sage BIONETWORKS

UCI University of California, Irvine

UCI: Strategy of Animal Model Development

GWAS variants

1. Spi1/PU.1
2. Clusterin



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.

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

INDIANA UNIVERSITY

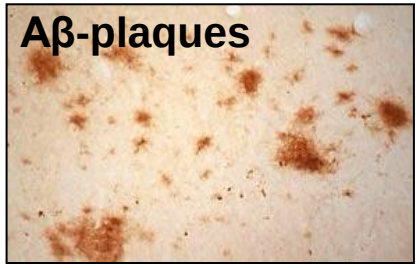
The Jackson Laboratory

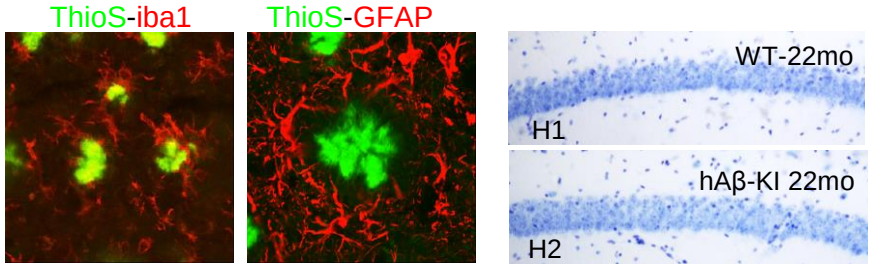
Sage BIONETWORKS

UCI University of California, Irvine

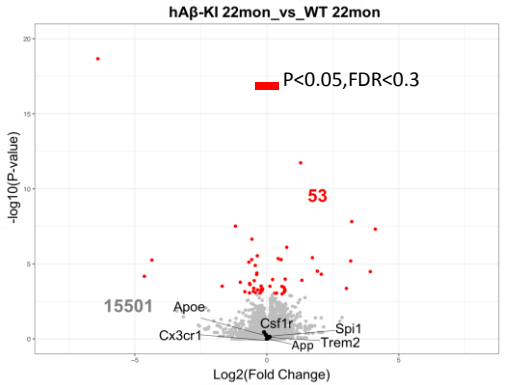
UCI: Phenotypic Evaluation

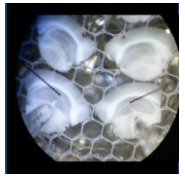
Neuropathology and Neurodegeneration

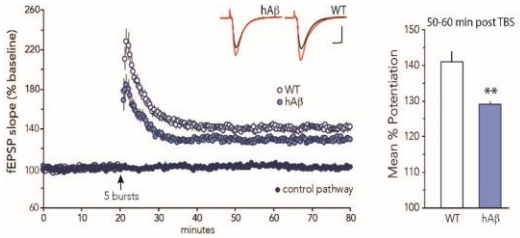




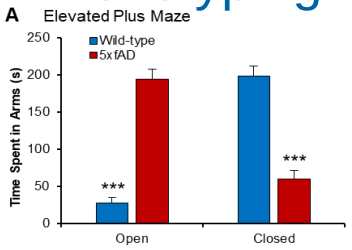
Network analysis: Molecular Profiling (RNA-Seq)

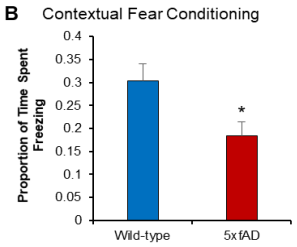






Behavioral and Cognitive Phenotyping





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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

UCI Supplements

Behavior

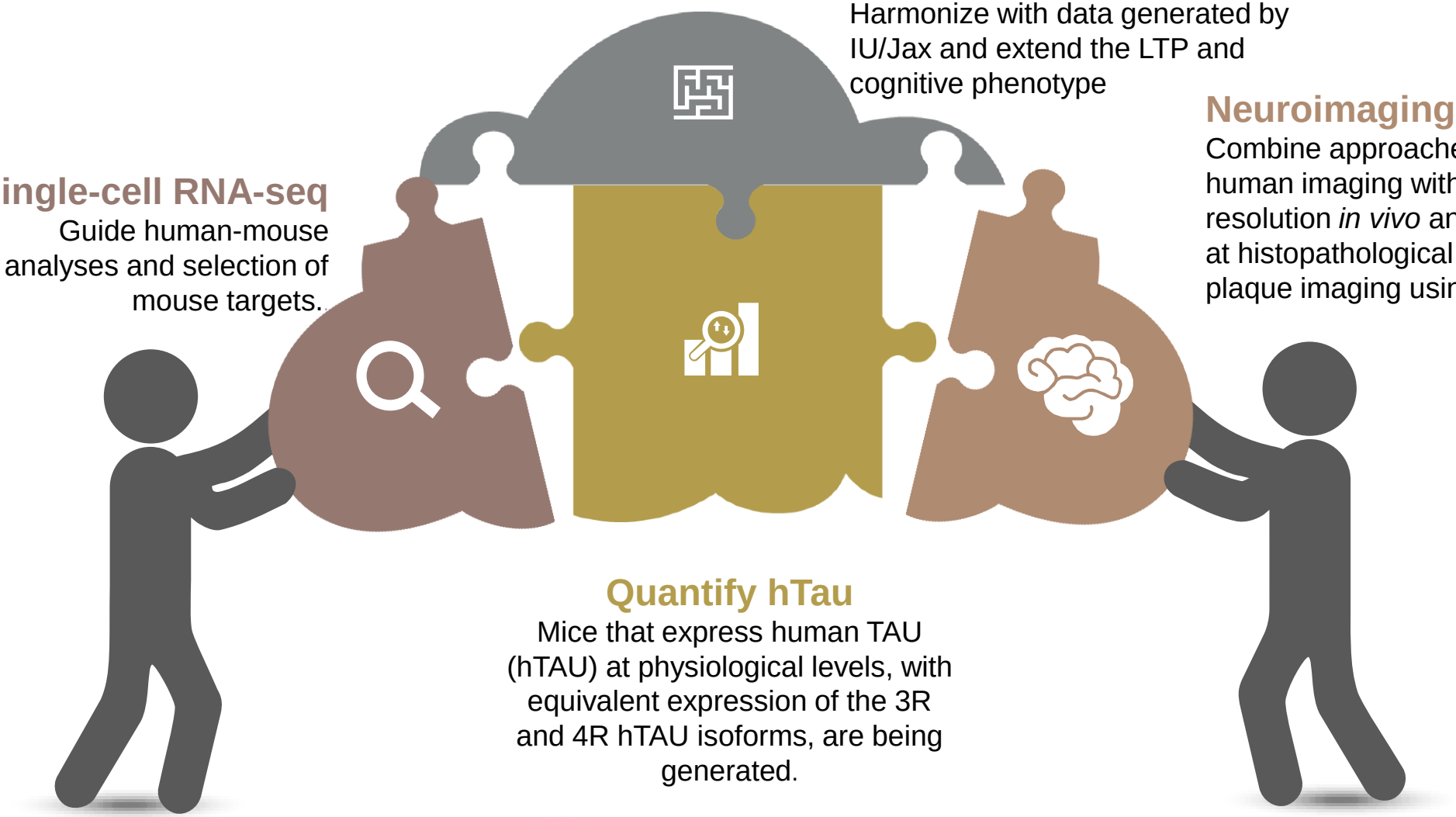
Harmonize with data generated by IU/Jax and extend the LTP and cognitive phenotype

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.



Quantify hTau

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

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

UCI: Model Production and Dissemination

Now available:

- Mouse *App* expressing humanized Aβ (floxed).

The Jackson Laboratory

B6(SJL)-*App*$^{tm1.1Aduci}$/J

Stock No: 030898 | **hAbeta-loxP-KI on mixed B6J and B6NJ**

Alzheimer's Association International Conference (AAIC) O #23414	**O1-01** Development of New Models and Analysis Methods: Novel Model Systems to Study Dementia, *Sunday, July 22, 2018: 8:00 AM - 9:30 AM*	**O1-01-04** Haβ-KI: A Knock-in Mouse Model for Sporadic Alzheimer's Disease

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

Resource Sharing

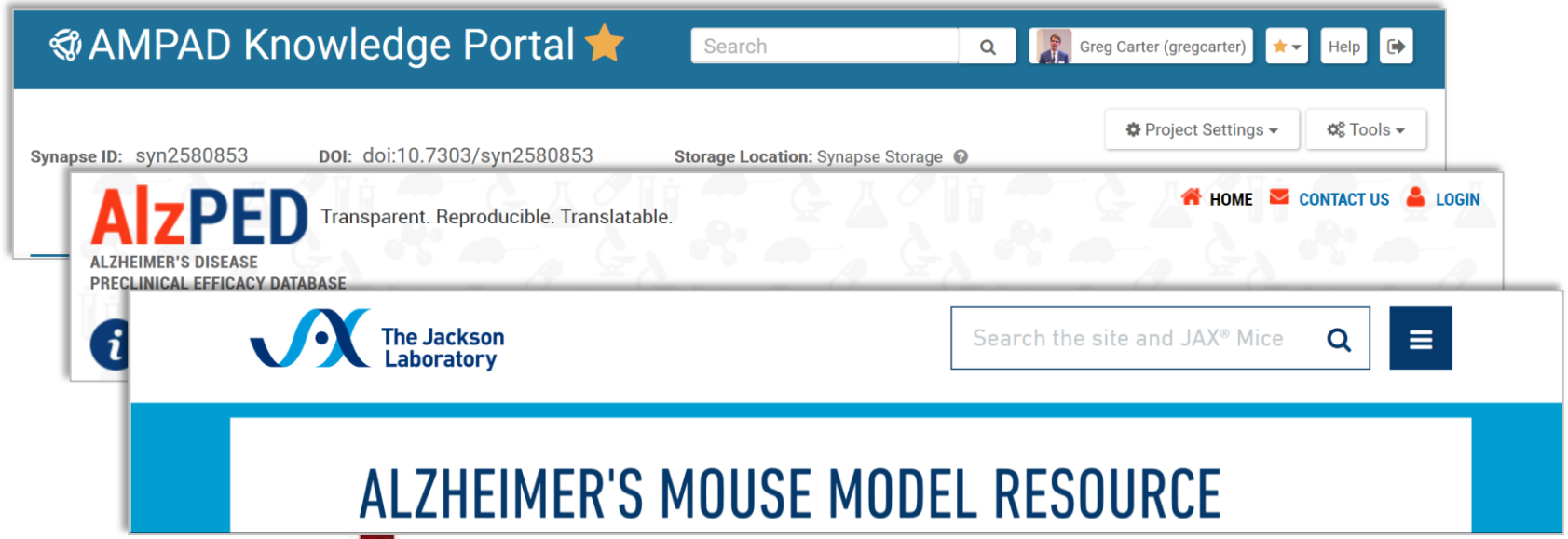
Enabling researchers to find the right model

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



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

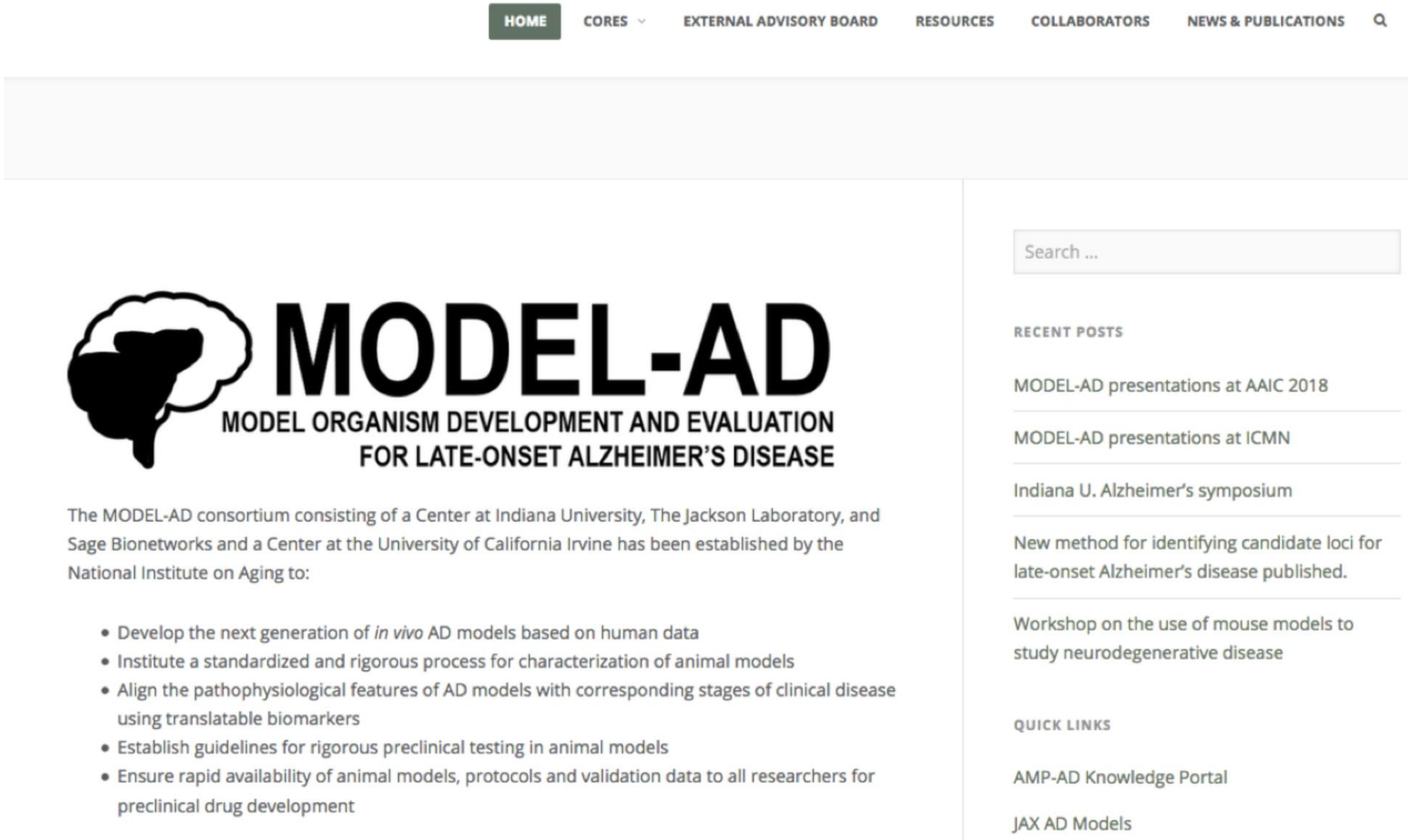
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

MODEL-AD.ORG



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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine

The MODEL-AD Consortium

Indiana University
Bruce Lamb, Program Director
Paul Territo, PTC Head
Andrew Saykin, BDMC Co-Head
Adrian Oblak, Project Manager
Kwangsik Nho
Li Shen
Tatiana Foroud
Dino Ghetti
David Jones
Sarah Quinney
Deborah DeBusk, Administrator

The Jackson Laboratory
Gareth Howell, DMP Head
Greg Carter, BDMC Head
Mike Sasner, DMP Co-Head
Stacey Rizzo, PTC Co-Head
Harriet Williams, Project Manager
Christoph Preuss
Asli Uyar
Yi Li
Ravi Pandey
Cai John
Nikhil Milind
Kristen Onos
Martha Abbott, Administrator

UC Irvine
Frank LaFerla, Program Director
Andrea Tenner, Program Director
Grant MacGregor, DMP Head
Ali Mortazavi, BDMC Head
Kim Green, DMP Co-Head
Marcelo Wood, DMP Co-Head
Stefania Forner, Project Manager
David Baglietto-Vargas
Shan Jiang
Shimako Kawauchi
Sherrilyn Collins
Jonathan Neumann
Eniko Kramar
Edna Hingco
Dina Matheos
Maria Fonseca
Andrea Wasserman, Administrator

Contact
www.model-ad.org
modelad@iupui.edu
@Model_ad_alz

National Institute on Aging
Suzana Petanceska
Lorenzo Refolo
U54 AG054345, U54 AG054349

Sage Bionetworks
Lara Mangravite, BDMC Co-Head
Larsson Omberg
Ben Logsdon
Mette Peters
Solveig Sieberts
Yooree Chae

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

INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

UCI University of California, Irvine