



# Lessons Learned of Mice (and Men)

*Developing the next-generation of AD mouse models*

Frank M. LaFerla, PhD

Dean and Chancellor's Professor  
Director, UCI ADRC  
co-Director, MODEL-AD

# Exciting News



**#1**

*Money* magazine ranked UCI #1 best college in the nation

**#1**

*Forbes* magazine named UCI #1 in nation among public universities for "best value"

**#1**

UCI named #1 college doing most for the American Dream in *NYT Upshot*

**#1**

*Sierra* magazine recognized UCI as top green university

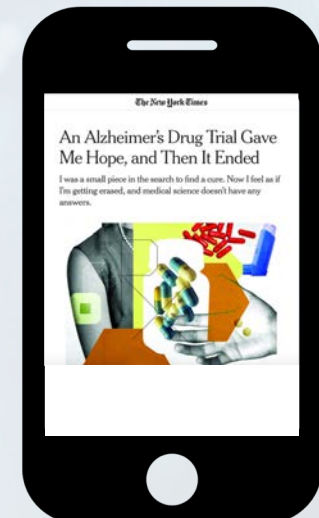
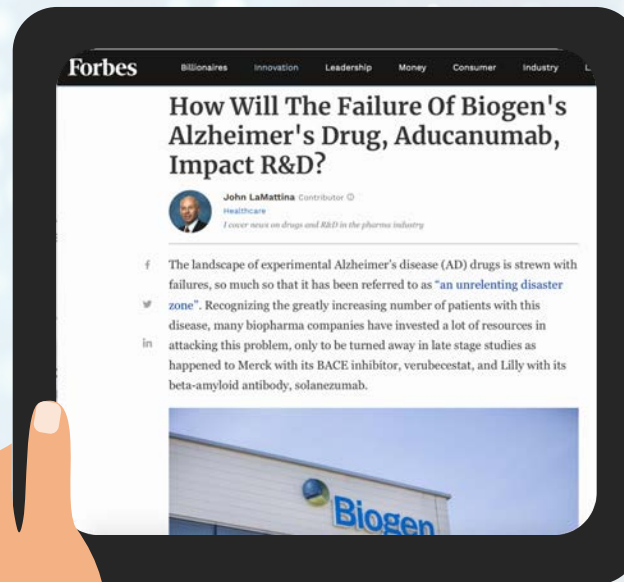
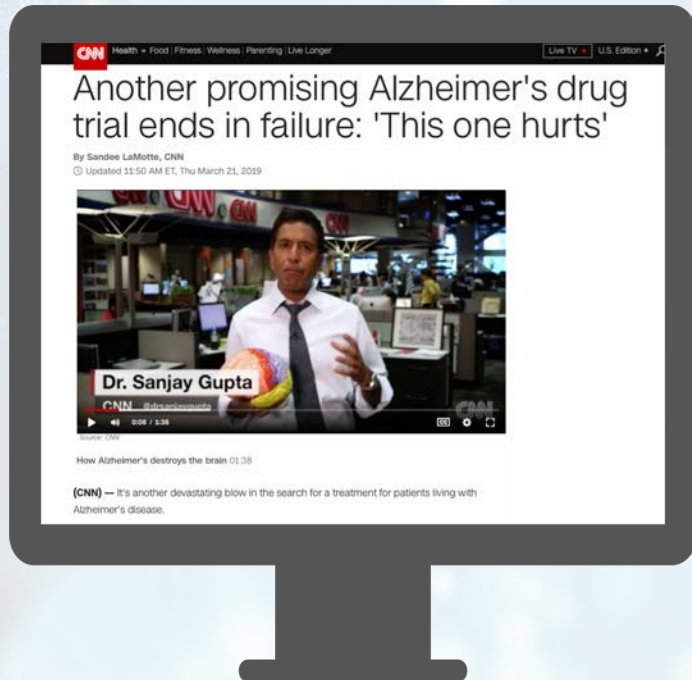
**9th**

UCI was ranked the 9<sup>th</sup> best Public University in U.S. *News & World Report*

**1 of 62**

Research universities elected into the prestigious Association of American Universities

# Recent Alzheimer's News

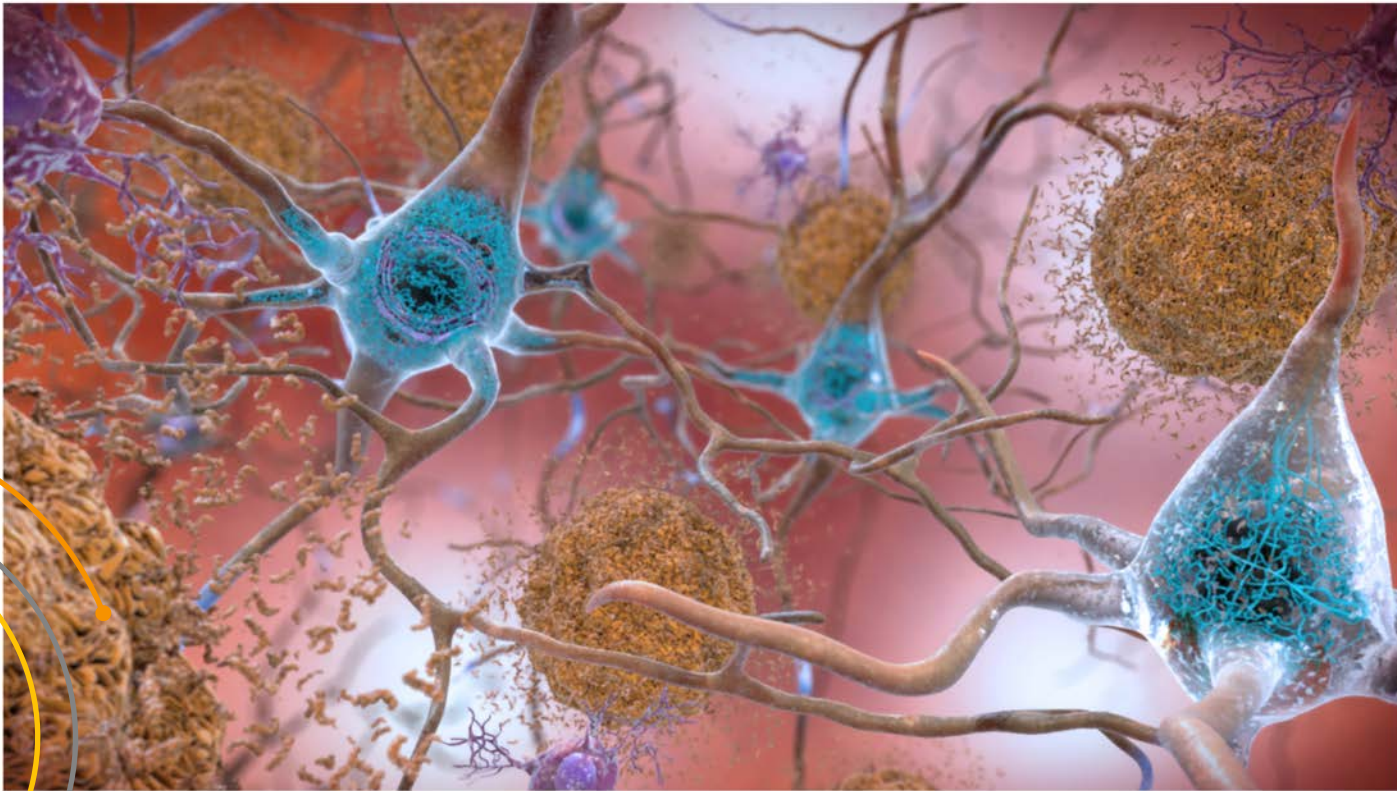




BIOTECH

# In shocking reversal, Biogen to submit experimental Alzheimer's drug for approval

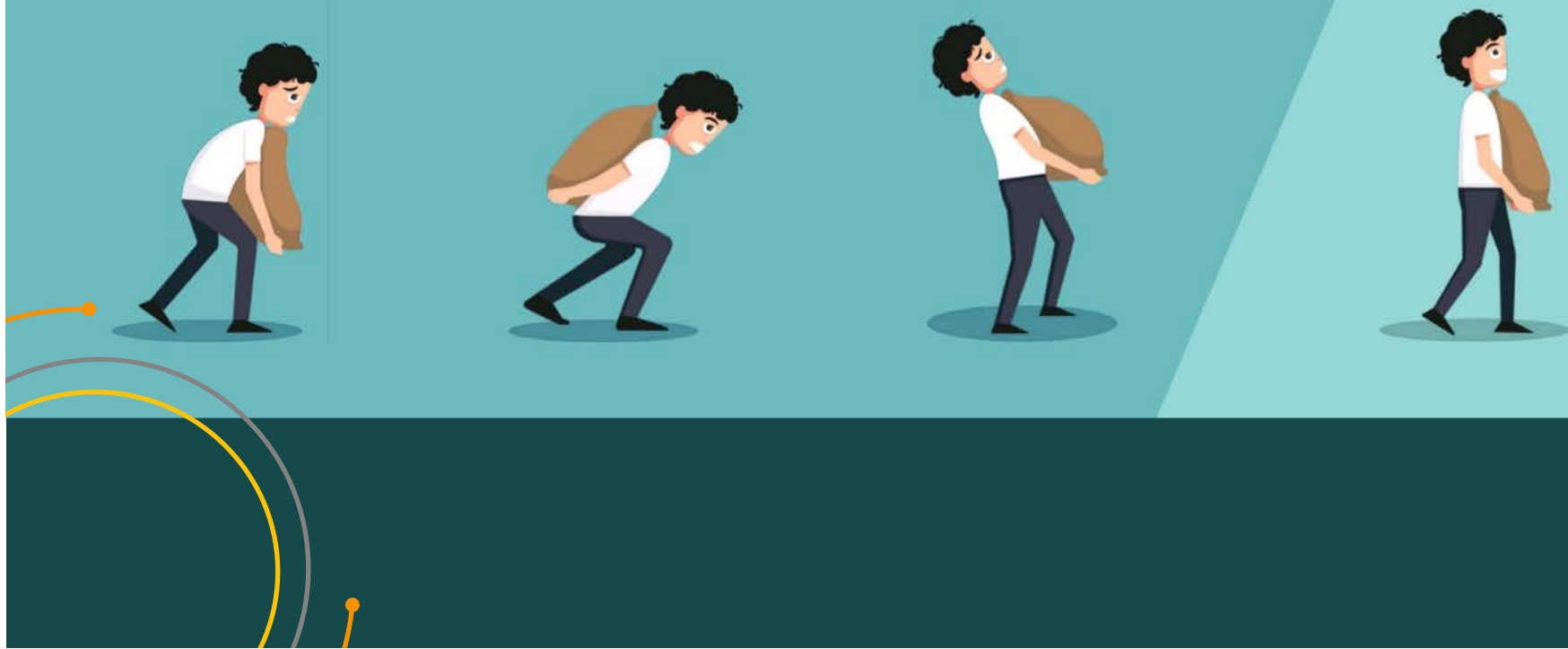
By MATTHEW HERPER [@matthewherper](#) / OCTOBER 22, 2019



NATIONAL INSTITUTE ON AGING, NIH

# PARTICIPANT BURDEN

*What is it to you?*



# Alzheimer's | 21<sup>st</sup> Century Plague



## Alzheimer's Disease

### In 2019

- » 5.8 million afflicted
- » Cost = \$290 **Billion**/yr
- » Medicare \$: 1 out of 5 for AD Care

### By 2050

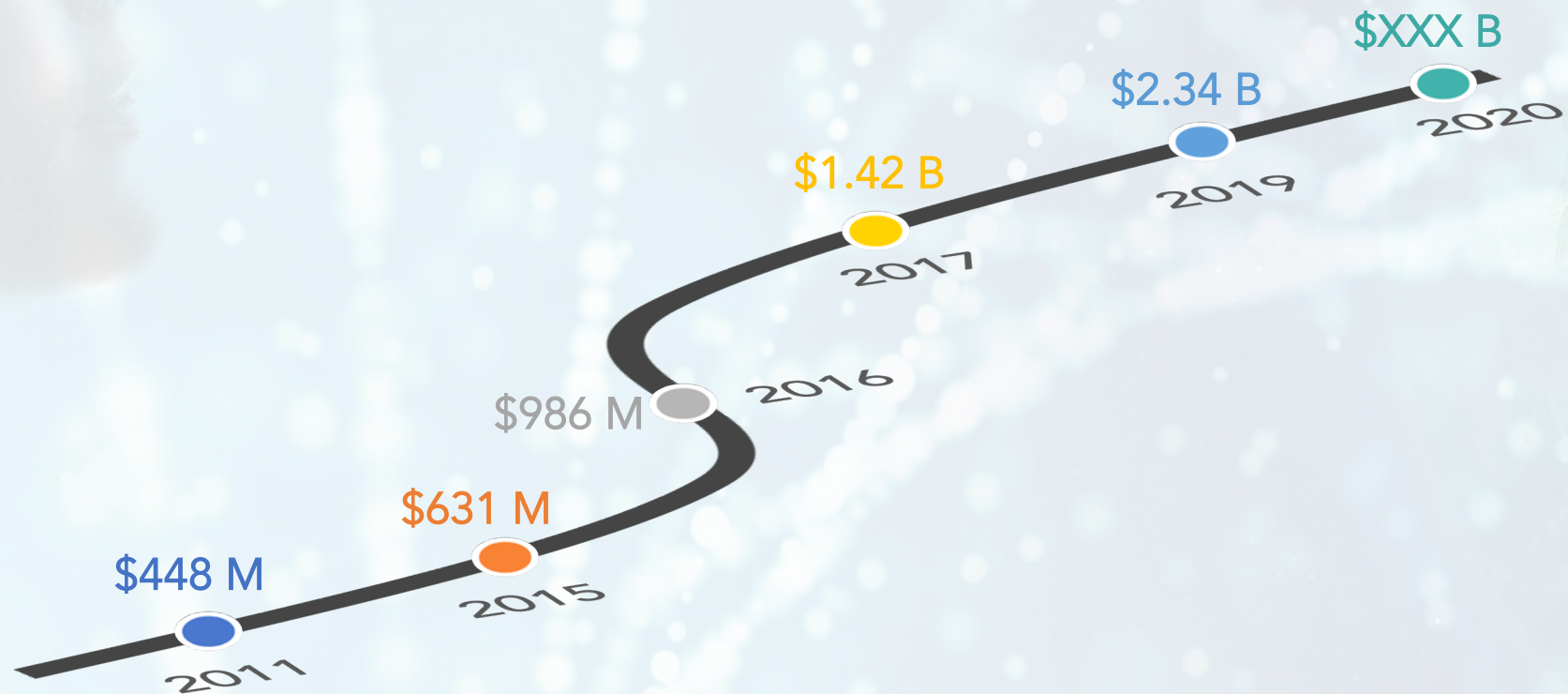
- » 14 million afflicted
- » Cost = \$1.1 **Trillion**/yr
- » Medicare \$: 1 out of 3 for AD care



# NIH Alzheimer's Disease Funding



...investing in a cure



# NIH Alzheimer's Disease Centers



## NIH Centers of Excellence were established in 1984

- USC/UCI was part of the original five funded centers (Drs. Finch/Cotman)

## Found at major medical institutions across the USA

- 31 centers across the network

## Goal

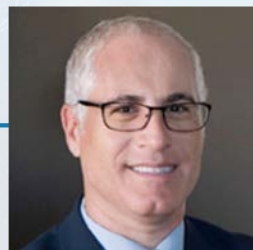
- Translate research advances into improved diagnosis and care and prevent and treat AD

## Each center has its own area of emphasis

- But the network shares new research ideas, approaches, and data (NACC)



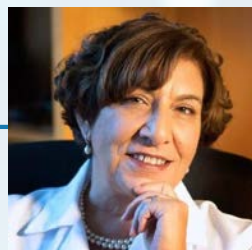
# ADRC | Core Leaders



**Frank LaFerla**  
Administrative Core  
Director



**Andrea Wasserman**  
Chief Administrative  
Officer



**Claudia Kawas**  
Clinical Core  
Director



**David Sultzer**  
Clinical Core  
Director



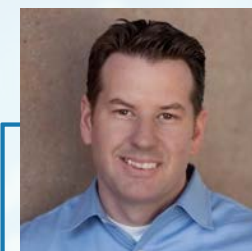
**Ira Lott**  
Down Syndrome Core  
Director



**Maria Corrada**  
90+ Core Director



**Joshua Grill**  
Associate Director  
ORE Core Director



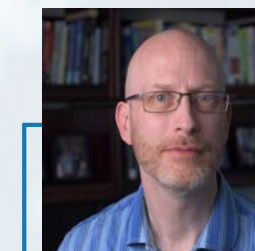
**Daniel Gillen**  
Data Management  
and Statistics Core  
Director



**Edwin Monuki**  
Neuropathology Core  
Director



**M Blurton-Jones**  
iPSC Core Director



**Craig Stark**  
Biomarker Core  
Director



**Elizabeth Head**  
Research Education  
Component Director



**Ten new faculty hires since 2015**



**Special Populations Cores Established:  
90+ and Down Syndrome**



**Biomarker Core**



**Research Education Component**

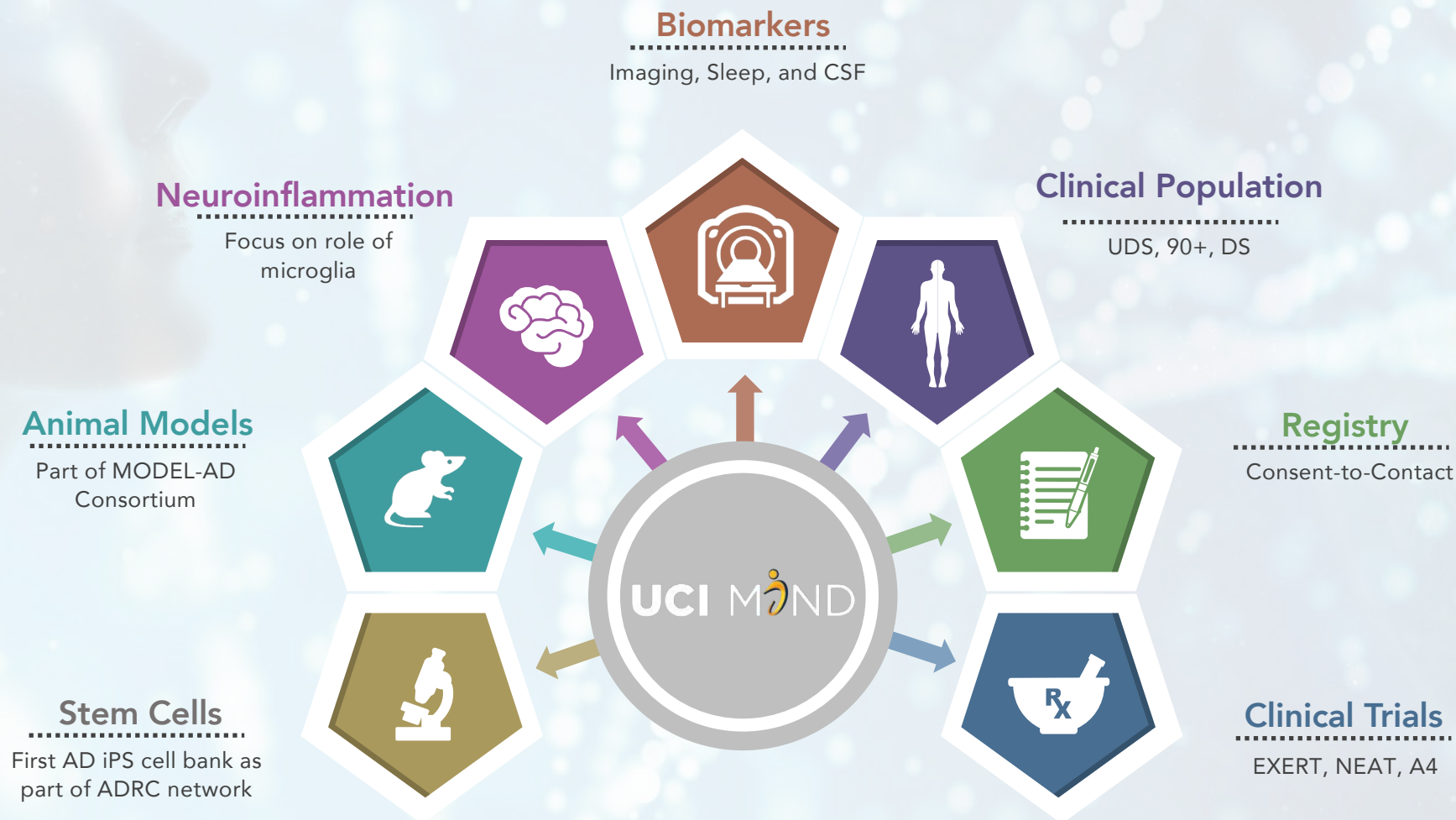


**Core Leadership**



**Recruitment Registry: Consent-to-Contact (C2C)**

# UCI ADRC | Research Overview





# Modeling Human Disease in Mice



## Practical Reasons

Mice breed quickly; age over 2-3 year lifespan

Brain organization is comparable to humans

Many genes/proteins/pathways are conserved between humans and mice

Relatively "cheap" versus human studies

Insert and express human genes in mice, allowing them to develop human diseases/pathology, even in brain

Study disease processes, which are not possible in living humans

Evaluate new treatments and determine mechanism of action



## A mouse is not an accelerated human!

- Many AD-related biochemical and neuropathologic events may not develop in the normal lifespan of a mouse
- Need to be realistic, as not all findings will be translatable to humans
- Need to develop the next generation of animal models of the disease, particularly those mimic late-onset Alzheimer's disease

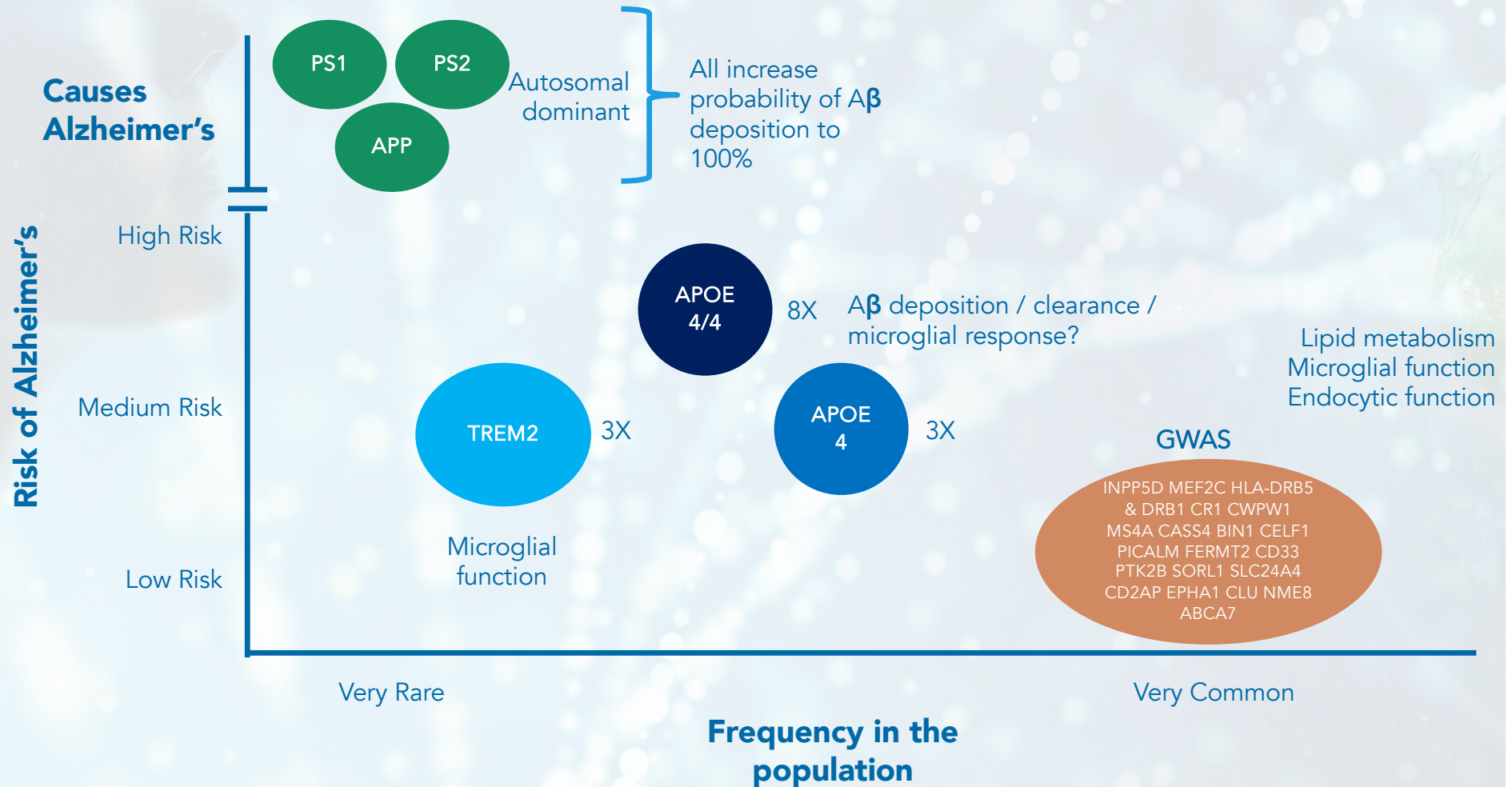
Preclinical studies need to be conducted in several different models to better mimic the heterogeneity in the human population

Even in animal models, the sooner treatment begins the more likely the cognitive impairments are improved

Targeting A $\beta$  after other pathologies set in, particularly phosphotau and NFT pathology, does not rescue cognitive impairments

Combination therapies are likely to be required

# Genetics of Alzheimer's





# Models of Human Disease (LaFerla)



## Alzheimer's Disease

*3xTg-AD*  
*Arctic-tau*



## Lewy body

*3x-Tg-AD x alpha-synuclein*



## Hippocampal sclerosis

*CaII-tTA x TRE-DTa*



## Inclusion body myositis

*MCK-APP*



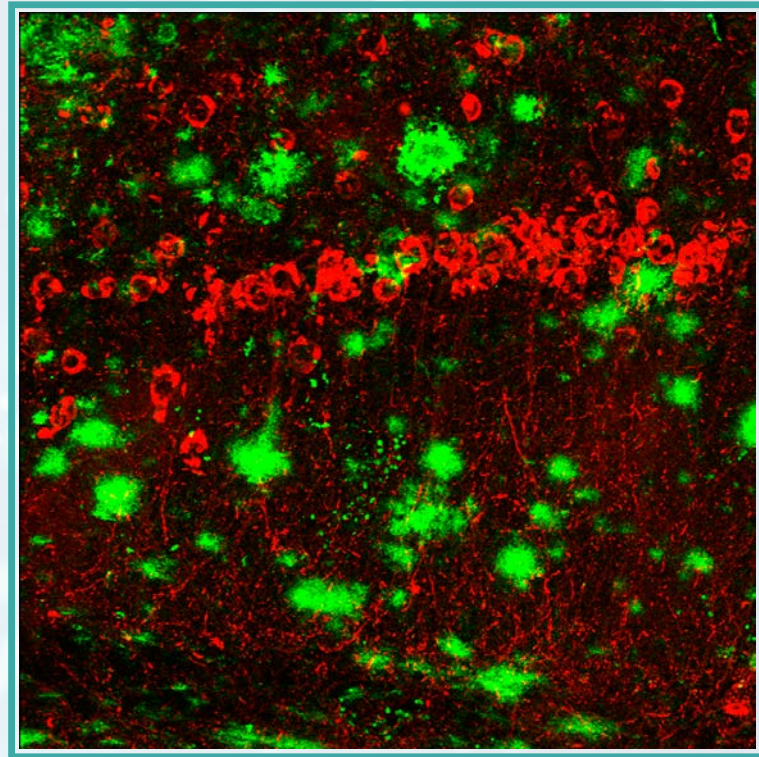
## Tauopathy

*hTau mouse*

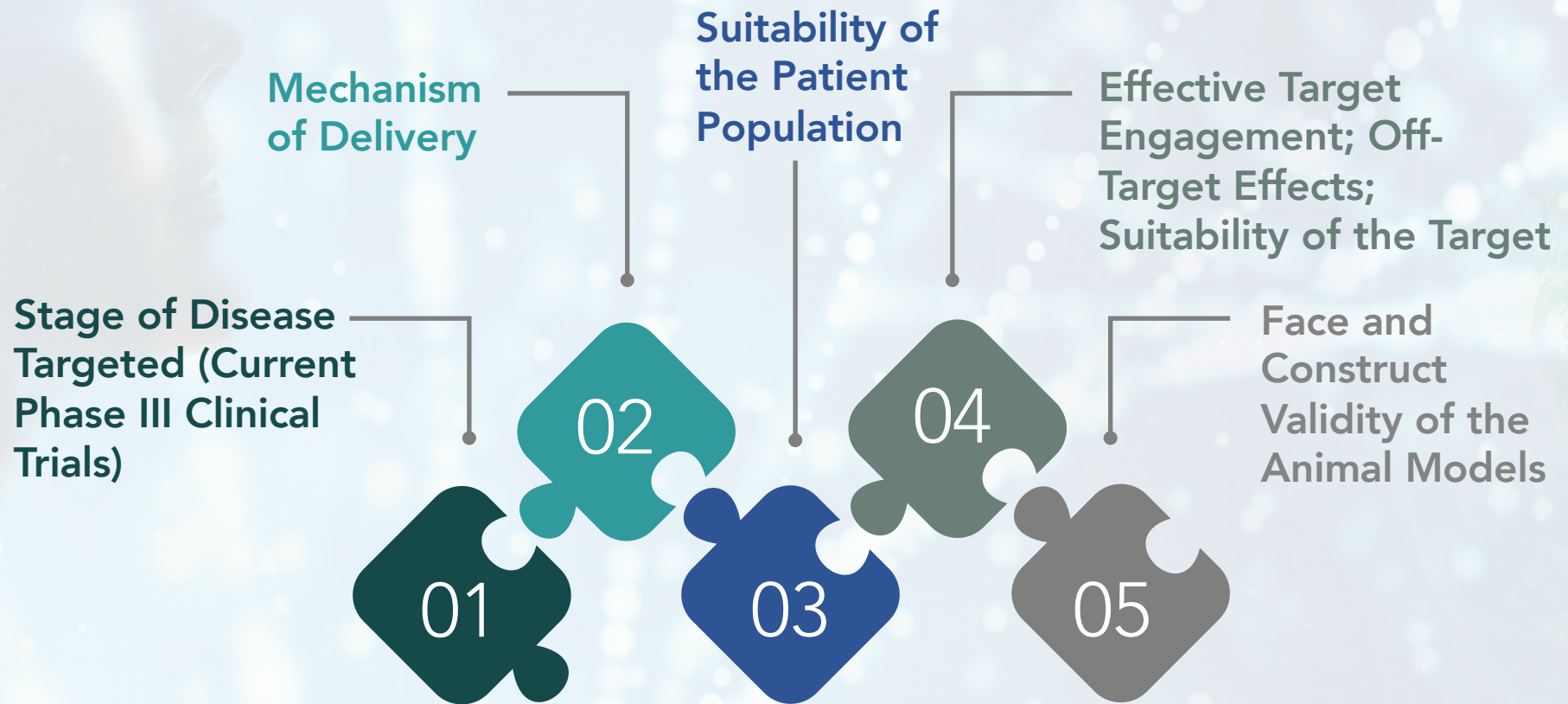


## Human A $\beta$ Knockin

*Humanized wildtype A $\beta$*   
*(floxed)*

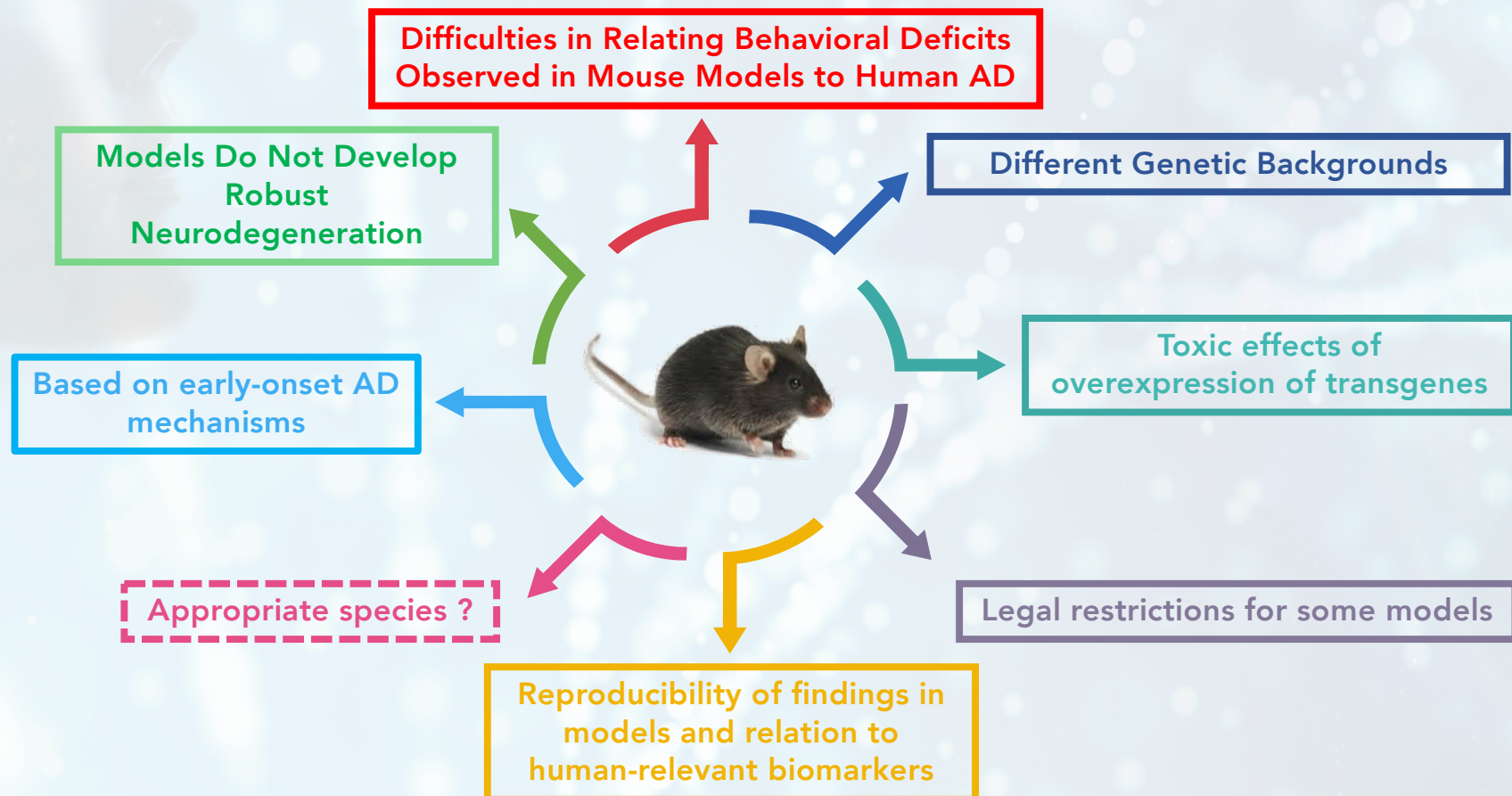


# Reasons for Clinical Trial Failure





# Concerns with Existing Animal Models of AD



# Recommendations from NIA AD Summit (2015)



NIH

1

**Develop** the next generation of *in vivo* models based on human data to explore ADRD



2

**Standardize** process to develop and characterize models; rapid availability to all researchers for preclinical drug development



3

**Align** pathophysiological features of AD models with corresponding stages of clinical disease using translatable biomarkers



4

**Establish** guidelines for rigorous preclinical testing in animal models and report positive and negative findings

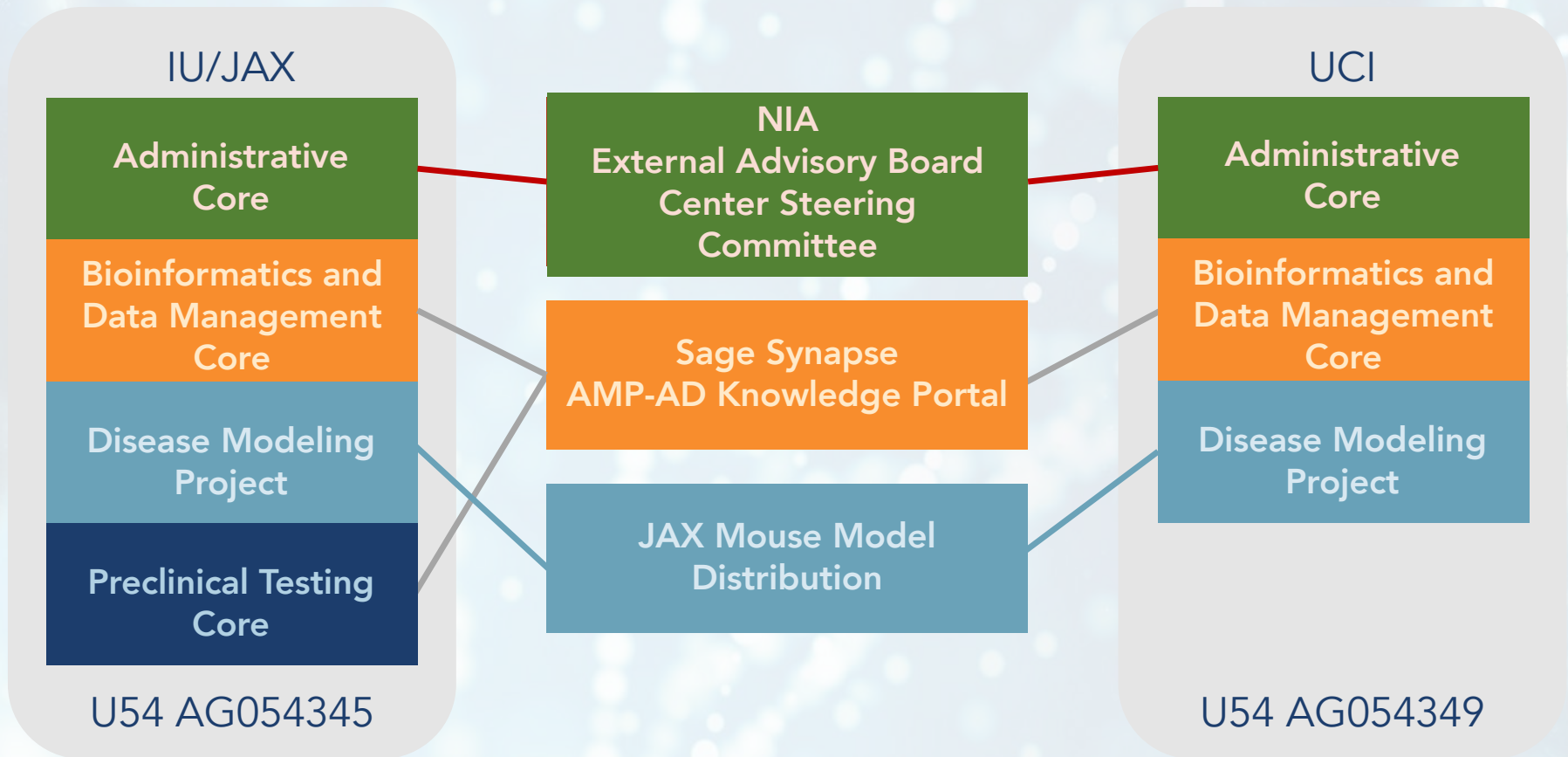




**M**odel  
**O**rganism  
**D**evelopment  
**E**valuation  
**L**ate-onset  
  
**A**lzheimer's  
**D**isease



# MODEL-AD Consortium



# Early versus Late-onset AD



## Early-onset



» <65 years

» Autosomal Dominant  
(APP, PS1, PS2)

» <1-2%

Age of onset

Etiology

% Cases

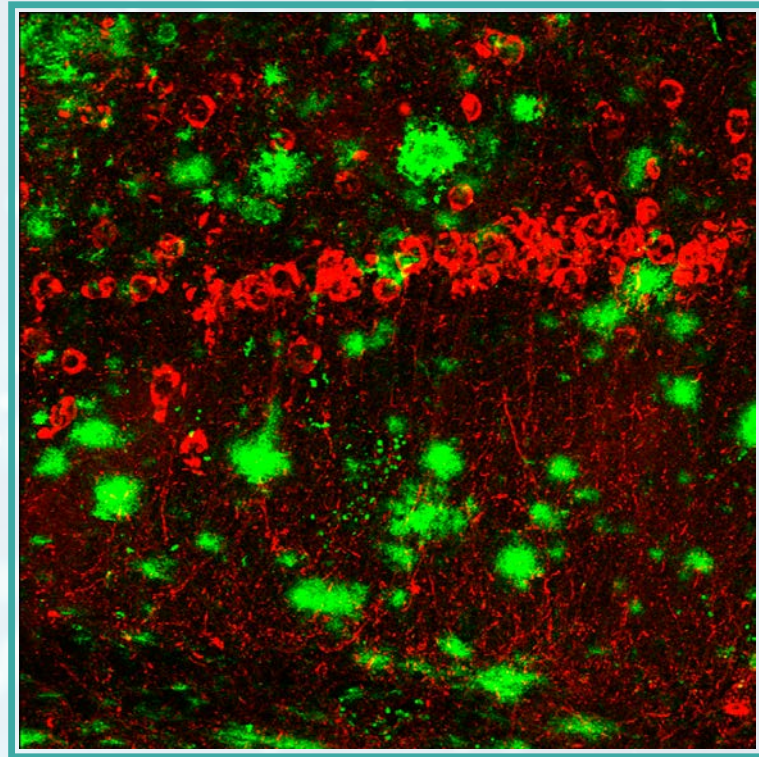
## Late-onset



» >65 years

» APOE; GWAS Genes  
» Aging

» >98%





# Rationale for Humanizing A $\beta$ in Mice



Human v. rodent A $\beta$



Wildtype A $\beta$  needed for modeling LOAD



Physiological gene expression



Cre/lox P – cell/time specific ablation



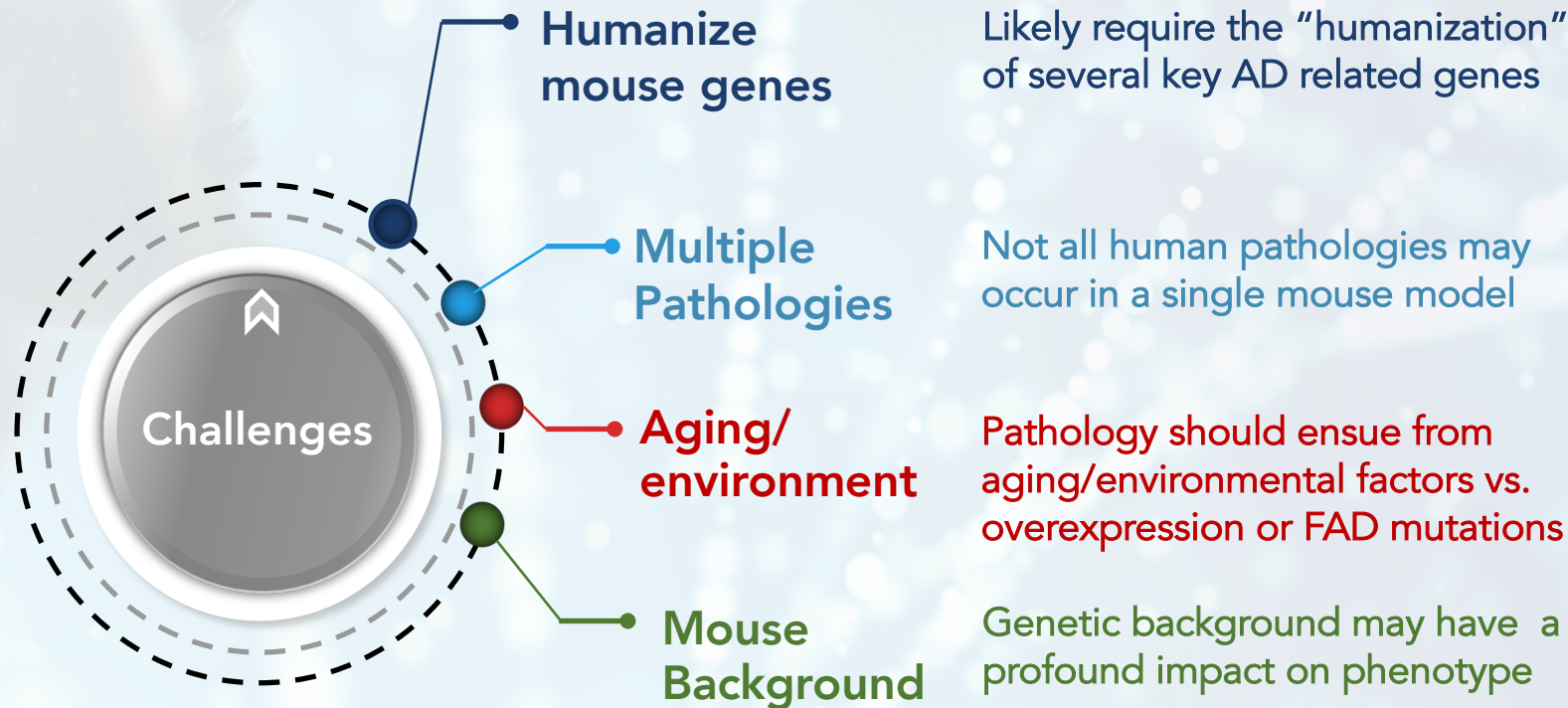
Use of these mice as a platform



Preclinical evaluation of potential therapies



# Key Challenges in Modeling Late Onset Alzheimer's



# Gene/Variant Prioritization



## Systematic assessment of LOAD loci

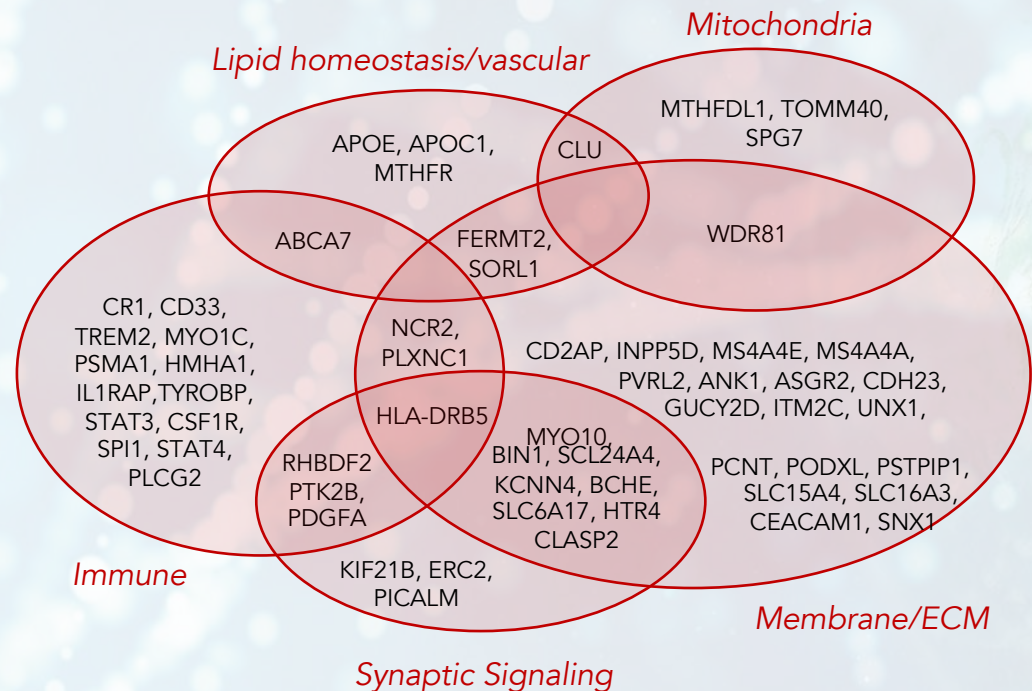
Significance in multiple studies 01

Predicted effect on function 02

Human-mouse sequence conservation 03

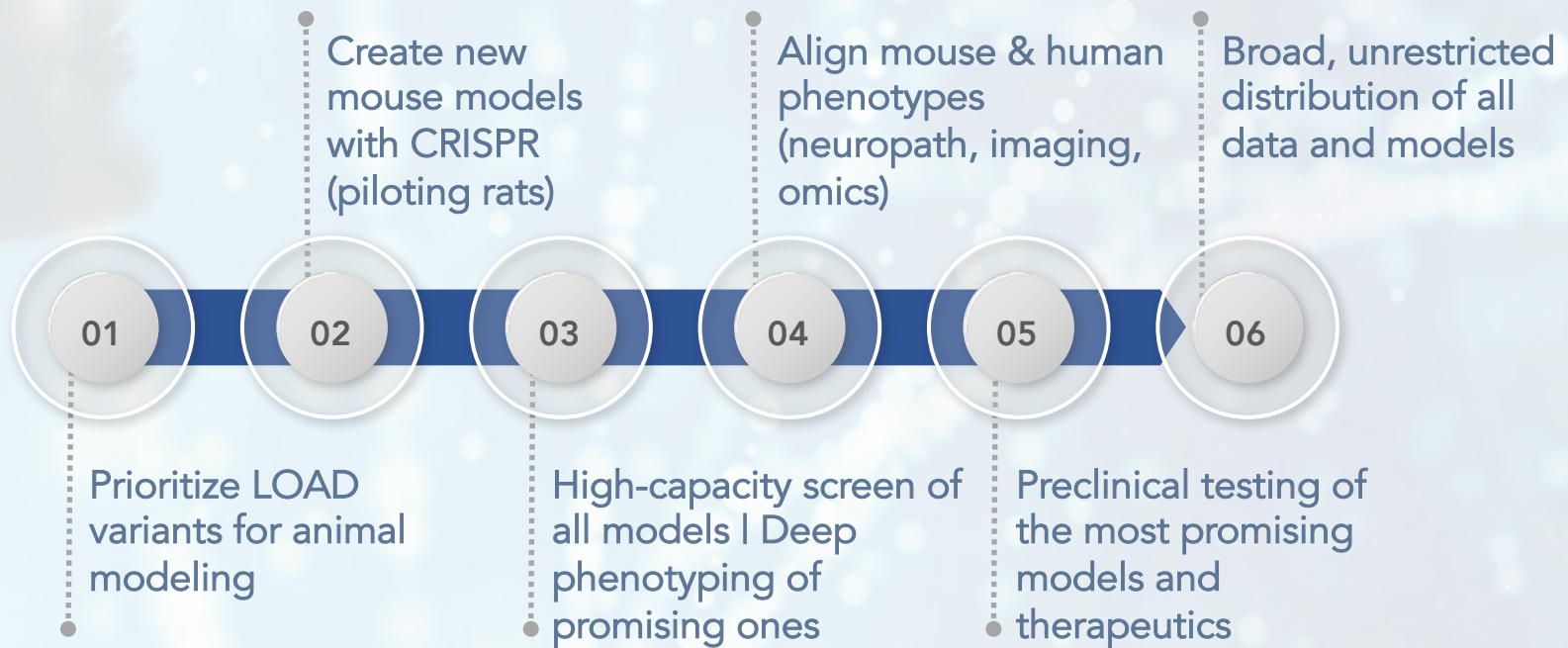
Differential expression in AD 04

Noncoding variant effects? 05





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



## Knockin mice

Use hA $\beta$  mice  
as platform



## Human Data + Other Variants

Maximize human data to  
identify relevant variants  
such as tau and others



## Environment & Diet

Introduce risk factors



Share

■ Funded  
■ Not Funded

# Deep Phenotyping Pipeline



TIMELINE PHENOTYPING PIPELINE (months)

2

4

6

8

10

12

14

18

22



hA $\beta$ -KI

Crosses  
hA $\beta$ -KI  
x  
variants

5xFAD

3x-TgAD

Pathology

Biochemistry

Functional  
Phenotyping (LTP)

Network analysis  
(RNAseq)



# Summary | hA $\beta$ -KI Mice



DNA sequence analysis shows that hA $\beta$ -KI mice **encode human wt A $\beta$**

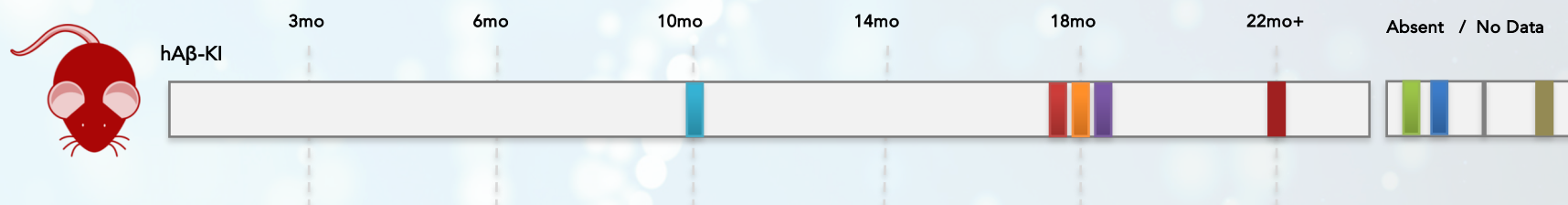
hA $\beta$ -KI and wt mice have **similar APP levels**

hA $\beta$ -KI mice display significant **synaptic and cognitive impairments** (CX and HC)

**Important gene expression** in metabolic, neuroplasticity and transcriptional regulation pathways are altered in the hA $\beta$ -KI mice

hA $\beta$ -KI mice shows **age-dependent** amyloid accumulation

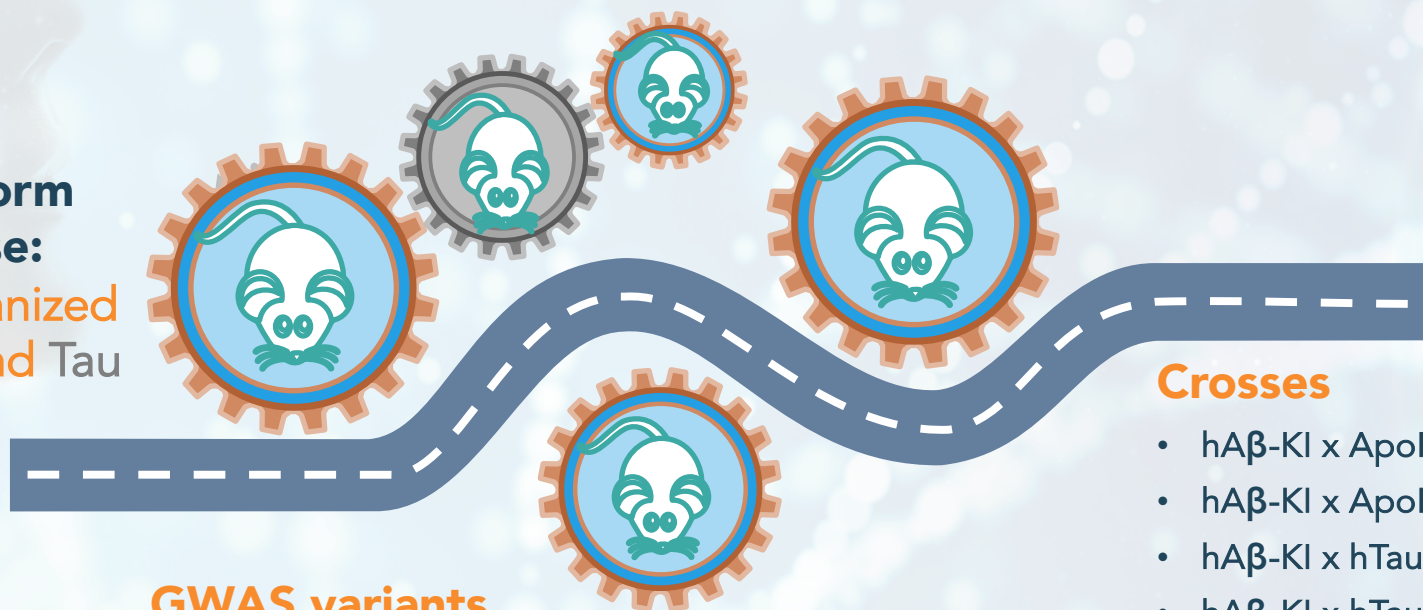
hA $\beta$ -KI mice contain seeds that **facilitate A $\beta$  aggregation**



# Construction Plan for Model Development



**Platform  
Mouse:**  
Humanized  
A $\beta$  and Tau



## GWAS variants

1. ABI3 S209F
2. ABCA7 V1599M
3. BIN1 K358R  
and rs2279590
4. EPHA1 P460L
5. PICALM H458R
6. CLU rs9331888

## Crosses

- hA $\beta$ -KI x ApoE4
- hA $\beta$ -KI x ApoE4 x variants
- hA $\beta$ -KI x hTau
- hA $\beta$ -KI x hTau x variants

# Resource Sharing



## Enabling researchers to find the right model

### Data

Mouse genetic information: variant(s), strain background

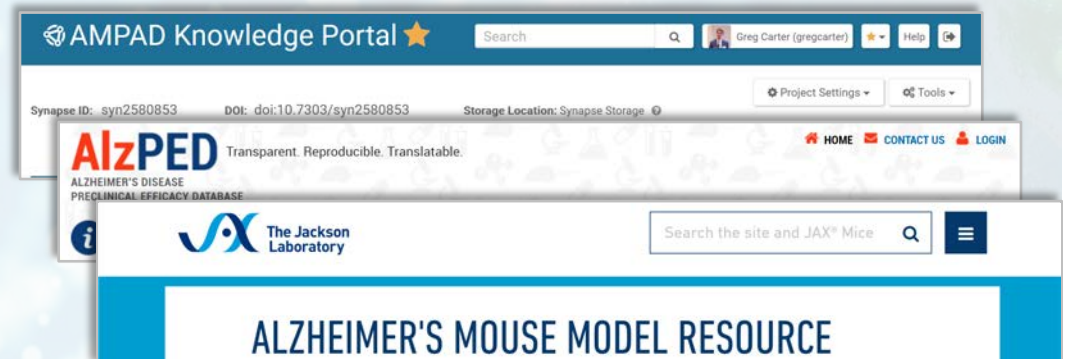
Mouse phenotype data: RNA-seq, imaging, etc.

Preclinical data: standards, protocols, results

Preclinical results searchable on AlzPED

### Mice

Available from JAX mouse repository without restrictions



# Approaches to Study Complex Disorders



such as Alzheimer's disease



## Clinical

- Neuropsychology
- Epidemiology
- Observational



## Imaging

- MRI
- PET
- Others



## Tissues

- Postmortem Brain
- Blood
- CSF



## Cell Models

- Primary
- Cell lines
- iPS



## Animal Models

- Natural
- Pharmacological
- Viral
- Genetic



# Value of AD Mouse Models



Mechanistic aspects with high relevance to the clinical scenario



Identify factors that exacerbate or attenuate phenotype



Pharmacodynamic vs. pharmacokinetic considerations



May inform clinical trial design



Direct comparison between new treatment vs. competitor drugs

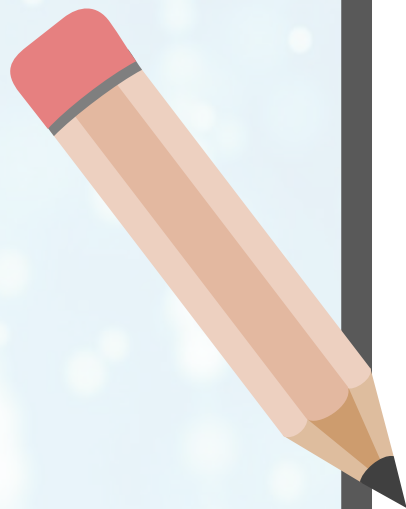


Potential liabilities

# Preclinical Studies:



## Considerations for Moving from Bench to Bedside



Multiple appropriate models (including sexes)



Studies across age spectrum



Multiple doses/reversal studies



Multiple sites



Mechanism of Action

# What does a successful model of late-onset AD look like?



## FACE

- Age-related, region-specific
- Plaques
- Tau 4/3; NFTs
- Synaptic Loss
- Neuronal Loss
- Neuroinflammation
- Cognitive Decline
- Behavior (Anxiety)
- Sleep



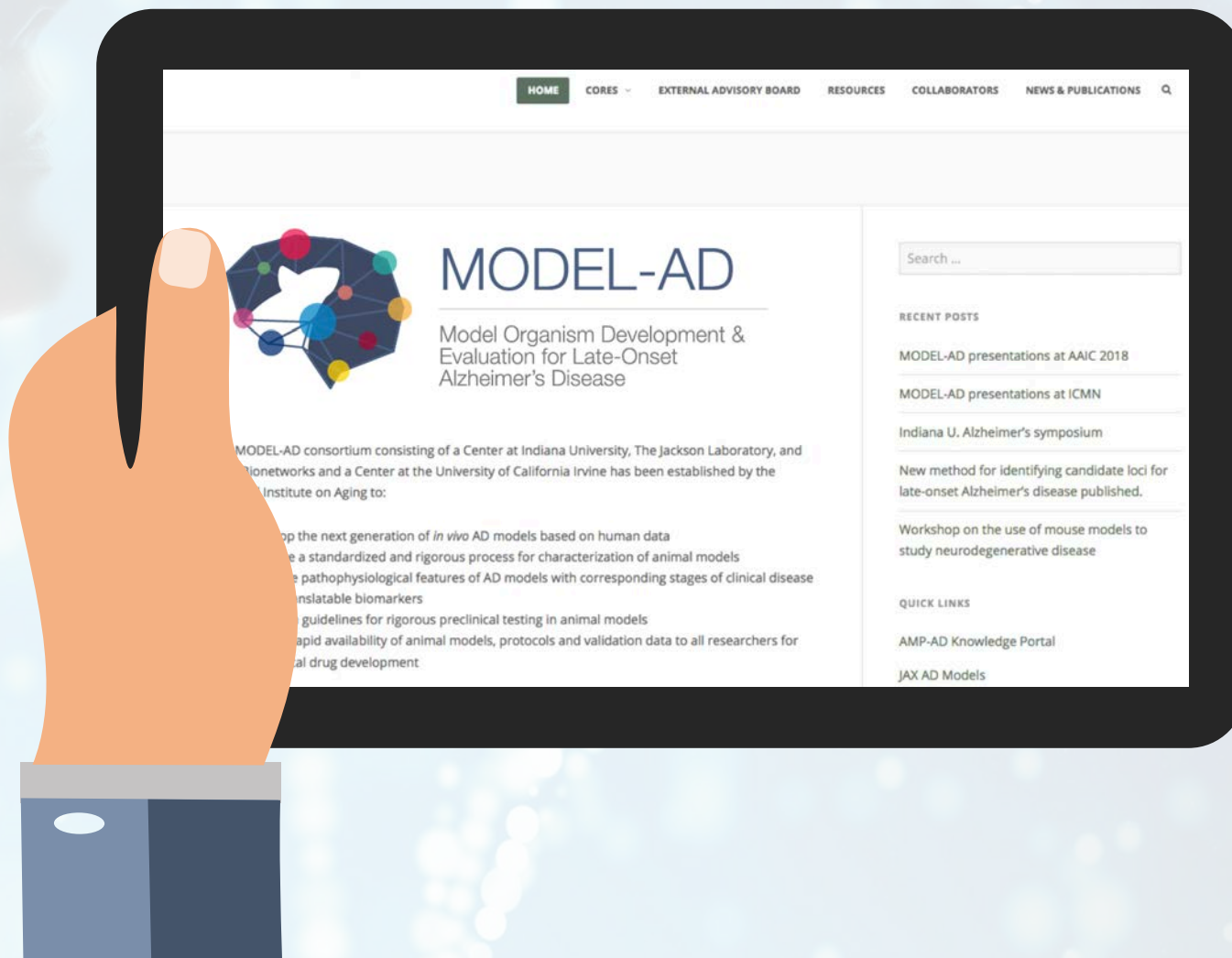
## CONSTRUCT

- No mutations
- Physiological expression
- Humanize all genes?



## PREDICTIVE

- Translatability
- Insights into the human disease
- Identification of novel targets
- Biomarkers
- Imaging
- 'Omics



## MODEL-AD

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

MODEL-AD consortium consisting of a Center at Indiana University, The Jackson Laboratory, and  
ion networks and a Center at the University of California Irvine has been established by the  
Institute on Aging to:

top the next generation of *in vivo* AD models based on human data  
e a standardized and rigorous process for characterization of animal models  
e pathophysiological features of AD models with corresponding stages of clinical disease  
nstable biomarkers  
guidelines for rigorous preclinical testing in animal models  
apid availability of animal models, protocols and validation data to all researchers for  
al drug development.

Search ...

### 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

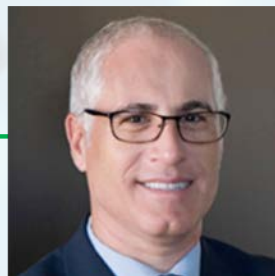
### QUICK LINKS

AMP-AD Knowledge Portal

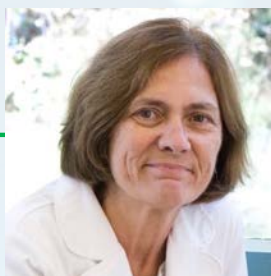
JAX AD Models



# Team



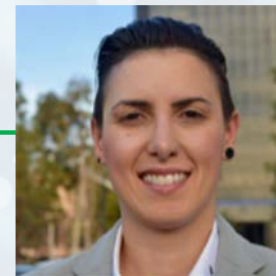
**Frank LaFerla**  
Co-Director



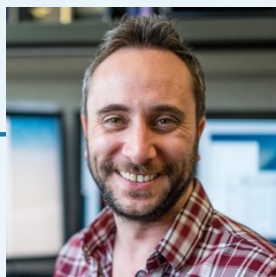
**Andrea Tenner**  
Co-Director



**Andrea Wasserman**  
Administrative  
Coordinator



**Stefania Forner**  
Project Manager



**Kim Green**  
"Phenotyping"  
(Disease Model Project)



**Marcelo Wood**  
"Phenotyping"  
(Disease Model Project)



**Grant MacGregor**  
Head  
(Disease Model Project)



**D. Baglietto-Vargas**  
Research Scientist  
(Disease Model Project)



**Ali Mortazavi**  
Head (Bioinformatics and  
Disease Modeling Core)

# 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 Ghatti  
David Jones  
Sarah Quinney  
Deborah DeBusk, Administrator

## Sage Bionetworks

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

## 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



## National Institute on Aging

Suzana Petanceska  
Lorenzo Refolo  
U54 AG054345, U54 AG054349

## 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  
Celia da Cunha  
Edna Hingco  
Dominic Javonillo  
Jimmy Phan  
Dina Matheos  
Maria Fonseca  
Andrea Wasserman, Administrator

## Contact

[www.model-ad.org](http://www.model-ad.org)  
[modelad@iupui.edu](mailto:modelad@iupui.edu)  
[@Model\\_ad\\_alz](https://twitter.com/Model_ad_alz)

## External Advisory Board

David Bennett  
Robbie Brinton  
Ron Demattos  
Joel Dudley  
Marcie Glicksman  
Barry Greenberg  
Cindy Lemere  
Frank Longo  
Lennart Mucke  
Steve Perrin  
Linda Van Eldik (Chair)

