Evaluating the Translational Validity of Mouse Models of Late-Onset AD (LOAD) through Deep-Phenotyping

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UCI MODEL-AD Disease Modeling Project (DMP)

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

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MODEL-AD Consortium - Disease Modeling Project (DMP)

- General strategy for model development and phenotyping platforms.
- Examples of hAβ-KI (completed) and hTau-KI (in progress).
- Phenotyping of *APOE4*, *Trem2*^{R47H} models.
- Effect of mouse genetic background on development of pathology.

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Concerns with Existing Animal Models of AD

Difficulties in Relating Behavioral Deficits
Observed in Mouse Models to Human AD

Models Do Not Develop
Robust Neurodegeneration

Many Models Generated/Maintained
on Different Genetic Backgrounds

Largely focused on early-onset
AD mechanisms

Toxic effects of overexpression
of transgenes

Appropriate species ?

Legal restrictions for some models

Reproducibility of findings in models and
relation to human-relevant biomarkers

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Using genome engineering to generate mouse models of Late-Onset Alzheimer's Disease (LOAD)

- Use CRISPR/Cas9 to introduce coding and conserved non-coding LOAD GWAS risk-variants into cognate loci in mouse genome – e.g. *Trem2*^{R47H}
- Overcomes limitations associated with -
  - Random integration of transgenes.
  - Supra-physiologic expression.
  - Lack of availability of matched negative controls.
- Accelerated production compared with previous HR / ES-cell based strategies.
- Improve reproducibility and reduce experimental variability by using consistent genetic background (C57BL/6J, initially).

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Using advanced genome engineering to generate mouse models of Late-Onset Alzheimer's Disease (LOAD) – UCI DMP

- Use CRISPR/Cas9 with long (~ 2kb) ssDNA homology dependent repair (HDR) templates to introduce non-conserved LOAD GWAS risk-variants into cognate loci in mouse genome – e.g. humanizing non-conserved regions of mouse clusterin locus (*Clu)*.
- Use of Recombinase Mediated Cassette Exchange (RMCE) to humanize entire loci – e.g. hTau-KI, hClu-KI.
- Generate LOAD mouse models on consistent genetic background (C57BL/6J, initially).
- Maximize researcher access to all models – available to both academics and pharma from Jackson Lab AD Mouse Model Resource, with minimal restrictions.

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A humanized platform for introduction of GWAS AD-risk variants to generate mouse models of LOAD

B6J. hAβ-KI; APOE$^{ε4/ε4}$; hTau-KI
base platform

Available now **In development**

Long-term goal

- Introduce different combinations of GWAS human LOAD risk alleles into *hAβ-KI; APOE^{ε4}; hTau-KI* via CRISPR/Cas9 or assisted reproduction.
- Perform initial screen, then deep-phenotyping on subset to analyze effects.
  - *Trem2 ^{R47H}*
  - *Abca7 ^{A1527G}*
  - *Plcg2 ^{M28L}*
  - *Mthfr ^{A222V}*

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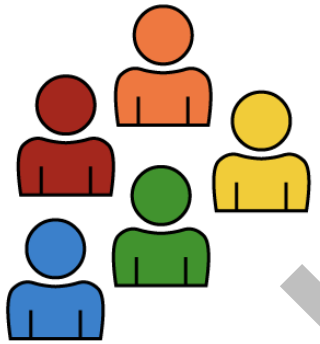
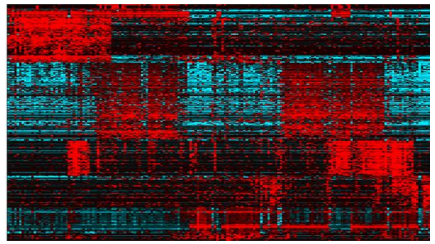
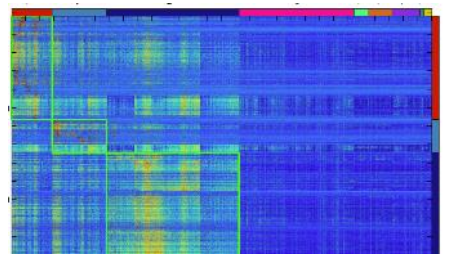
Goal - alignment of mouse models with clinical measures

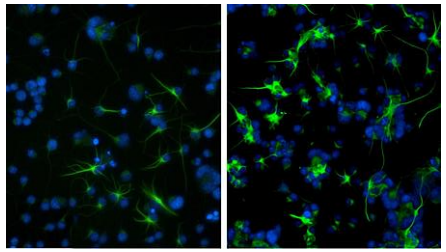
clinical study cohorts



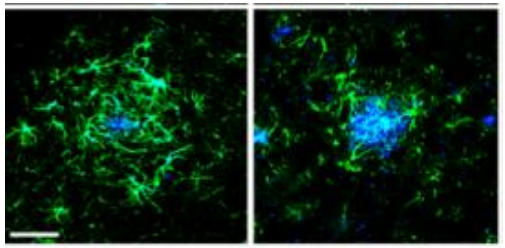


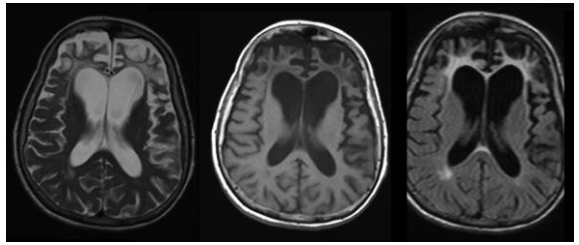
‘Omics



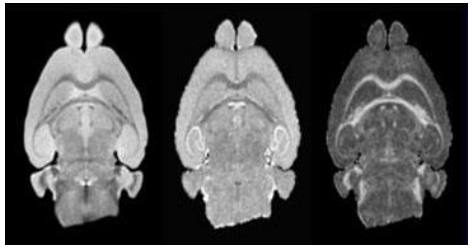


Neuropathology





Brain Imaging



mouse models

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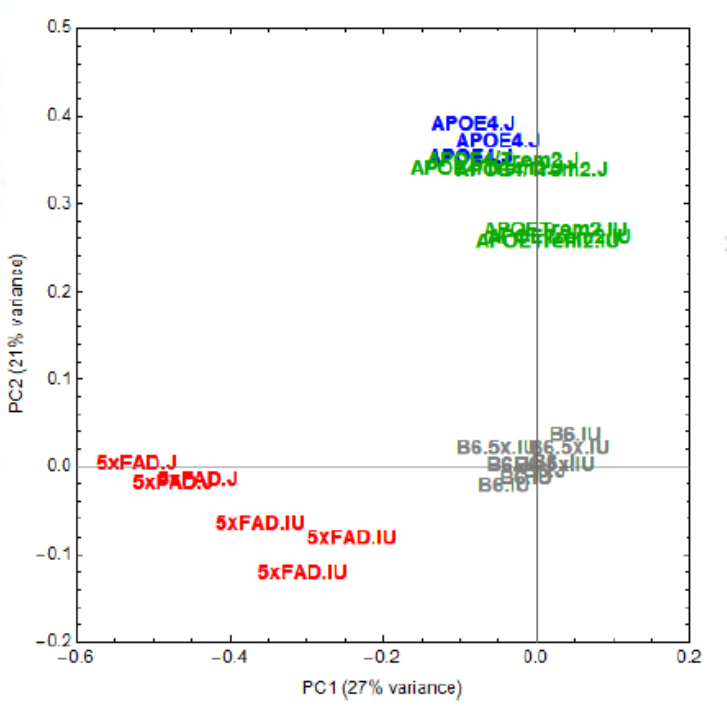
Assessing reproducibility of findings at different sites

- Phenotype = Genes + Environment
- Harmonize environment and methodology to extent possible at each site.
- Assess reproducibility of data generated from deep-phenotyping.



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- 5xfAD
- APOE4
- APOE4;Trem2^{R47H}
- B6J

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- 5xfAD
- hAβ-KI
- hAβ-KI; APOE4
- hAβ-KI; APOE4;Trem2^{R47H}
- B6J

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e.g. IU v JAX mice nanoString Analysis

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Deep phenotyping pipeline for LOAD models – UCI DMP

Pathology	Biochemistry	Functional Phenotyping	Network Analysis
Aβ/plaque load: Thio-S, 6E10	Soluble and insoluble brain fractions (Aβ38, Aβ40, Aβ42) - MSD	Behavior / Cognition	Gene expression via RNA-seq
Tau/NFT load: HT7, AT8, Gallyas	Tau, phospho-Tau	Long Term Potentiation (LTP)	–
Glial densities/activation: Microglia (Iba1, CD68) Astrocytes (Gfap, S100b)	Soluble brain fractions (Inflammatory cytokines) -MSD	–	–
Neurodegeneration: Brain Volume, Neuronal Loss	Plasma Biomarkers	–	–
Vascular Damage: CD31/fibrin	Colon / Fecal Sampling for Microbiome*		

4, 8, 12, 18 month timepoints
18M / 18F available per timepoint
* proposed

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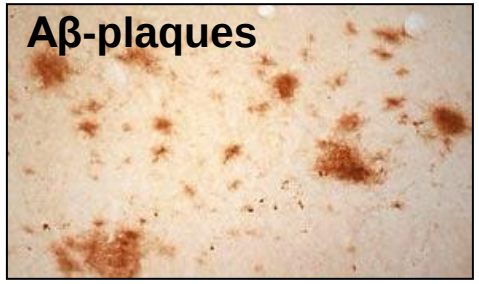
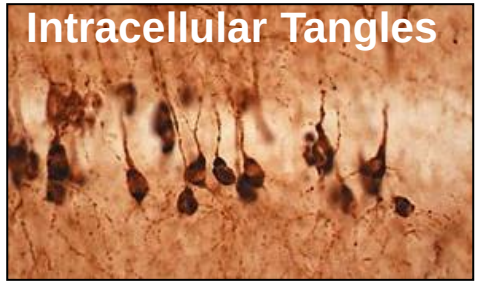
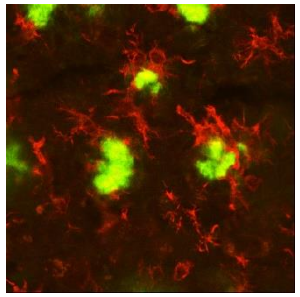
Model Characterization at UCI – 4,8,12,18 month timepoints

Neuropathology and Neurodegeneration

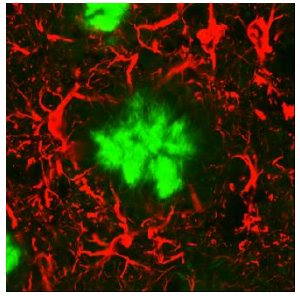


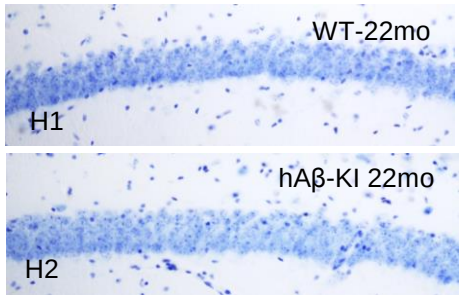


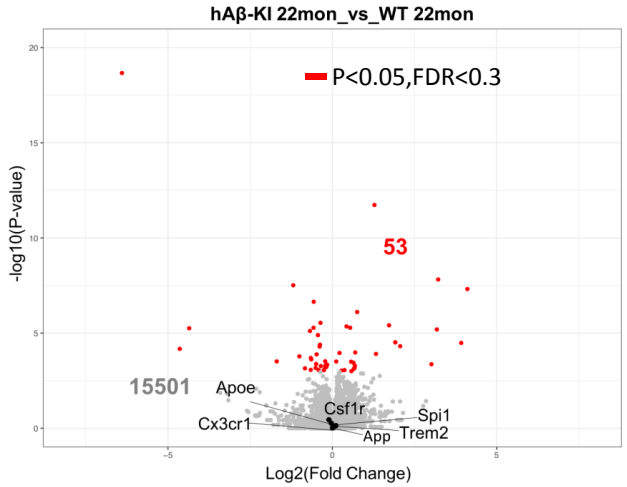
ThioS-iba1



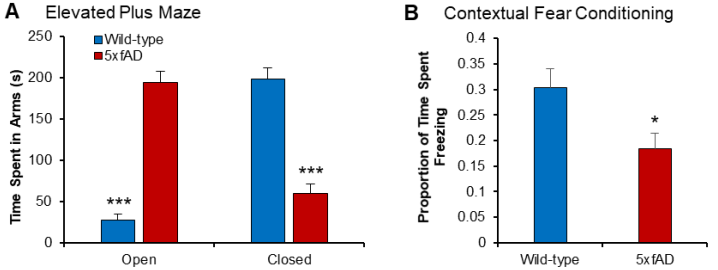
ThioS-GFAP



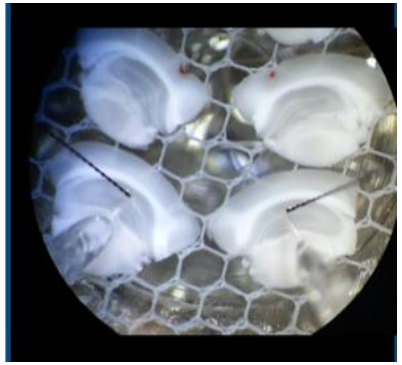


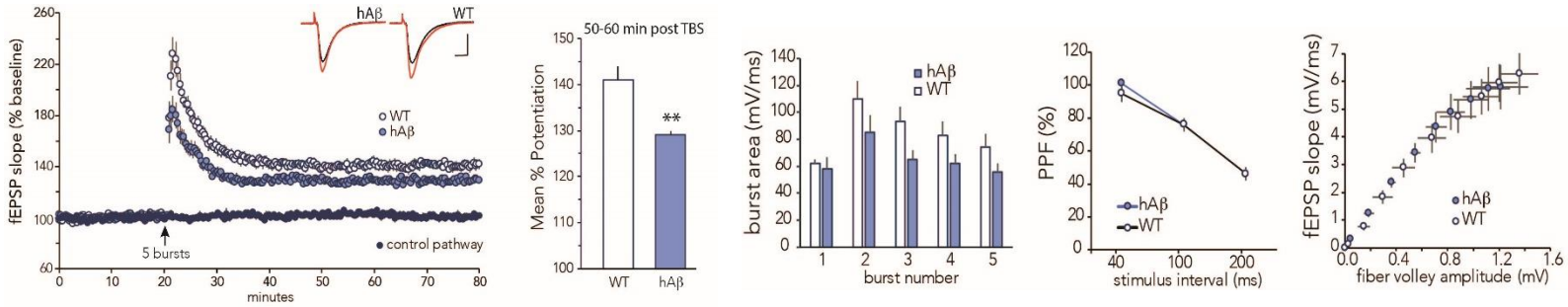


Network analysis: Molecular Profiling (RNA-Seq)



Behavioral and Cognitive Phenotyping





Electrophysiology

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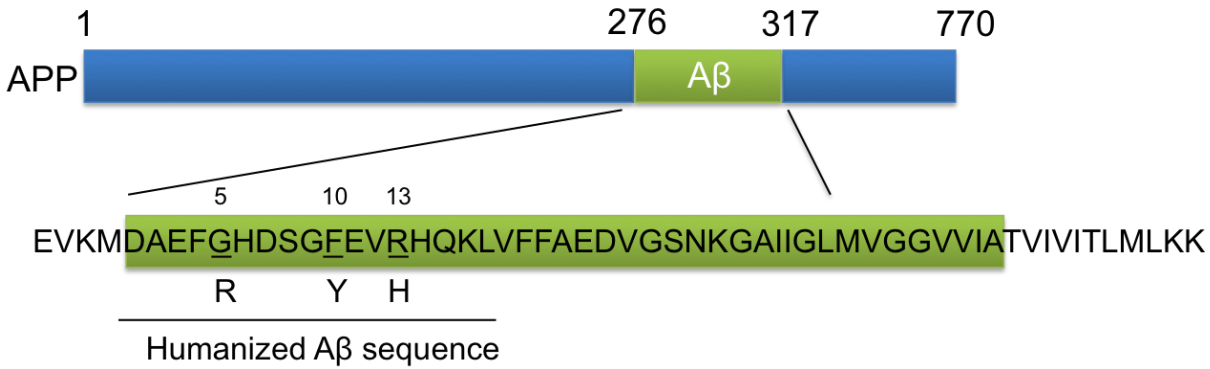
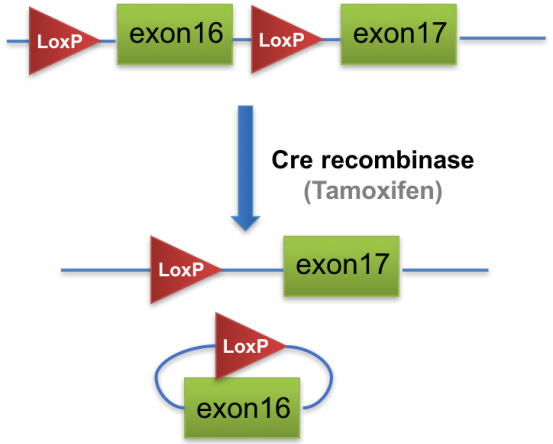
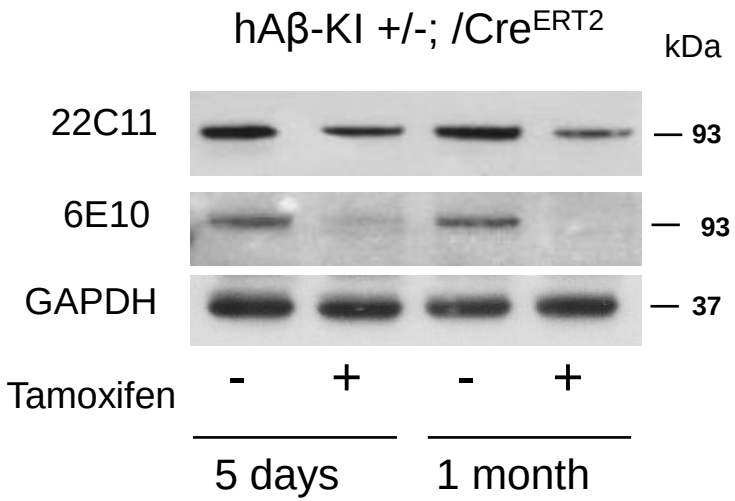
Generation of mice expressing a *cre-loxP* conditional allele of humanized wild-type Aβ □hAβ-loxP-KI model – UCI DMP

- No published allele of mouse *App* expresses normal human Aβ.
- Exon 16 humanized Aβ sequence is floxed, enabling cre-mediated cKO of humanized allele.
- IU/JAX has generated mice with complementary hAβ-KI allele without *loxP* sites.
- Important models to investigate inherent difference in Aβ biology, plus provide platform for LOAD modeling.







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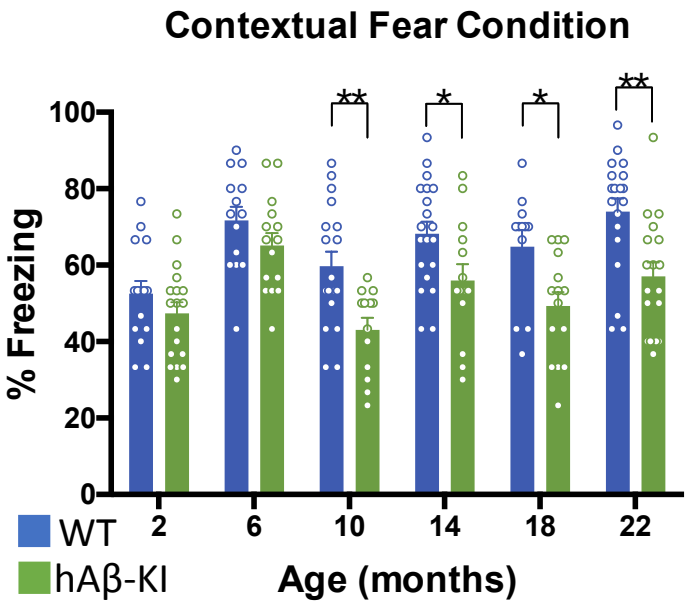
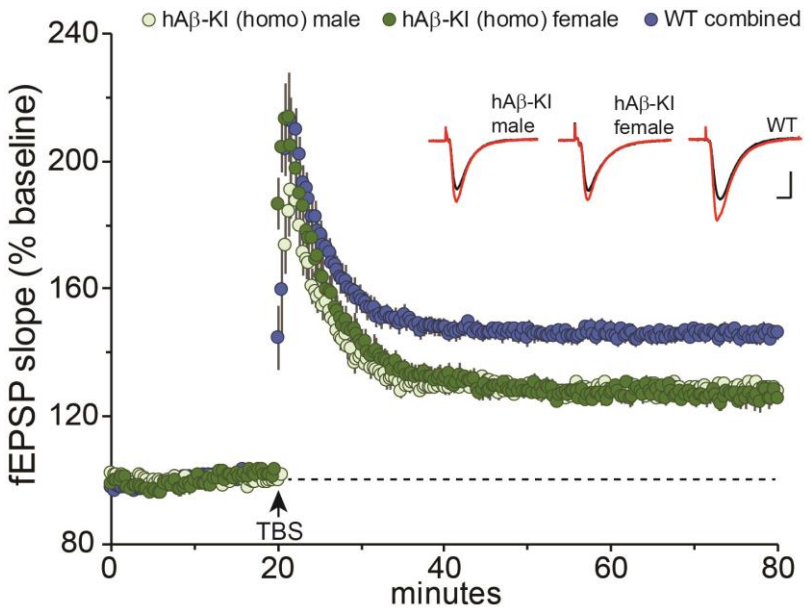
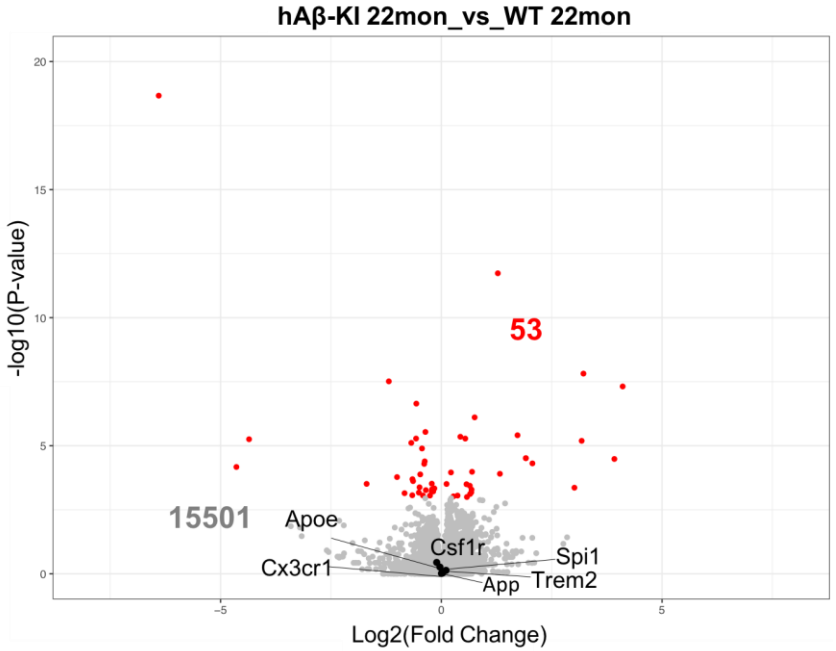
Mice expressing humanized wild-type Aβ display age-related altered cognition, electrophysiology and gene-expression







Program, Approved Format, and original ID	Session Name, Date, Time	Presentation Title	Accept	Decline	Role	Presentation Time
Alzheimer's Association International Conference (AAIC)	**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, McCormick Place, Room - 184*	**O1-01-04** Haβ-KI: A Knock-in Mouse Model for Sporadic Alzheimer's Disease	◉	○	Presenting Author	8:45 AM-9:00 AM

David Baglietto-Vargas

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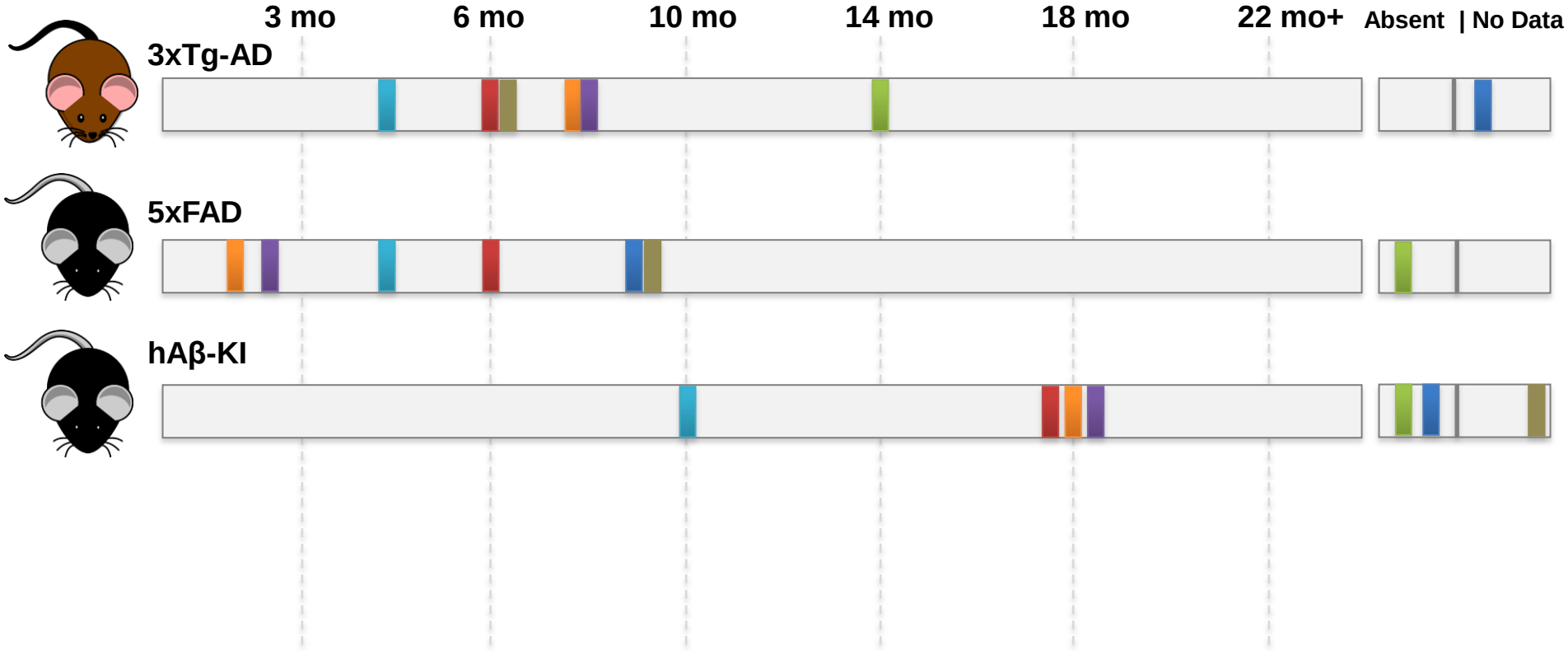
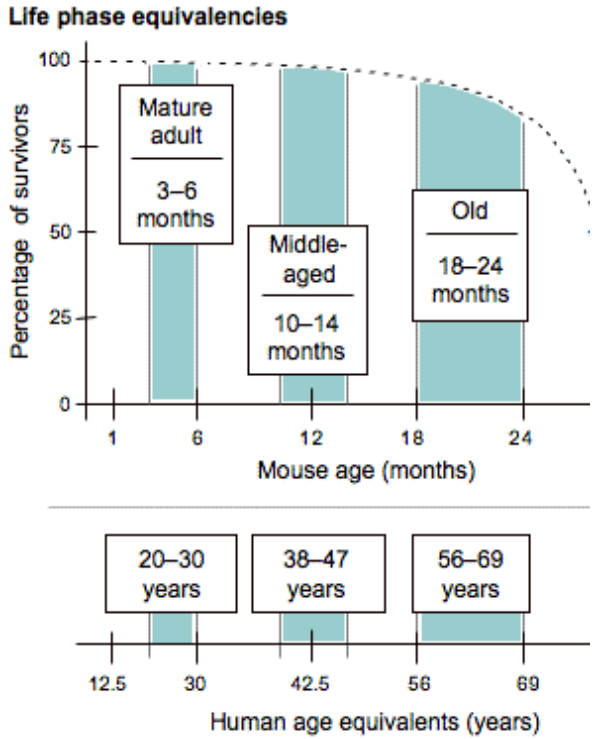
Timeline for Development of Pathology in Mouse AD MODELS

Neuronal Loss | Plaques | Tangles | Gliosis | Cognitive Impairment | LTP/LTD Change | Synaptic Loss





Flurkey K, Currer JM, Harrison DE. 2007.

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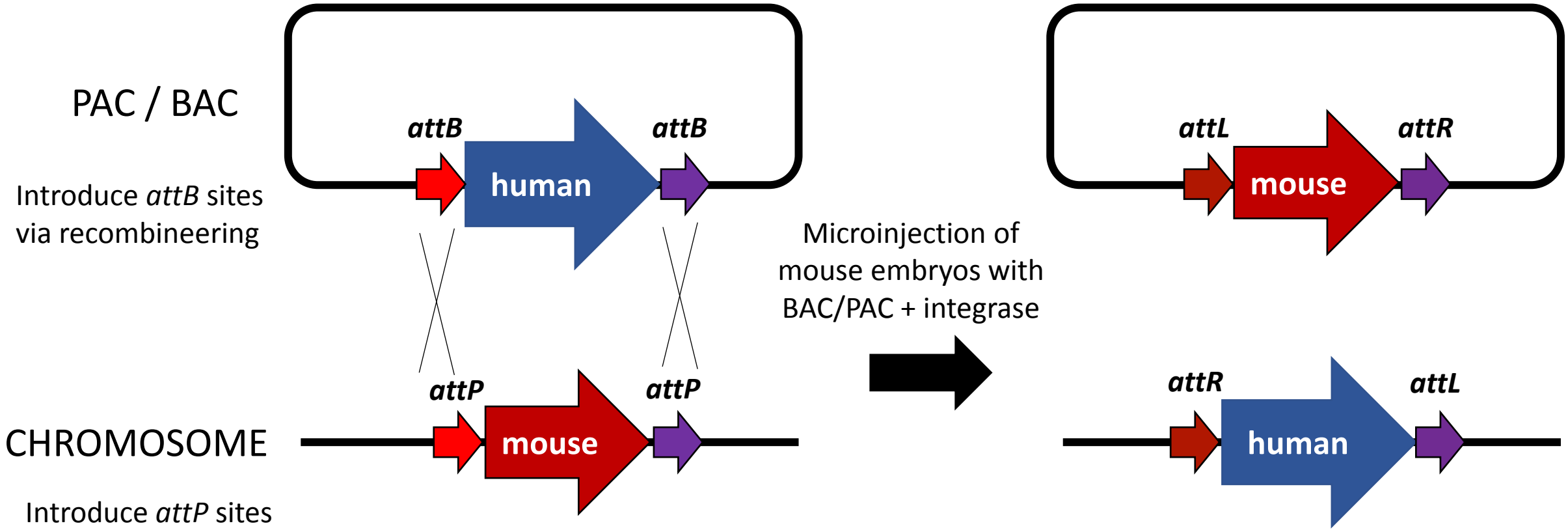
Strategy to humanize mouse *Mapt* (TAU), *Clu* and other loci using Recombinase Mediated Cassette Exchange (RMCE)



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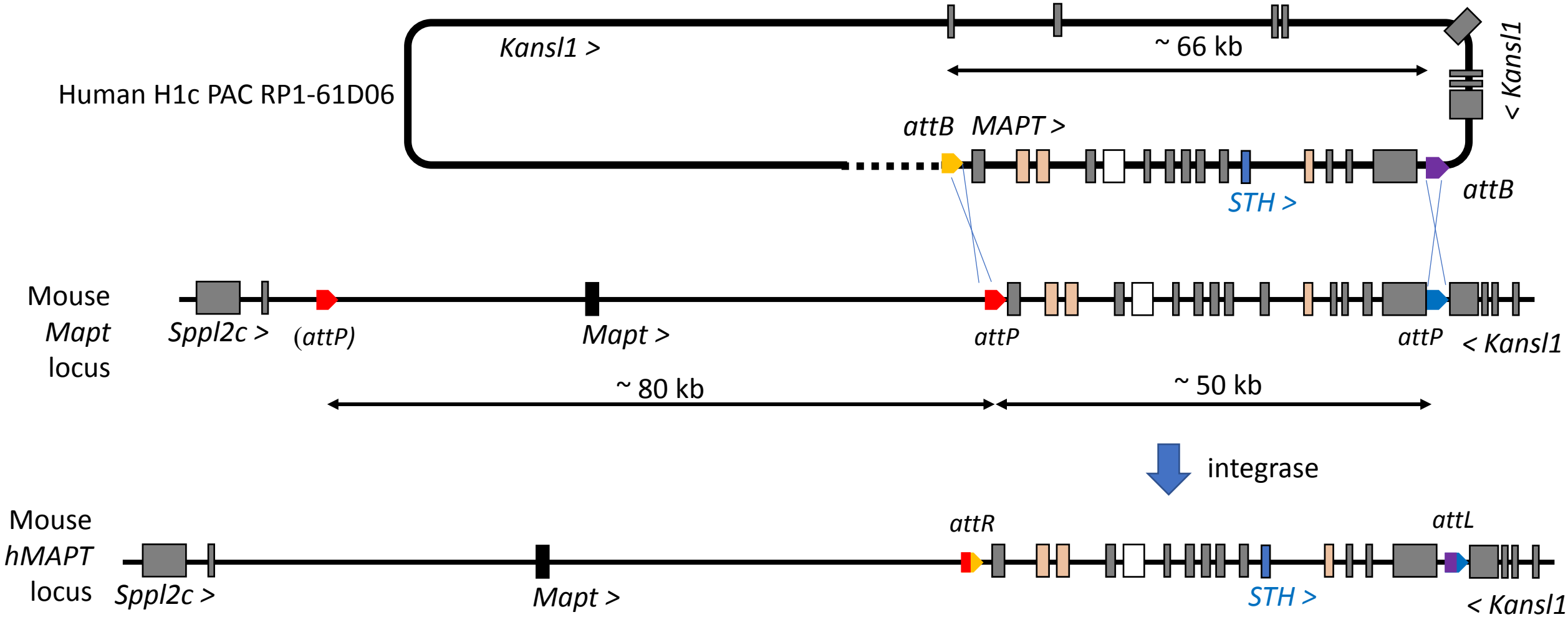
hTau-KI mice - humanization of mouse *Mapt* via RMCE



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IU/JAX Disease Modeling Project: 40 new models of LOAD

B6J.APOE$^{E4/E4}$TREM2$^{R47H/R47H}$

Common name: B6J.hAT

Early goals of IU/JAX DMP

- Characterize commonly used EOAD models
  - *APP/PS1* (Borchelt)
  - 5xFAD (Vassar)
  - hTau (Davies)
- Characterize newly created B6J.hAT LOAD model
- Introduce known GWAS human variants into *APOE/TREM 'sensitizer' strain*.
- Characterize and stage F344-Tg(PrP-APP, PrP-PS1) – rat model of EOAD

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Clinically-relevant deep phenotyping

AMP-AD, ADNI etc.	MODEL-AD	
Assay	**Primary Screening** 2, 6,12 months 24 models	**Deep Phenotyping** 4, 8, 12, (18 months) Prioritized models
Amyloid and tau pathology	•	•
Neuroinflammation	•	•
Neuronal cell loss	•	•
Biomarkers	•	•
Biomarkers (Quanterix)		•
Transcriptomes (NanoString)	•	
Transcriptomes (RNA-seq)		•
Transcriptomes (scRNA-seq)		pilot study*
Proteomics		pilot study*
Metabolomics		pilot study*
Imaging (FDG, PET/MRI)		•
Cognitive tests		•

Human-mouse assay

• identical

• similar

Pilot studies

using B6J.5xFAD and B6J.*hAT*

scRNA-seq:
de Jager

Proteomics:
Seyfried

Metabolomics:
Kaddurah-Daouk

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Clinically-relevant deep phenotyping

Aspects of deep phenotyping occurs at IU and JAX for reproducibility

12M/12F per genotype at each time point for scientific rigor

4mo	8mo	12mo	(18+ mo)
Behavioral battery	Behavioral battery	Behavioral battery	Behavioral battery
-CSF collection	-CSF collection	-CSF collection	-CSF collection
-Serum collection	-Serum collection	-Serum collection	-Serum collection
-Fecal sample	-Fecal sample	-Fecal sample	-Fecal sample
-Brain dissection	-Brain dissection	-Brain dissection	-Brain dissection
-Eye collection	-Eye collection	-Eye collection	-Eye collection
-Biomarker assessment	-Biomarker assessment	-Biomarker assessment	-Biomarker assessment
-RNAseq	-RNAseq	-RNAseq	-RNAseq
-Histological analysis	-Histological analysis	-Histological analysis	-Histological analysis
-*In vivo* imaging	-*In vivo* imaging	-*In vivo* imaging	-*In vivo* imaging

In vivo imaging by MR/PET:
Amyloid: 18F-AV45
Tau: 18F-1451
Glucose: 18F-FDG
Blood flow: 64Cu-PTSM

Biomarkers:
AB, Tau
Nfl
Neurogranin
sTREM2

Histology:
Gross morphology/white matter: Luxol fast blue and Cresol Violet
Neurons: NeuN and CTIP
Plaques, dystropic neurites and myeloid cells: X34, LAMP1 and IBA1
TAU: AT8 and H&E
Neuroinflammation: IBA1 and GFAP
Vascular health: CD31 and IBA1

Pilots: Proteomic and metabolomics profiling
Considering: Microbiome

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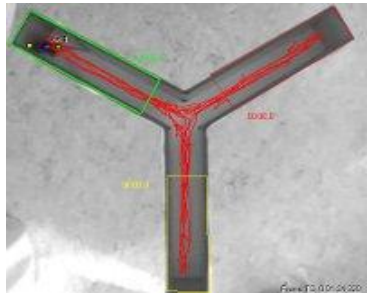
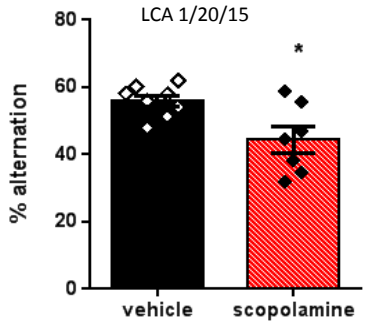
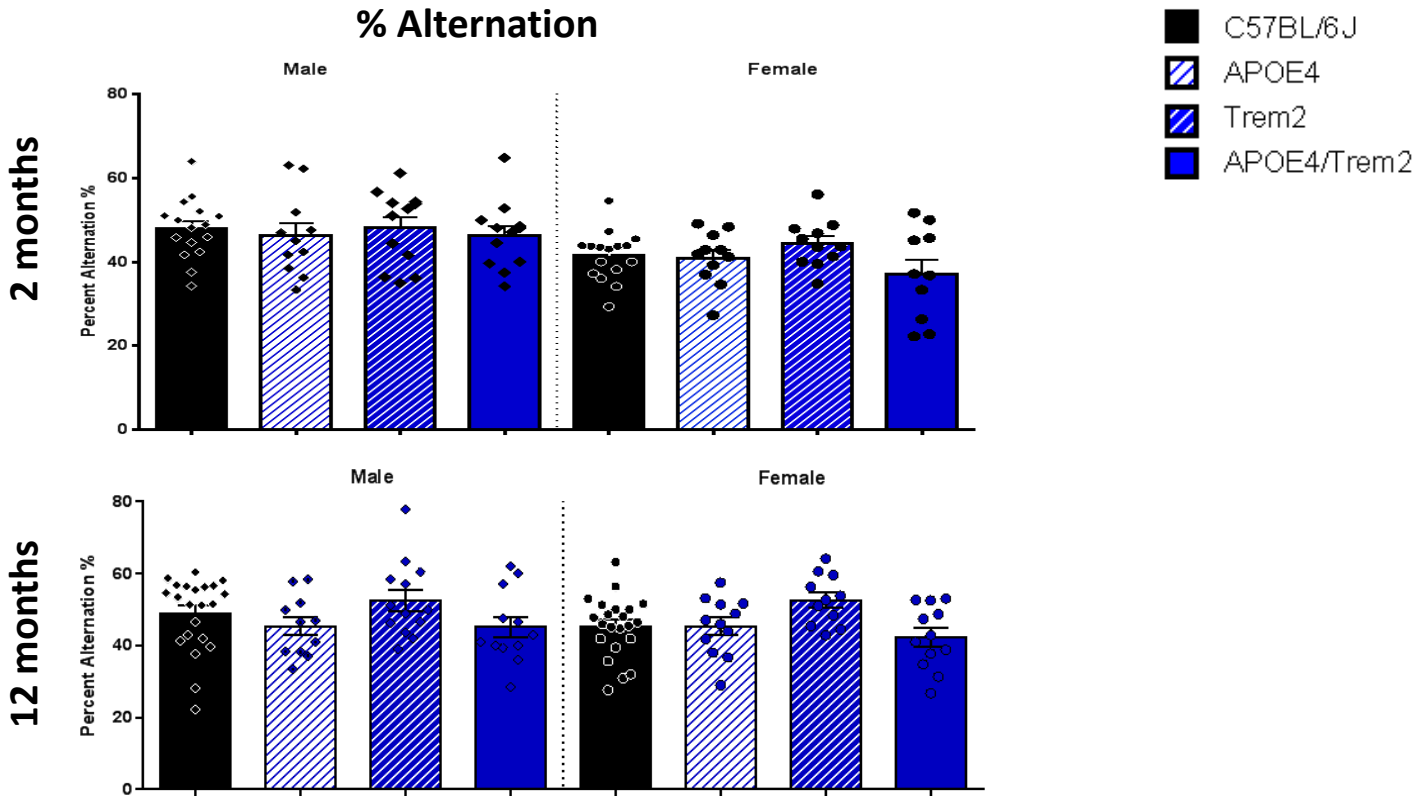
B6J.*hAT:* No differences in hippocampal working memory between genotypes and ages

Spontaneous Alternation



Task validation





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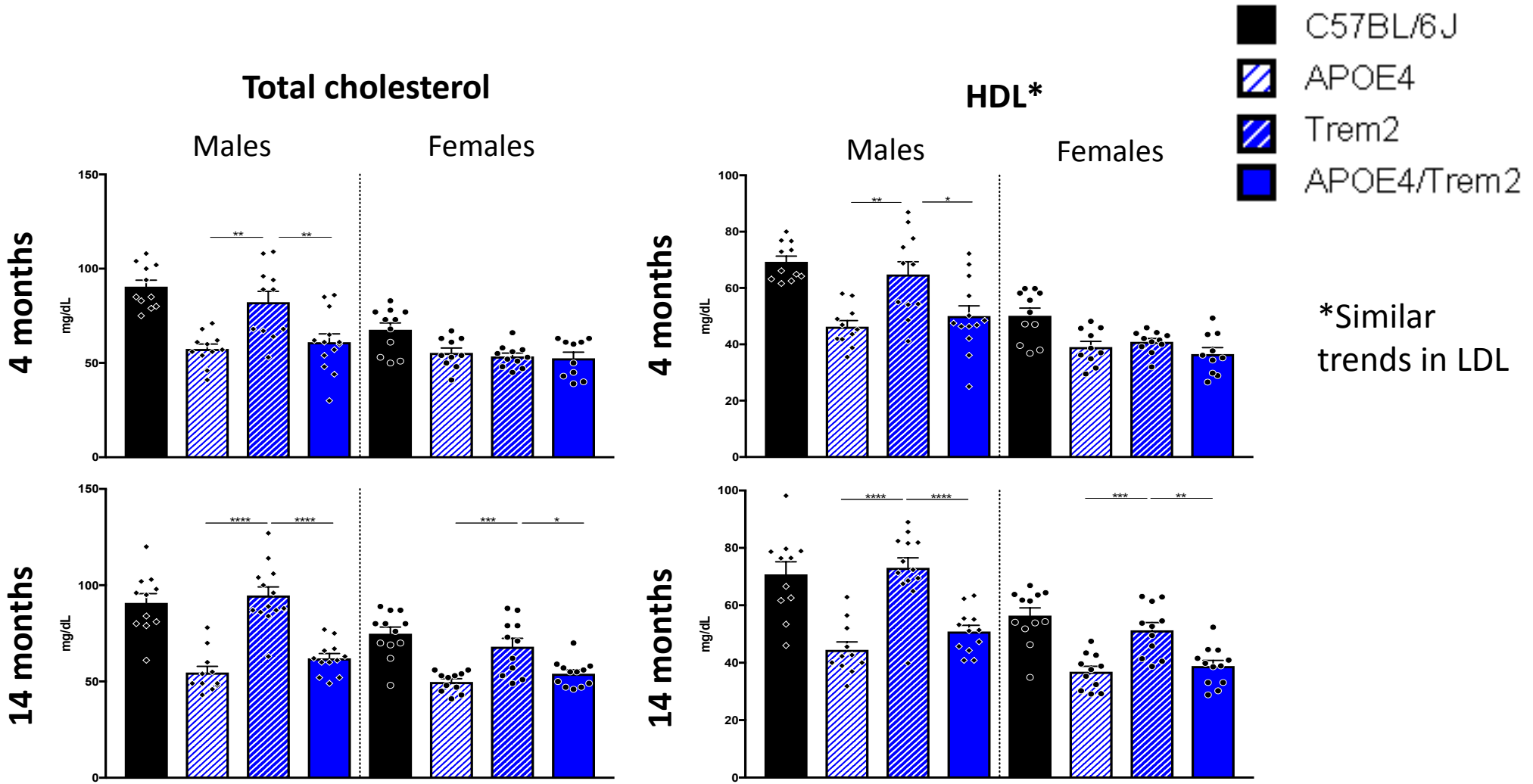
B6J.hAT: Differences in lipid profiles driven by *APOE^{E4}*

Blood collected at harvest (non-fasted)

Assessed for:
Total Cholesterol
LDL
HDL
Triglycerides
Non-essential FA
Glucose



*Similar trends in LDL

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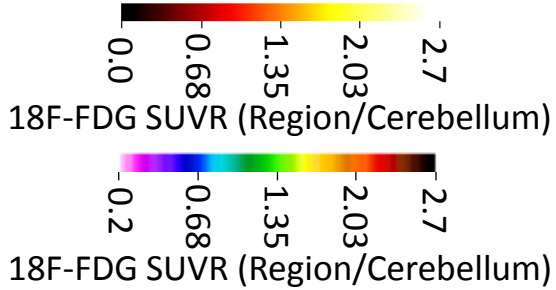
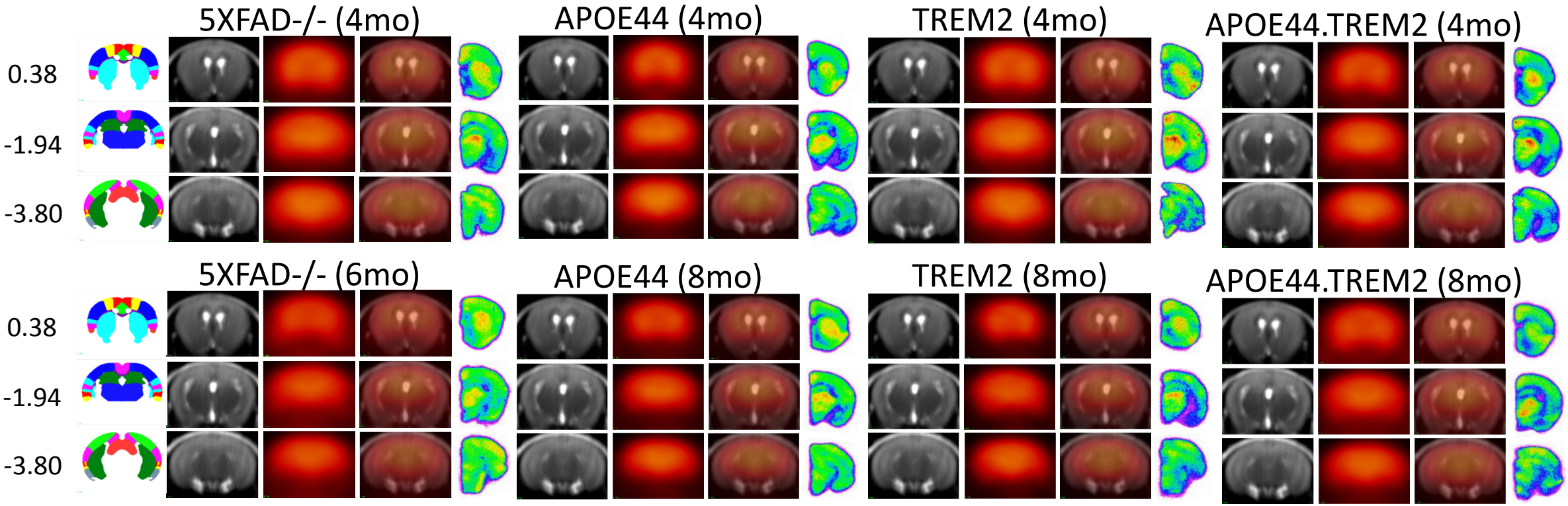
B6J.hAT: PET/MR imaging (3T) with 18F-FDG





Preliminary findings: No significant changes across 27 brain regions comparing all genotypes at 4 and 8 mos

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B6J.hAT. Summary and Future plans

- *APOE*^{E4}-dependent changes in lipid profiles
- No age-dependent decline in glucose uptake across all genotypes
- No evidence of cognitive decline (measured using spontaneous alternation) up to 12 months of age

- Analyses of RNA sequence data of half brains underway
- Histological and biochemical assessment of tissue underway
  - Neuroinflammation, cerebrovascular health, amyloid and Tau

Next step: Deep phenotyping *B6J.APOE*$^{4/4}$ *TREM2*$^{<R47H>}$ mice with humanized *APP*

B6J.hATA

B6J.APOE$^{E4/E4}$*TREM2*$^{R47H/R47H}$*App*$^{h/h}$

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Primary screen of novel variants on sensitized genetic background

Current

B6J.hAT

Future

B6J.hATA

- New strains created and in the primary screening pipeline
  - *Abca7^{A1527G}, Il1rap^{KO}, Ceacam1^{KO}, Plcg2^{M28L}, Mthfr^{A222V}*
- Ten others in CRISPR pipeline using *B6J.APOE$^{4/4}$ TREM2$^{<R47H>}$*
- Up to 40 variants to be created with 24 to be screened

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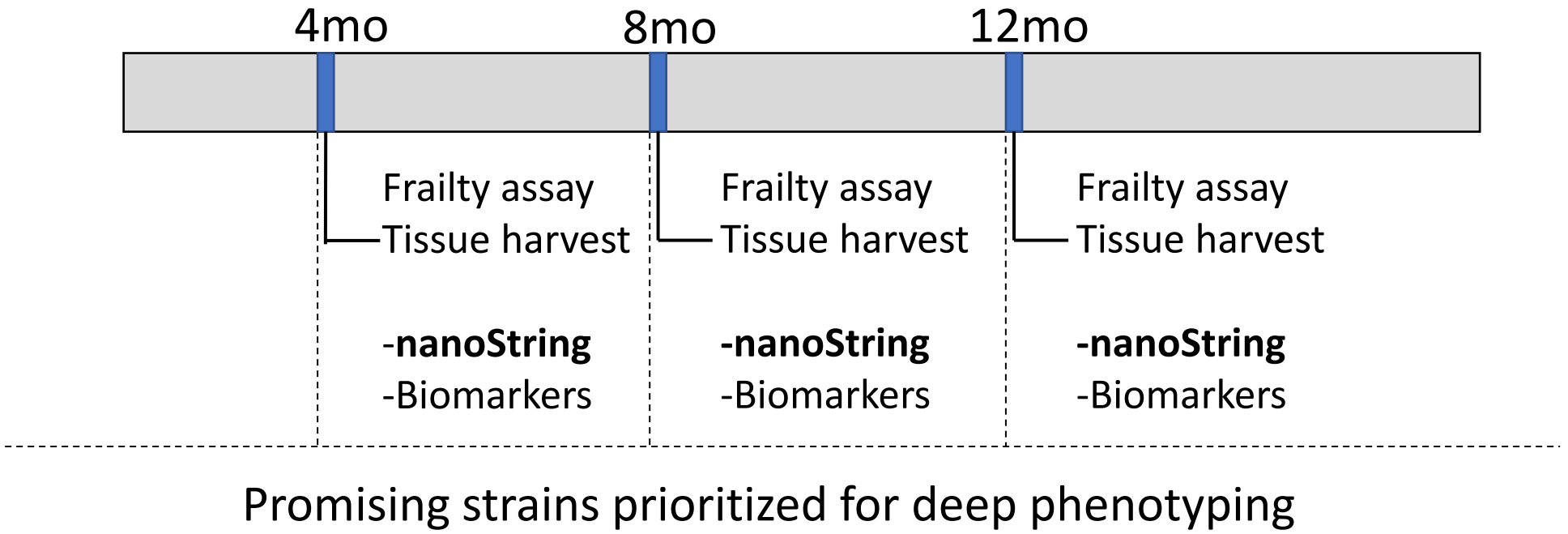
A primary screen to prioritize candidate variants for deep phenotyping



A nanoString panel to align mouse models to human data: AMP-AD panel

- Panel of 770+30 mouse gene probes
  - Maximize coverage of 30 AMP-AD modules
  - Include top AMP-AD candidates (Top 30, AGORA targets)
  - Genes ranked by
    - representation of module PCs (gene score)
    - ortholog expressed in mouse brain at 6 months of age
    - 10 housekeeping genes

AMP-AD Module	Nanostring probes per module	AMP-AD Module Size	% of Module Covered
aggregateCBEblue	177	4505	3.93
aggregateCBEbrown	95	504	18.85
aggregateCBEturquoise	200	1977	10.12
aggregateCBEyellow	157	1738	9.03
aggregateDLPFCblue	183	1751	10.45
aggregateDLPFCbrown	139	882	15.76
aggregateDLPFCturquoise	144	2489	5.79
aggregateDLPFCyellow	192	3016	6.37
aggregateFPblue	278	1991	13.96
aggregateFPbrown	76	1287	5.91
aggregateFPturquoise	107	1001	10.69
aggregateFPyellow	188	4420	4.25
etc			

Coverage ranges from 76-278 genes per module

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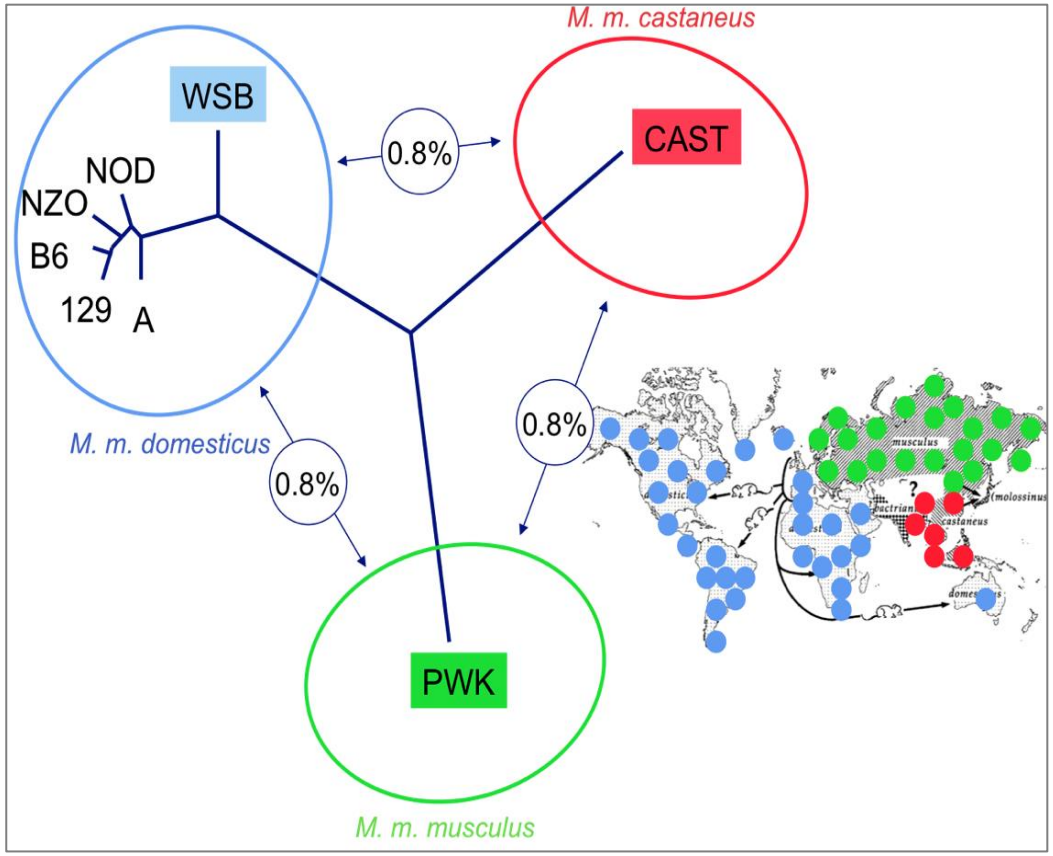
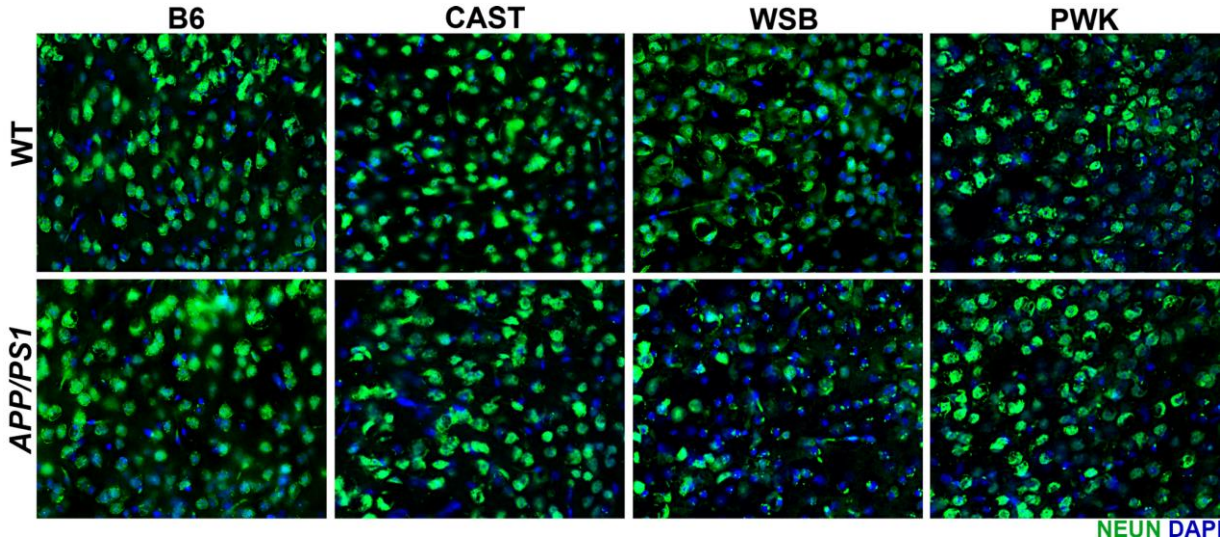
Kristen Onos
Howell Lab, JAX

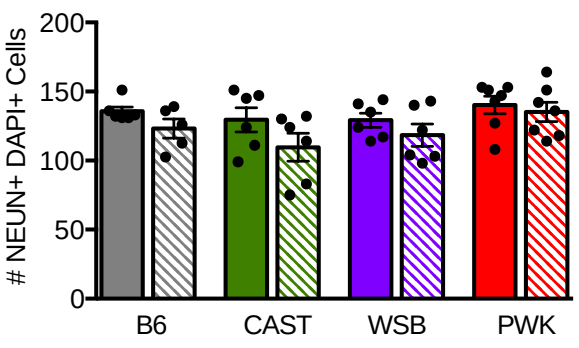
Genetic context is important



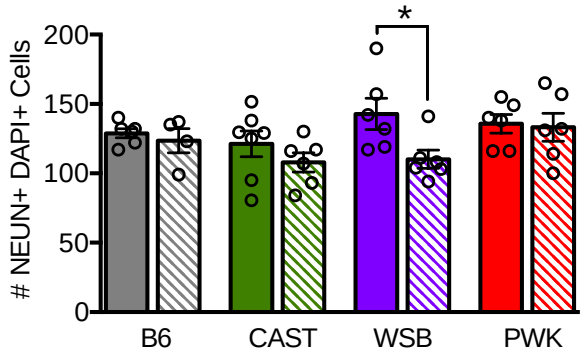
APP/PS1 on B6J and wild-derived strains



Male Cortical Neuron Counts



Female Cortical Neuron Counts



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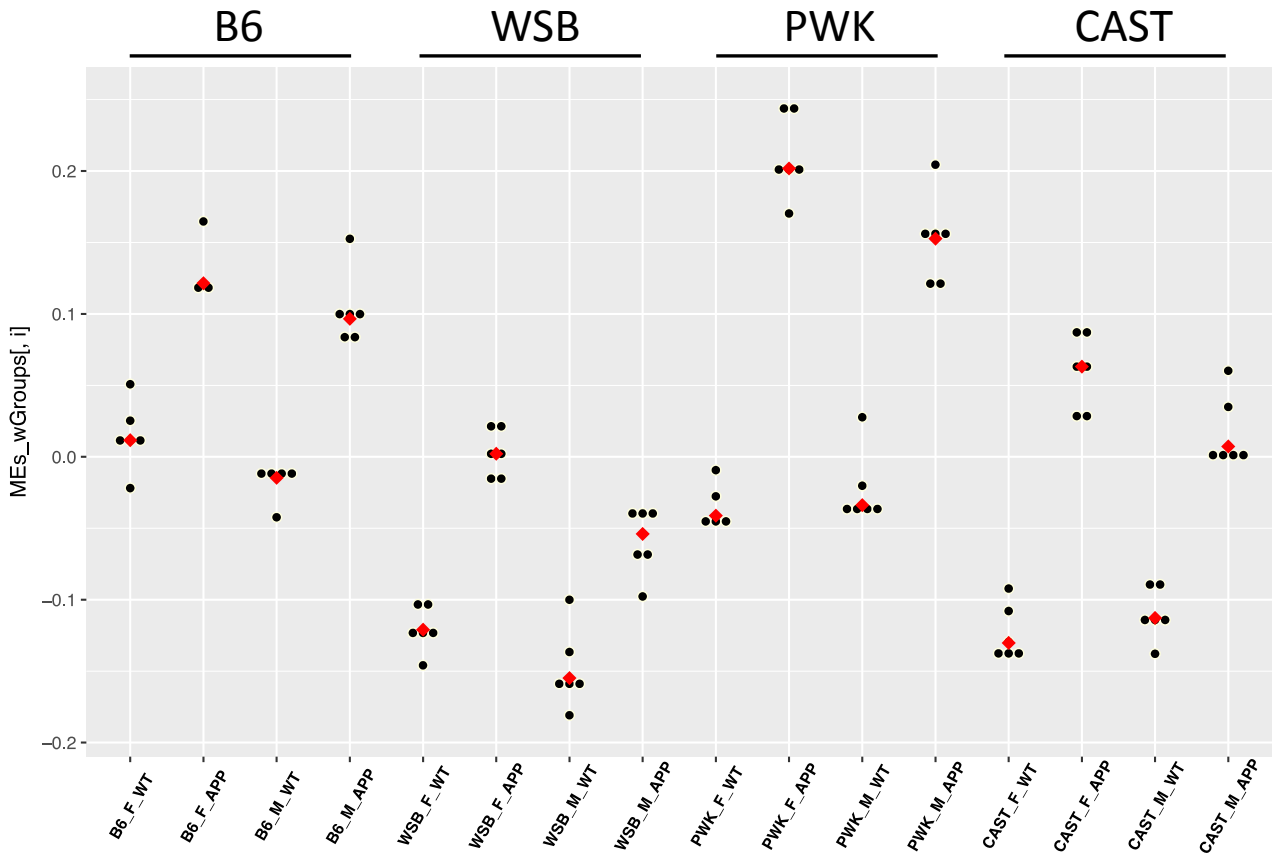
Transcriptome analyses by WGCNA shows variation in amyloid response between strains



Genes in module	
Itgb2	Tbxas1
Cd52	Tyrobp
Spi1	Tgfbr2
Ptpn6	Arpp21
Ctsd	Vav1
Ctsz	Cd84
Abi3	Ctss
Cd68	Gpr34
Cd180	Cd53
Fyb	Irf8
App	Fam46c
Pros1	Tlr7
Trem2	Mpeg1
Csf1r	Gpr84
Cndp2	Csf2rb
Ptprc	Prnp
Slamf9	
Laptm5	2900079G21Rik

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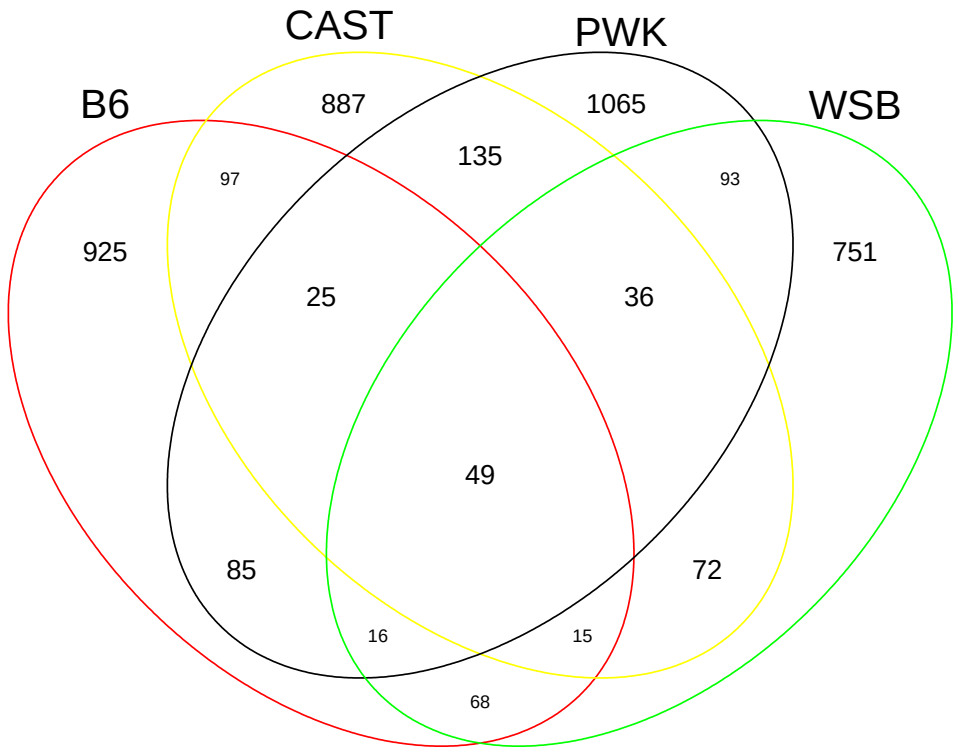
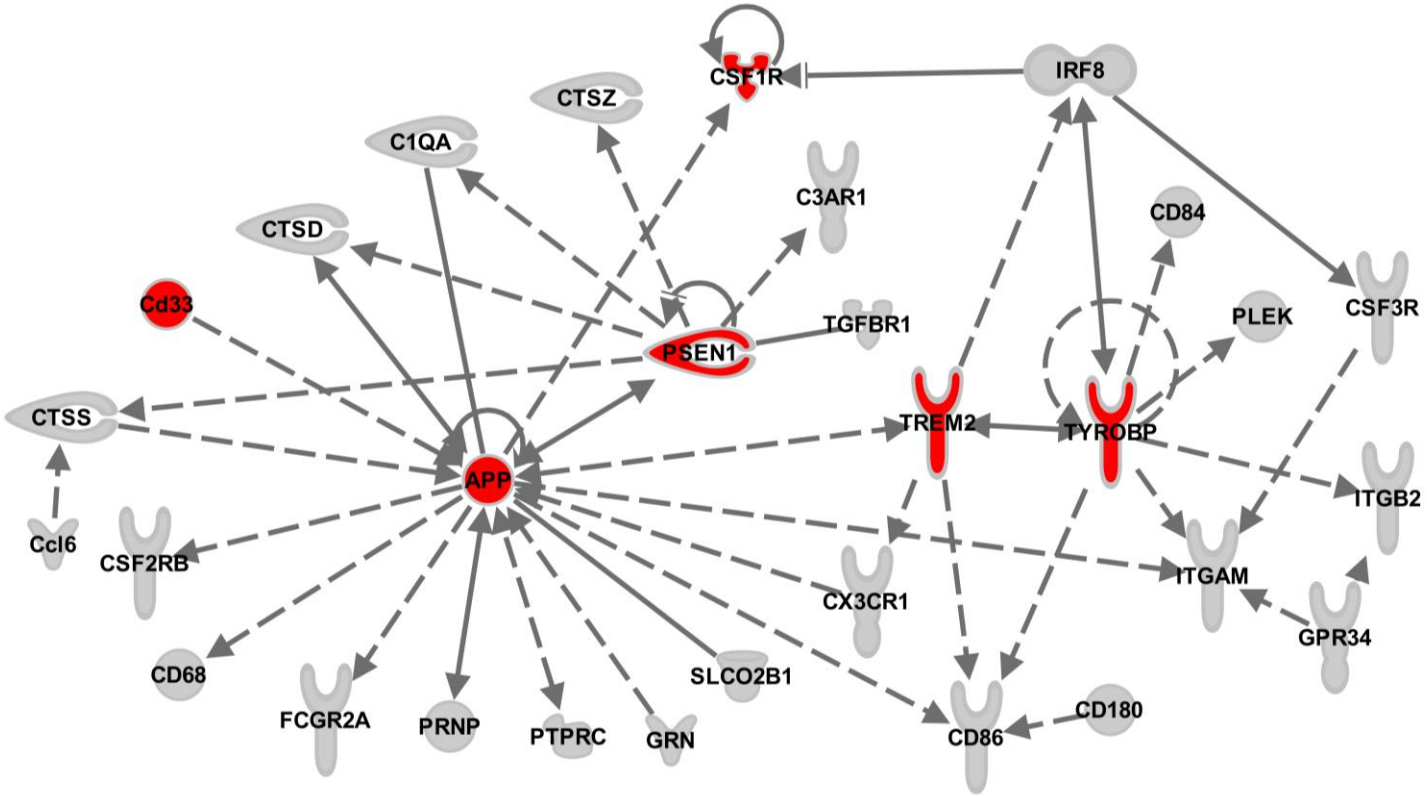
Strain-specific transcriptome analyses shows variation in genetic ‘drivers’ of AD

Generalized linear modeling





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Summary: Evaluating the Translational Validity of Mouse Models of LOAD by clinically relevant deep phenotyping

- Creating up to 50 mouse models relevant to Alzheimer's disease
  - Includes creating a humanized platform (*APP*, *TAU*, *APOE*) for testing novel variants
  - Approximately 20 models created or in progress including AB-KI, hAT
- Perform clinically-relevant deep phenotyping of key (>10) models
  - Including in vivo imaging (MR/PET) and RNA-seq
  - Data available for 4 existing (5xFAD, 3xTG, APP/PS1, hTau) and 2 new models (hAB-KI, APOE4/TREM2<R47H>)
  - Pilots for proteomics and metabolomics underway
- All data and mouse strains made available through Synapse and JAX mouse repository (as well as other sources)
  - 23 models either available to order, available for preorder, or in preparation
  - ~265 RNA-seq data files submitted/being submitted to Synapse (many more to come!)

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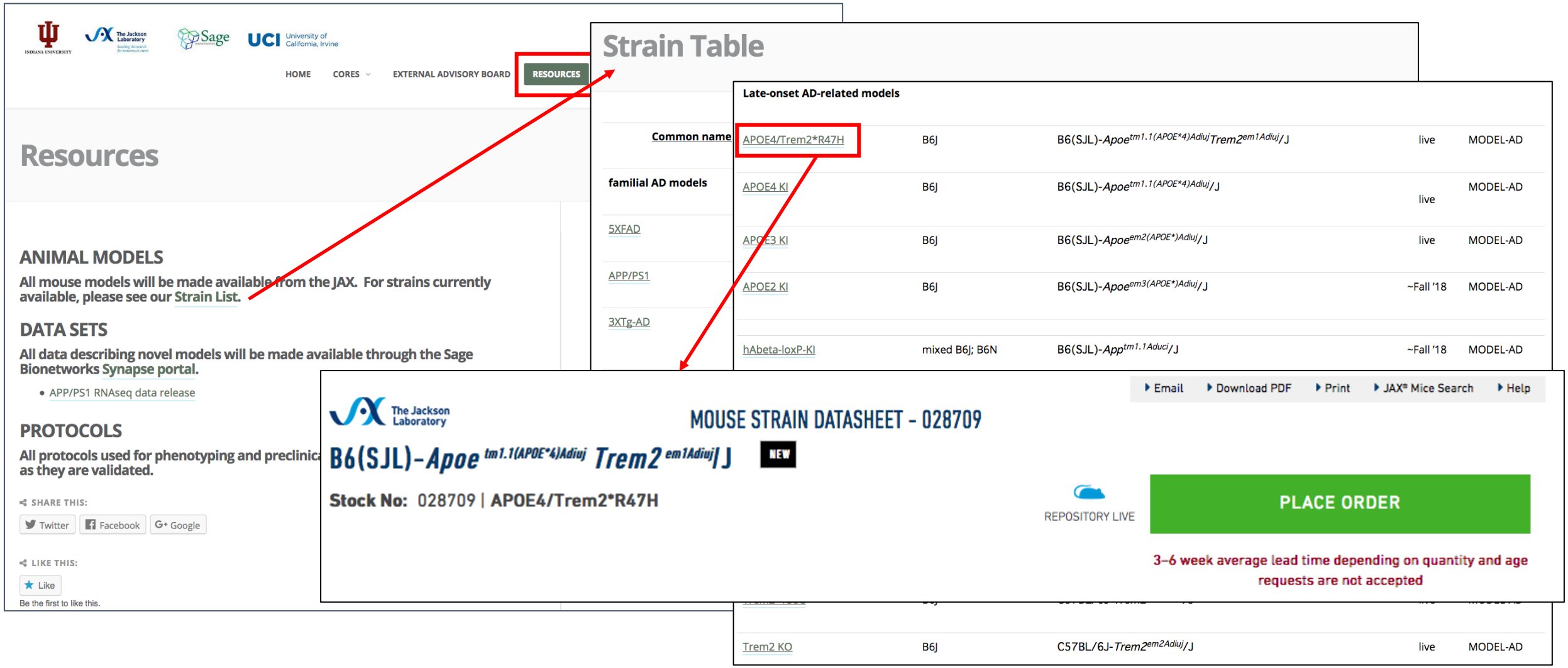
Strains and data available from model-ad.org



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