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

Infrastructure for Next-Gen Animal Model Development and Rigorous Preclinical Efficacy Testing

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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

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

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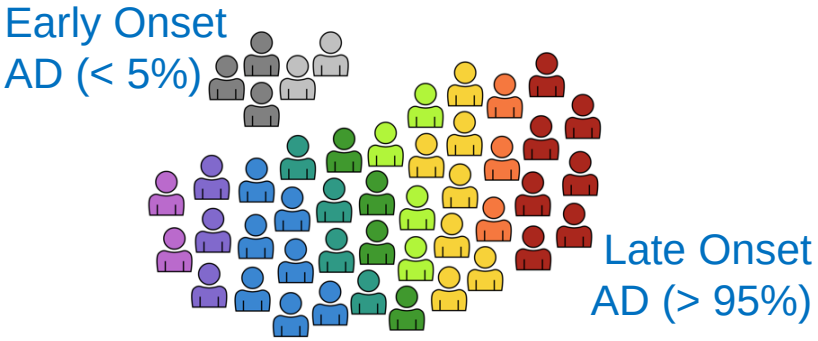
MODEL-AD Goals



- **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

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Disease Modeling Project

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Preclinical Testing Core

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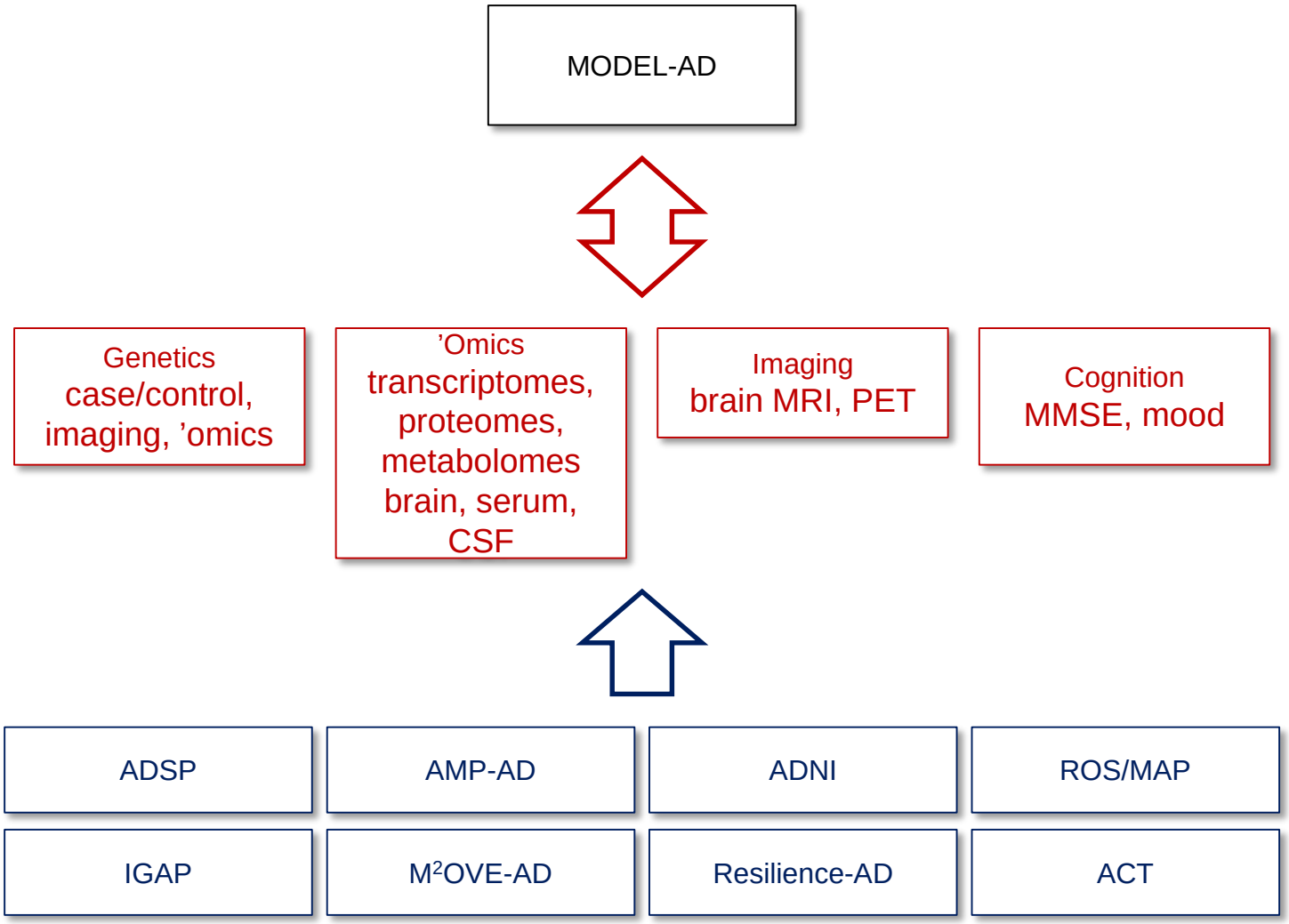
Leveraging the AD Data Universe



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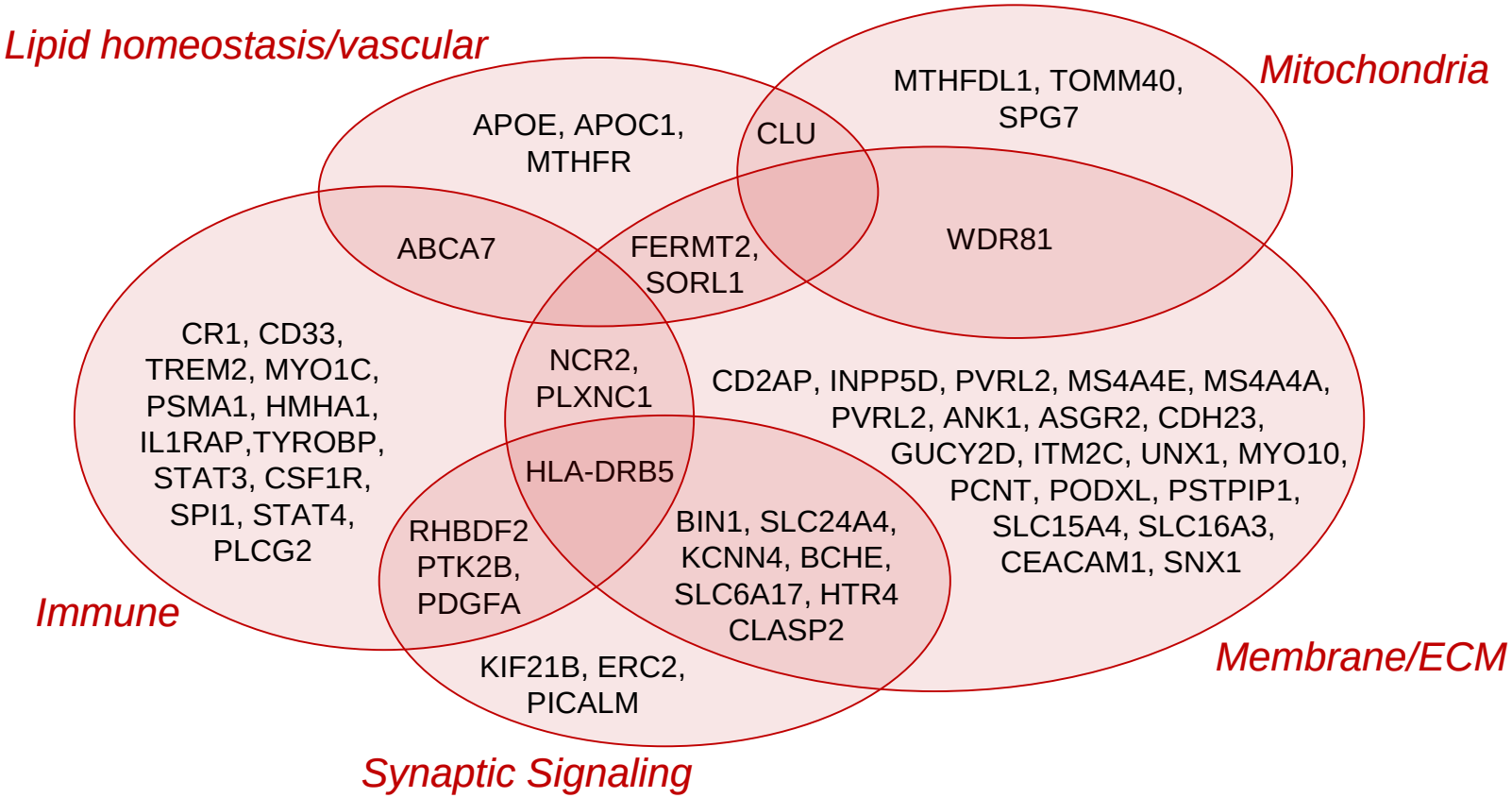
Variant Prioritization: IU/JAX

Systematic assessment of AD loci



- Significance in multiple studies
- Predicted effect on function
- Human-mouse sequence conservation
- Differential expression in AD

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Model Creation and Dissemination: IU/JAX

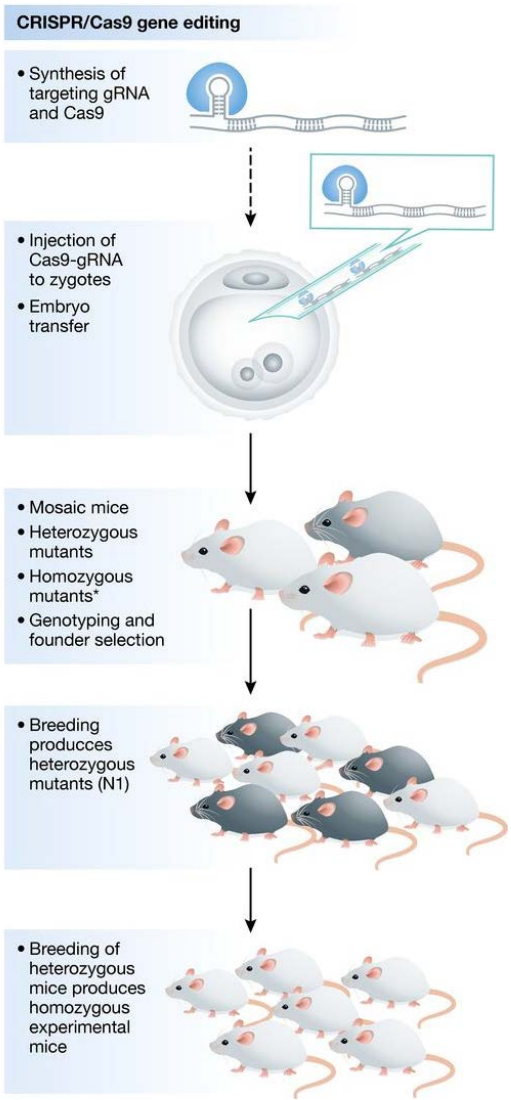
CRISPR/Cas9 enabled

Now available:

- *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
  - ➢ First group available summer 2018
- Combinations of variants for broad pathology



ET Liu *et al*. EMBO Rep. 2017

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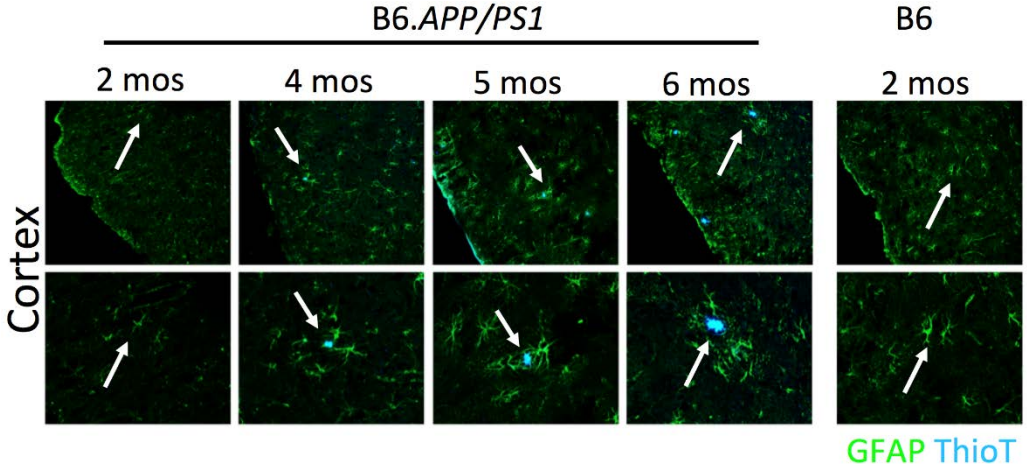
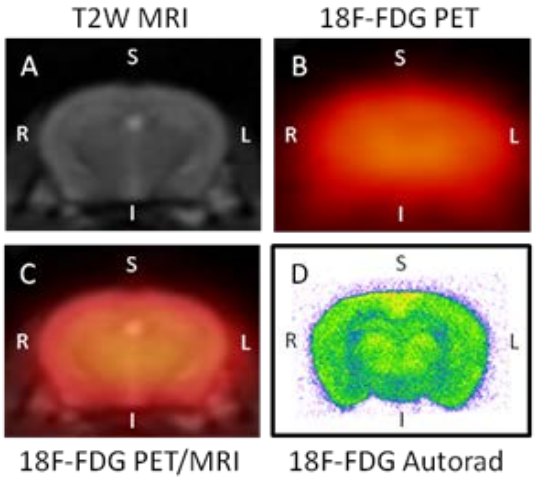
Model Characterization: IU/JAX

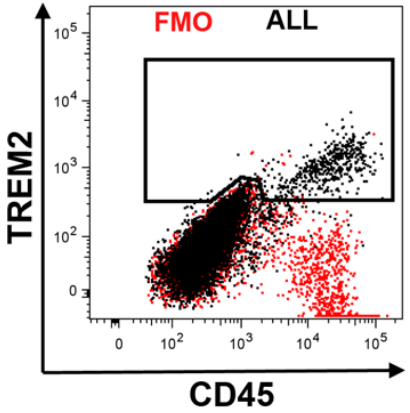
neuropathology



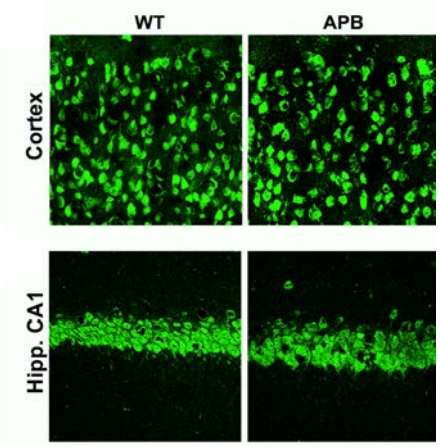
in vivo imaging



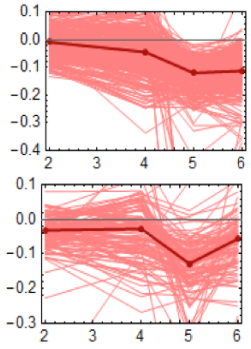
blood biomarkers



neurodegeneration



molecular profiling (RNA-seq)



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

nervous system development	1×10^{-6}
Jak-STAT signaling pathway	$\mathbf{3 \times 10^{-4}}$

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Model Characterization: IU/JAX

AMP-AD, ADNI	MODEL-AD	
Assay	**Initial Screening** 12 months all models	**Deep Phenotyping** 4, 8, 12, 18 months selected models
Amyloid and tau pathology	•	•
Neuroinflammation	•	•
Synaptic and neuronal loss	•	•
Biomarkers (Quanterix)	•	•
Biomarkers		•
Transcriptomes (nanoString)	•	
Transcriptomes (RNA-seq)		•
Transcriptomes (scRNA-seq)		pilot study
Proteomics		•
Metabolomics		•
Imaging (FDG, PET/MRI)		•
Cognitive tests		•

Human-mouse assay

• identical

• similar

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Preclinical Testing: IU/JAX

- 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

Newest member of consortium-UC Irvine

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Variant Prioritization: UCI

1. **Humanize Aß and Tau**
2. **Focus on non-coding variants, especially in enhancers**

- Variants cross-checked with available human open chromatin accessibility and other functional genomics data from ENCODE as well as GTEx eQTL results

- If best candidate regulatory element is not conserved in mouse, then introduce human sequence and flanking regions into mouse

- **Current targets being pursued include:**

  Spi1/PU.1

  Clusterin

  CSF1 and/or CSF1R

Coordinated with IU/JAX

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Model Production and Dissemination: UCI

HR / ES cells, CRISPR/Cas9 enabled

Now available:

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

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

Stock No: 030898 | hAbeta-loxP-KI

Additional variants to engineer

- **Humanized *MAPT* (TAU) via substitution of mouse *Mapt* locus with human H1c *MAPT* via RMCE – in progress**
- Humanized *CLU* via substitution of mouse *Clu* locus with human *CLU* via RMCE.
- GWAS variants of *SPI1* (PU.1) via CRISPR.

RMCE = recombinase-mediated cassette exchange.

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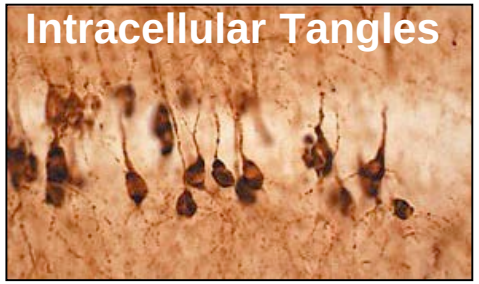
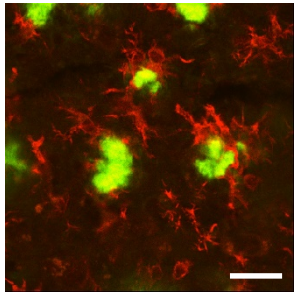
Model Characterization: UCI

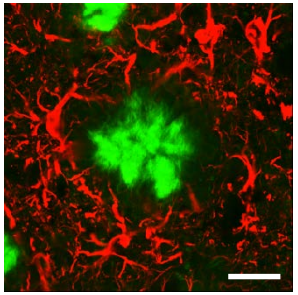
Neuropathology and Neurodegeneration

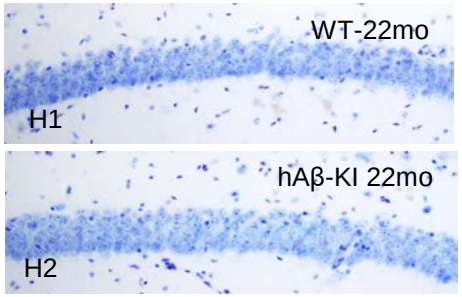


ThioS-iba1

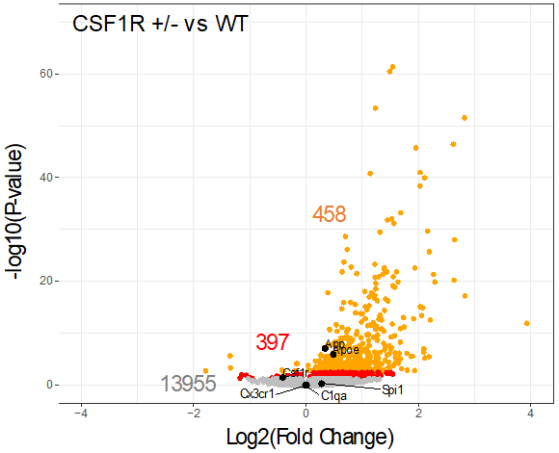


ThioS-GFAP



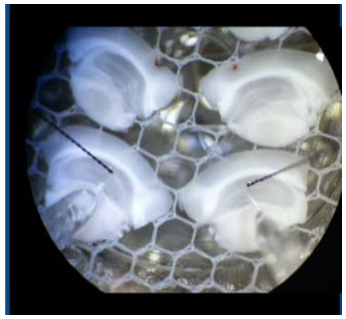


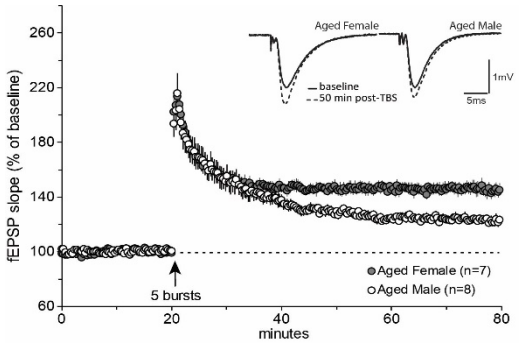
Network analysis

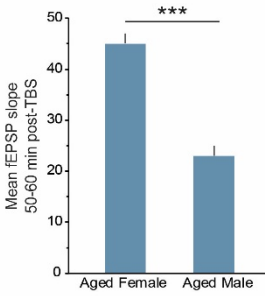


APP and APOE are significantly higher in the CSF1R +/- mice

Electrophysiology







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Resource Sharing

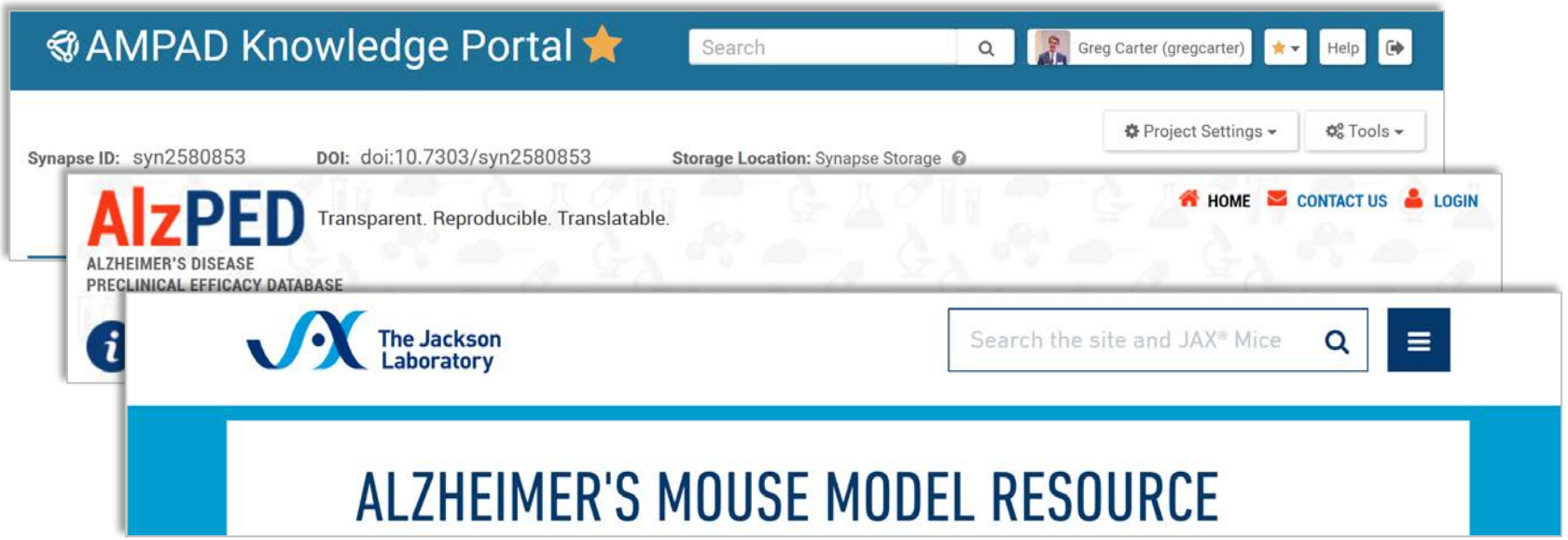
Enabling researchers to find the right model

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



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Currently seeking a Center Research Manager (PhD-level neuroscientist) at JAX

NIH National Institute on Aging

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