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The Mechanistic-Observational Divide in Translational Research

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MODEL-AD MARMO-AD TREAT-AD

Failure to Translate

Neuron, Vol. 41, 27–33, January 8, 2004, Copyright ©2004 by Cell Press

Report

BACE1 Deficiency Rescues Memory Deficits and Cholinergic Dysfunction in a Mouse Model of Alzheimer's Disease

Published in final edited form as:
J Neurochem. 2010 April ; 113(1): 248–261. doi:10.1111/j.1471-4159.2010.06608.x.

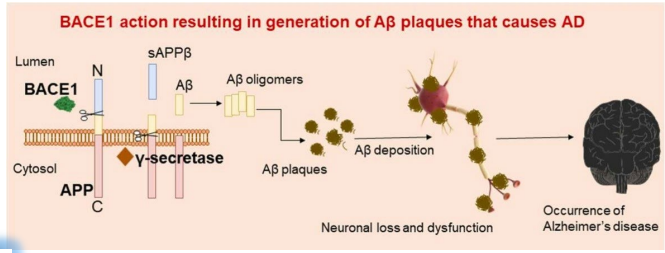
Partial reduction of BACE1 improves synaptic plasticity, recent and remote memories in Alzheimer's disease transgenic mice

JEM

Article

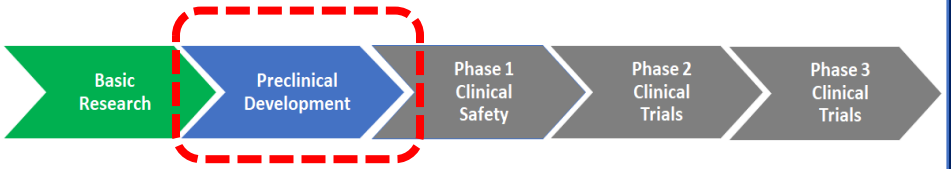
BACE1 deletion in the adult mouse reverses preformed amyloid deposition and improves cognitive functions





Iram et al 2024 Ageing Research Reviews

Failure to Translate - Lessons learned from BACE1

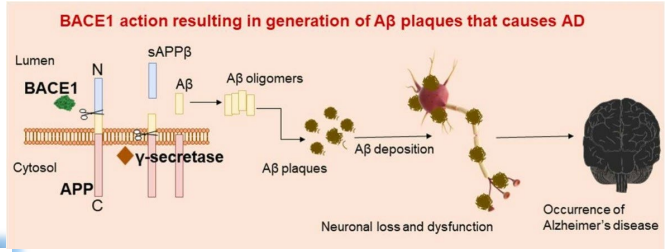


Neuron, Vol. 41, 27–33, January 8, 2004, Copyright ©2004 by Cell Press

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Iram et al 2024 Ageing Research Reviews

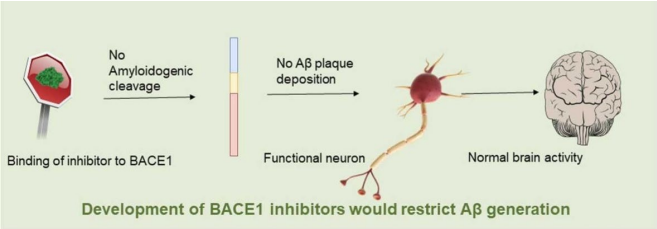
JEM Article

BACE1 deletion in the adult mouse reverses preformed amyloid deposition and improves cognitive functions

The Journal of Neuroscience, August 18, 2010 • 30(33):11157–11166 • 11157

Neurobiology of Disease

A Noncompetitive BACE1 Inhibitor TAK-070 Ameliorates Aβ Pathology and Behavioral Deficits in a Mouse Model of Alzheimer's Disease



Iram et al 2024 Ageing Research Reviews

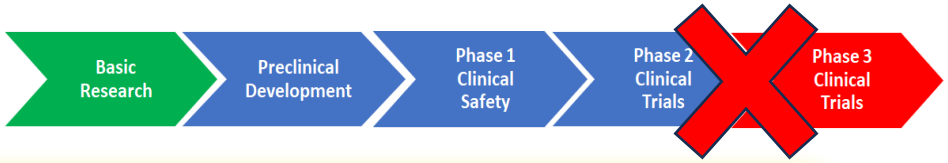
The Journal of Neuroscience, April 29, 2015 • 35(17):6931–6936 • 6931

Brief Communications

Centrally Delivered BACE1 Inhibitor Activates Microglia, and Reverses Amyloid Pathology and Cognitive Deficit in Aged Tg2576 Mice

Failure to Translate - Lessons learned from BACE1

ALZFORUM
NETWORKING FOR A CURE



Merck P
Trial
15 Feb 2017

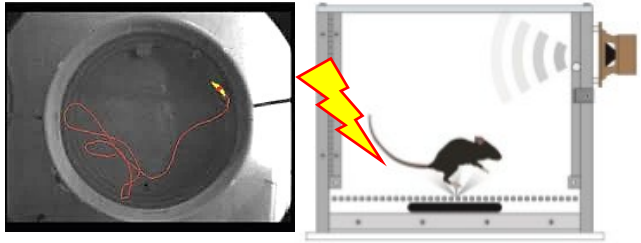
- **Predictive strengths of preclinical studies:**
  - ➢ In vivo Target Engagement
  - ➢ Pharmacokinetics
  - ➢ Pharmacodynamics

- **Failure:**
  - Rodent cognitive assays failed to translate

End of the BACE Inhibitors? Elenbecestat Trials Halted Amid Safety Concerns
13 Sep 2019

Failure to Translate…….

Clinical Relevance?



- **Rodent behavioral outcomes that don't translate**
  - Assays with poor translational validity and cross-species utility
  - Behavioral confounds: hyperactivity, visual impairments
  - Mis-interpretation of data: binary measures

Neuroscience and Biobehavioral Reviews 116 (2020) 452–453

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Commentary

Lost in translation: At the crossroads of face validity and translational utility of behavioral assays in animal models for the development of therapeutics

J.L. Silverman[a], J. Nithianantharajah[b], A. Der-Avakian[c], J.W. Young[c], S.J. Sukoff Rizzo[d,*]

[a] University of California, Davis, MIND Institute, School of Medicine, Department of Psychiatry and Behavioral Sciences, Sacramento, CA, USA
[b] The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia
[c] Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
[d] University of Pittsburgh School of Medicine, Department of Medicine, Pittsburgh, PA, USA

Neurochemical Research (2023) 48:3027–3041
https://doi.org/10.1007/s11064-023-03956-2

ORIGINAL PAPER

Luvadaxistat: A Novel Potent and Selective D-Amino Acid Oxidase Inhibitor Improves Cognitive and Social Deficits in Rodent Models for Schizophrenia

American College of Neuropsychopharmacology

www.nature.com/npp

ARTICLE OPEN

A phase 2 randomized controlled trial of luvadaxistat in treatment of adults with cognitive impairment associated with schizophrenia: results from the ERUDITE study

Ni A. Khin[1], Reuben H. Fan[1], Tingting Ge[1], Hans S. Klein[1], Jacob S. Ballon[2], Satjit Brar[1], Philip D. Harvey[3], Joshua T. Kantrowitz[4,5,6], Richard S. E. Keefe[7], Mahnaz Asgharnejad[8], Venkatesha Murthy[8], Eiry Roberts[1] and Jaskaran B. Singh[1]

© The Author(s) 2026

The phase 2 ERUDITE (NCT05182476) study evaluated the efficacy and safety of luvadaxistat, a selective D-amino acid oxidase inhibitor, for cognitive impairment associated with schizophrenia. ERUDITE was a randomized, double-blind, placebo-controlled, parallel-group study in adults with schizophrenia receiving background antipsychotic therapy. Following a 2-week placebo run-in, participants were randomized 2:1:1 to receive placebo, luvadaxistat 20 mg, or luvadaxistat 50 mg once daily for a 12-week treatment period. The primary endpoint was change from baseline to Day 98 in the Brief Assessment of Cognition in Schizophrenia (BACS) composite score. Safety outcomes included the incidence of treatment-emergent adverse events (TEAEs). Overall, 203 participants were randomized (placebo, $n = 101$; luvadaxistat 20 mg, $n = 50$; luvadaxistat 50 mg, $n = 52$), and 178 (87.7%) completed the treatment period. Luvadaxistat did not significantly improve performance (change from baseline) in BACS composite score versus placebo at Day 98 (least-squares mean difference [95% confidence interval]: 20 mg, −0.7 [−2.8, 1.4], $p = 0.75$; 50 mg, −0.5 [−2.7, 1.6], $p = 0.69$). TEAEs were reported in approximately one-third of participants across groups, with comparable rates observed between the luvadaxistat and placebo groups. TEAEs were mostly mild or moderate, and no safety concerns were identified. Luvadaxistat 20 mg or 50 mg did not show statistically significant changes in cognitive performance or functioning within the ERUDITE study. Trial registration: ClinicalTrials.gov identifier NCT05182476.

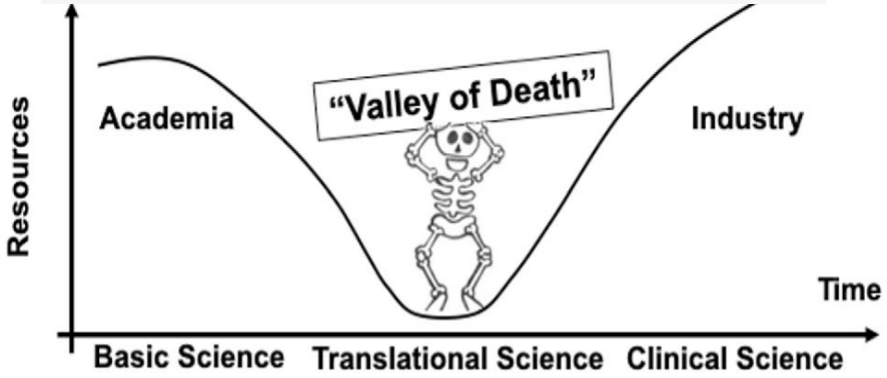
Neuropsychopharmacology; https://doi.org/10.1038/s41386-026-02410-5

Failure to Translate…….

Experimental Design — AlzPED

Is the following information reported in the study?:

✗ Power/Sample Size Calculation	✓ Randomized into Groups
✗ Blinded for Treatment	✓ Blinded for Outcome Measures
✗ Pharmacokinetic Measures	✗ Pharmacodynamic Measures
✗ Toxicology Measures	✗ ADME Measures
✗ Biomarkers	✓ Dose
✓ Formulation	✓ Route of Delivery
✓ Duration of Treatment	✓ Frequency of Administration
✓ Age of Animal at the Beginning of Treatment	✓ Age of Animal at the End of Treatment
✓ Sex as a Biological Variable	✓ Study Balanced for Sex as a Biological Variable
✗ Number of Premature Deaths	✗ Number of Excluded Animals
✓ Statistical Plan	✗ Genetic Background
✗ Inclusion/Exclusion Criteria Included	✓ Conflict of Interest



Seyhan, A.A. Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles. transl med commun 4, 18 (2019). https://doi.org/10.1186/s41231-019-0050-7

- **Rodent behavioral outcomes that don't translate**
  - Assays with poor translational validity and cross-species utility
  - Behavioral confounds: hyperactivity, visual impairments
  - Mis-interpretation of data: binary measures
- ***Opportunistic* choice of mouse models**
  - What is accessible to the lab
  - Young subjects that do not incorporate biological aging
  - Artifacts of transgenic overexpression models
  - Often limited to single sex
- **Poor rigor, reproducibility, transparency**
  - Biased experimental design and approach
  - Lack of appropriate controls, insufficient sample size, no blinding nor apriori inclusion/exclusion criteria
- **Limited Translational PK/PD relationship**
  - Lack of correlating exposure levels in the target tissue
  - Arbitrary selection of dose, route, frequency, duration, etc
  - No understanding of target engagement beyond "Aβ lowering"
  - PK and safety data in young healthy ≠ aged with disease



NIA AD/ADRD Research Summits:

Recommendations Aimed at Increasing the Predictive Validity of Preclinical Studies in AD Animal Models

1. **Improved animal models to study the biology of LOAD (genetic risk x aging x environment)**
   - No restrictions for use to any laboratory or drug company

2. **Rigorous SOPs for model characterization which align with the pathophysiological features of AD**
   - Characterize phenotype in alignment with clinical disease staging
   - Prioritization of *translationally relevant outcome measures (biomarkers, MRI/PET)*

3. **Establish resources for the research community for rigorous preclinical testing of potential therapeutics**
   - Prioritization of translational outcome measures (PK/PD, in vivo target engagement)
   - Reporting of both positive and negative findings

NIH National Institute on Aging

NIA Funding Initiative

RFA AG16-04

MODEL-AD Consortium

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

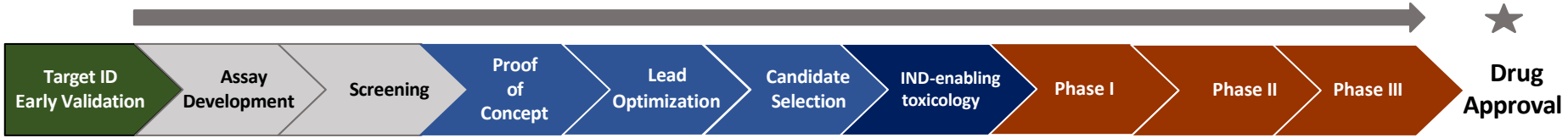
U54 AG054345 (IU/JAX/PITT), U54 AG054349 (UCI)

MODEL-AD

STOP-AD

IU/JAX/PITT Preclinical Testing Core

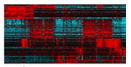
Leveraging the NIA/ADRD Open Science Infrastructure Enterprise

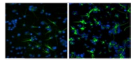


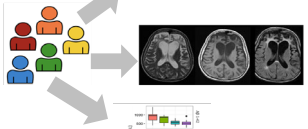
Enabling Discovery Programs and Translational Infrastructure for Data Driven and Predictive Drug Development

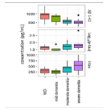
- Genetics and Systems Biology Consortia
  - ADSP
  - AMP AD
  - CLEAR-AD
  - AGMP
- TREAT-AD Centers
- MODEL-AD Centers
- MARMO-AD Center
- *MPS-AD Centers*
- ACTC
- ADNI
- ABC-DS
- HABS-HD

Clinical Data


'Omics


Neuropathology


Neuroimaging


Fluid Biomarkers

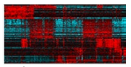
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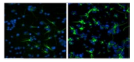
Target ID Early Validation → Assay Development → Screening → Proof of Concept → Lead Optimization → Candidate Selection → IND-enabling toxicology → Phase I → Phase II → Phase III → Drug Approval

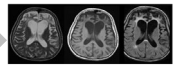
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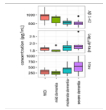
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- ACTC, ADNI, ABC-DS, HABS-HD

Clinical Data


'Omics


Neuropathology



Neuroimaging


Fluid Biomarkers

Drug Targets & Novel Candidate Compounds

TREAT-AD
EMORY | SAGE | SGC



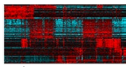
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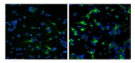
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Enabling Discovery Programs and Translational Infrastructure for Data Driven and Predictive Drug Development

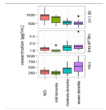
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Clinical Data


'Omics


Neuropathology


Neuroimaging

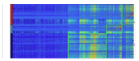

Fluid Biomarkers

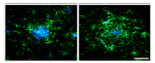
Drug Targets & Novel Candidate Compounds

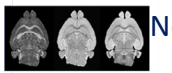
TREAT-AD
EMORY | SAGE | SGC

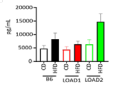


Model Systems & Translational Measures


'Omics


Neuropathology



Neuroimaging


Fluid Biomarkers

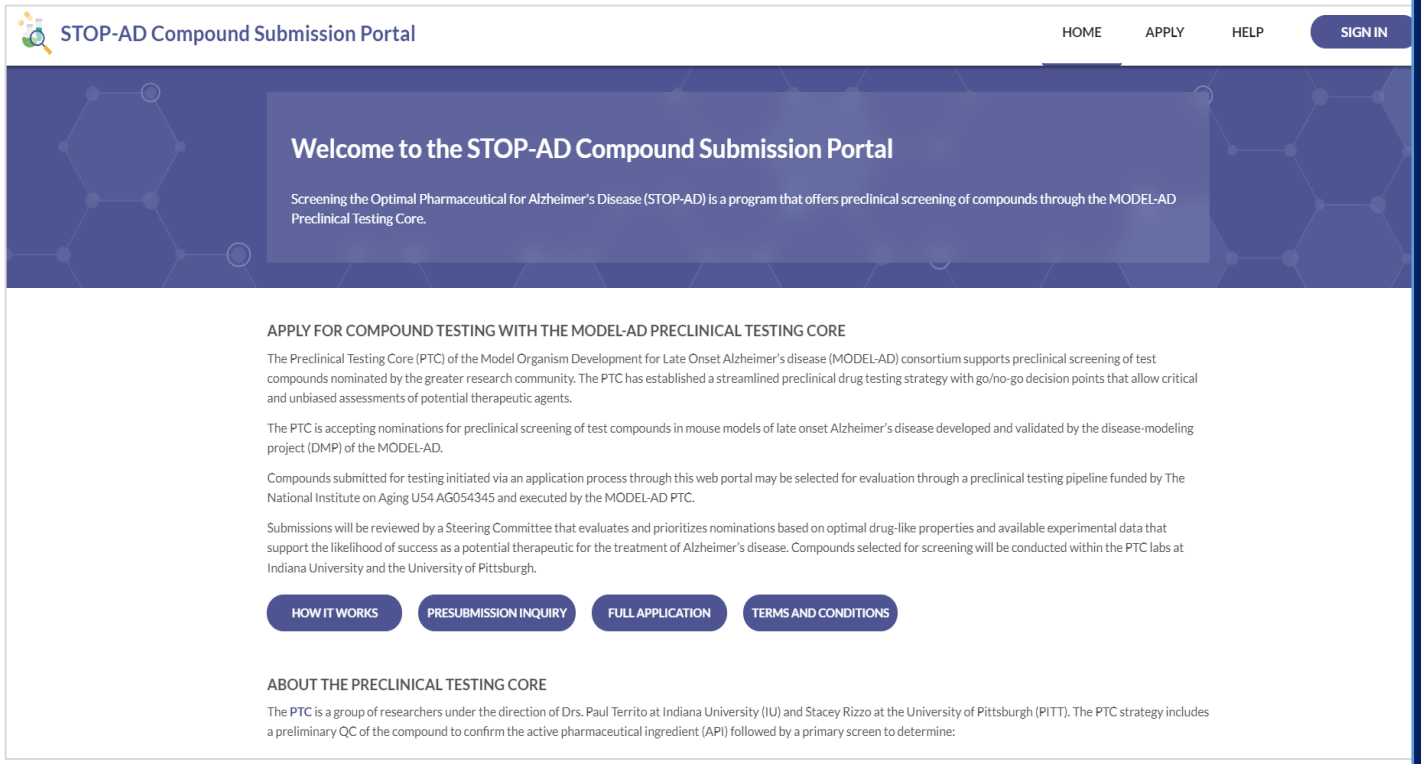
Unbiased Drug Testing Resource

STOP-AD

MARMO-AD

MODEL-AD PTC: Rigorous Open Access Resource for Drug Screening for the Research Community

- **Testing pipeline is funded by the NIA**
  - Compound provided by the investigator
- **Application Process**
  - Data Submission
    - In Vitro
    - In Vivo
    - Pharmacokinetics
    - Toxicology
    - Clinical Data
  - Expert Panel Review
    - Scoring rubric
    - Panel discussion
    - Applicant Presentation
    - Results & Feedback



Learn more at https://stopadportal.synapse.org/

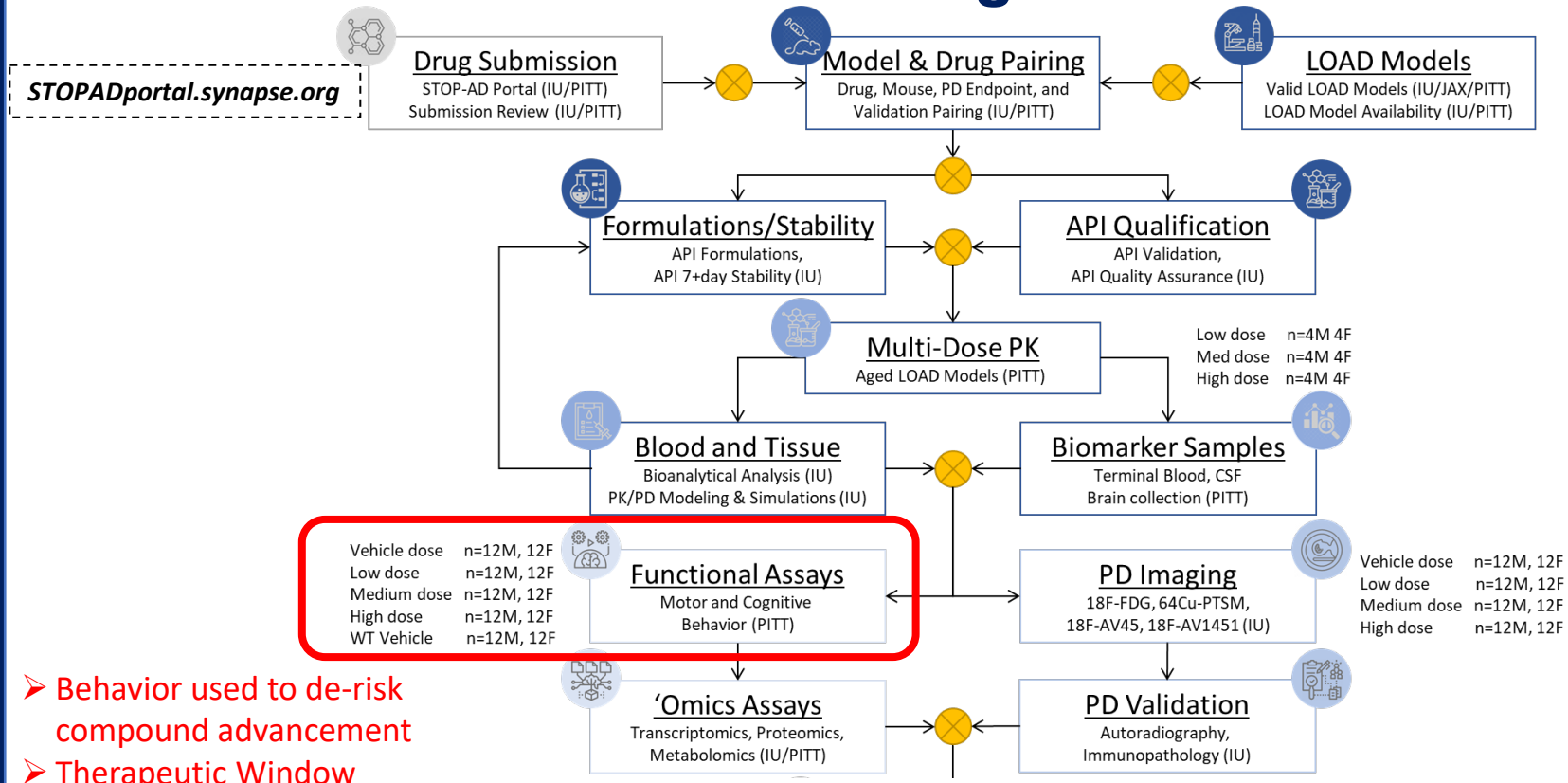
AD Knowledge Portal

AlzPED ALZHEIMER'S DISEASE PRECLINICAL EFFICACY DATABASE
Transparent. Reproducible. Translatable.

MODEL-AD
Model Organism Development & Evaluation for Late-Onset

MODEL-AD Preclinical Testing Core

STOP-AD Compound Submission Portal



- Behavior used to de-risk compound advancement
- Therapeutic Window

University of Pittsburgh

alzheimer's association | Alzheimer's & Dementia: Translational Research & Clinical Interventions

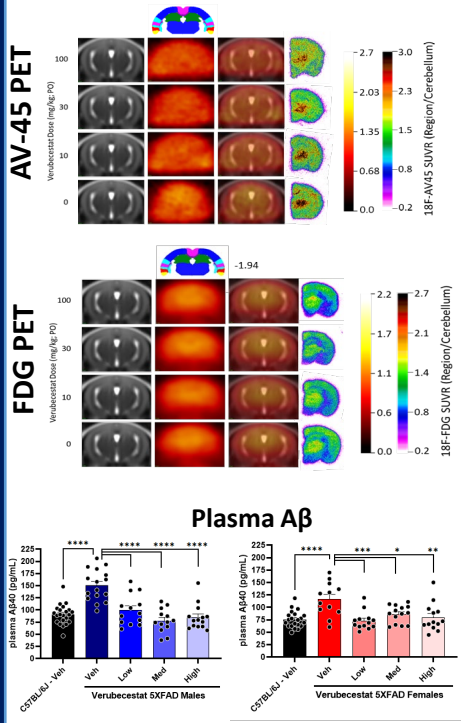
RESEARCH ARTICLE | Open Access

Prophylactic evaluation of verubecestat on disease- and symptom-modifying effects in 5XFAD mice

Adrian L. Oblak, Zackary A. Cope, Sara K. Quinney, Ravi S. Pandey, Carla Biesdorf, Andi R. Masters, Kristen D. Onos, Leslie Haynes, Kelly J. Keezer, Jill A. Meyer, Jonathan S. Peters, Scott A. Persohn, Amanda A. Bedwell, Kierra Eldridge, Rachael Speedy, Gabriela Little, Sean-Paul Williams, Brenda Noarbe, Andre Obenaus, Michael Sasner, Gareth R. Howell, Gregory W. Carter, Harriet Williams, Bruce T. Lamb, Paul R. Territo, Stacey J. Sukoff Rizzo ... See fewer authors

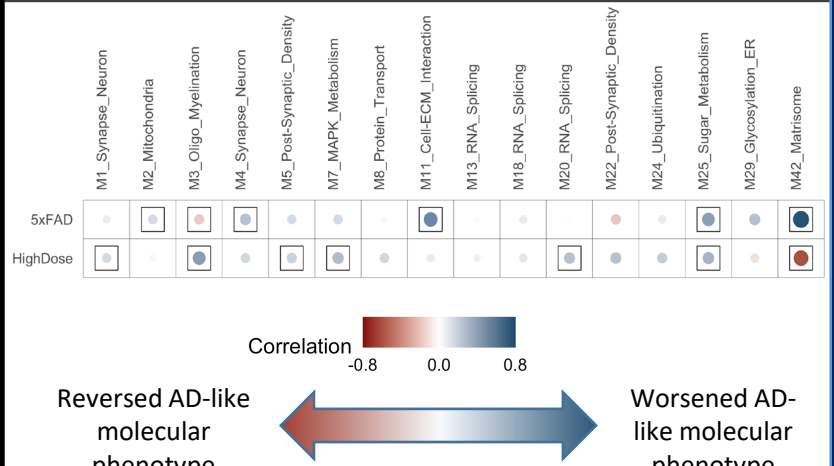
First published: 14 July 2022 | https://doi.org/10.1002/trc2.12317 | Citations: 1

Verubecestat reduced Aβ in the absence of cognitive improvement, with a limited therapeutic window indicative of minimal therapeutic benefit



Verubecestat Clinical Report Egan et al 2019 NEJM	Analogous Mouse Assay	Verubecestat Effects in 5XFAD Mice
Exposure related change in hair color	Frailty Index	Exposure related increase in coat color loss
Dizziness and increased risk of falls	Motor Coordination	Exposure related increase in falls and reduced activity versus vehicle controls
Worsened Cognitive Outcomes	Spatial working Memory	No change at dose range tested (no impairment or improvement)

Post-treatment proteomic analysis of Verubecestat in 5XFAD reveals alterations of proteins that may be associated with side-effects

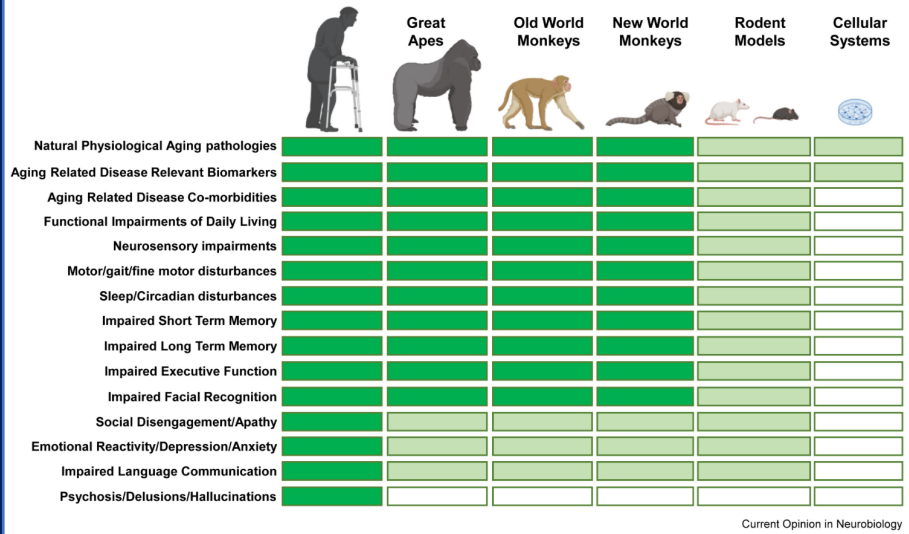


Non-human Primates Bridge the Translational Gap Between Humans and Rodent Models of AD

Current Opinion in Neurobiology
Volume 95, December 2025, 103138

Recent advances in model systems for interrogating diseases of brain aging and associated dementia: Toward human-relevant endophenotypes

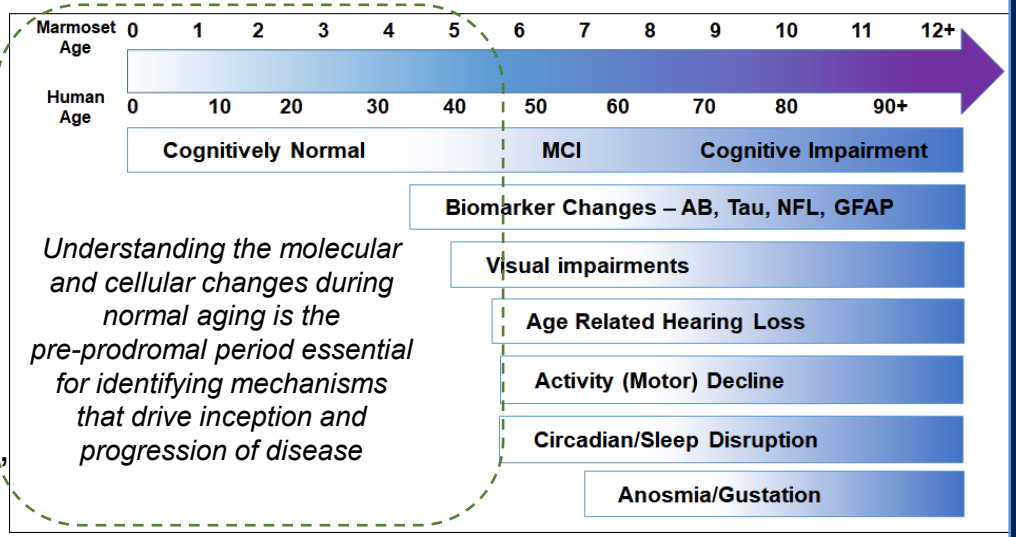
Stacey J. Sukoff Rizzo [1 2 a]



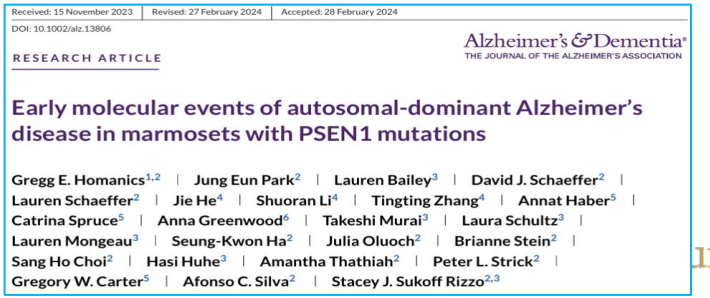
- **Overcome limitations of other model organisms**
  - ➢ Natural presentation of AD related pathologies
    - ➢ Co-morbidities with aging related cancers, cardiovascular diseases, diabetes
  - ➢ Prolonged aging timeframe
  - ➢ Leverage genetic heterogeneity
  - ➢ Comparative primate immune system
    - ➢ Sporadic virus infections (Herpesviruses, Epstein Barr)
  - ➢ Mature prefrontal cortex critical for higher-order cognitive processes

Marmosets are an ideal NHP species for studying ADRD

- Small genetically diverse New-World primates
- Sophisticated behavioral repertoire
  - Monogamous pairs, co-parenting, highly social
  - Age-dependent changes in motor, sensorimotor, hearing, vision, cognitive function
- Gestation: Multiple offspring every ~5 mo.
- Lifespan: 12+ years; ‘aged’ at 8 years
- Sporadic presentation with aging of Aβ plaques, hyperphosphorylated Tau, NFTs including both 3R/4R isoforms; TDP-43 and alpha-synuclein
- Successful genetic manipulation approaches including mutations in AD risk genes



Modified from Murai and Sukoff Rizzo 2020


Received: 15 November 2023 | Revised: 27 February 2024 | Accepted: 28 February 2024
DOI: 10.1002/alz.13806
RESEARCH ARTICLE
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Early molecular events of autosomal-dominant Alzheimer's disease in marmosets with PSEN1 mutations

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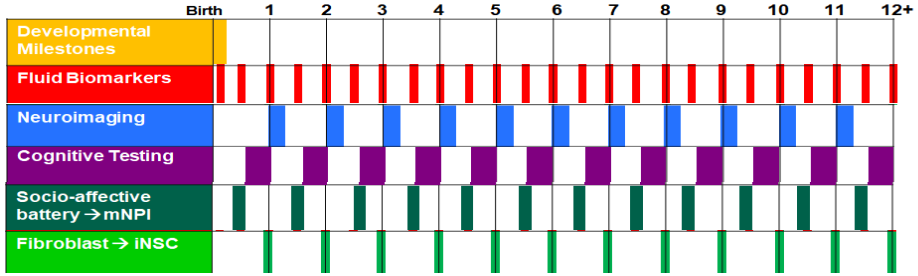
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Development, Characterization, and Validation of Marmoset Models of Alzheimer's Disease

MARMO-AD

NIA U19AG074866 Silva, Rizzo, Carter

- **Marmoset *is the patient* approach**
  - Employ non-invasive, clinically-analogous measures that capture the spectrum of AD
  - Leverage genetic heterogeneity with longitudinal tracking of individuals to enable within subject analysis
  - Establish normative values for aging phenotypes across the lifespan in > 150 WT and ADRD model marmosets
  - Capture behavioral and cognitive changes with aging and association with social and affective behaviors
  - Open Science: all data, SOPs, tissues available @ *ADKnowledgeportal.synapse.org*



- **Alignment with the NIA-AA framework**

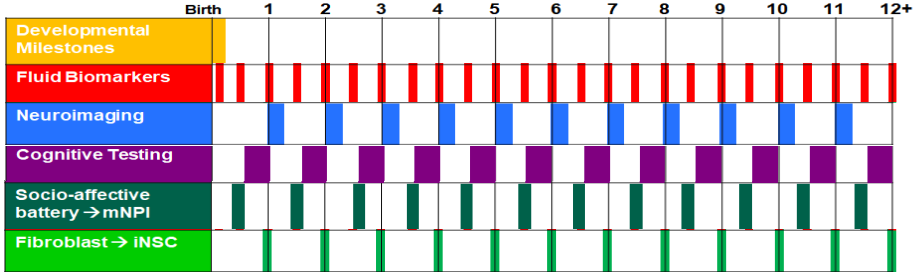
✓ **Multi-modal *Awake* Neuroimaging**
- Amyloid-PET: 11C-PiB
- Metabolism-PET: 18F-FDG
- Tau-PET: 18F-JSS20-183A
- Synaptic Density: 18F-SynVesT-1
- Structural and functional MRI

✓ **Fluid Biomarkers (plasma)**
- MSD: Aβ40, Aβ 42, NfL, GFAP, tTau
- NULISA CNS 120 panel: pTau 231, pTau181, pTau217

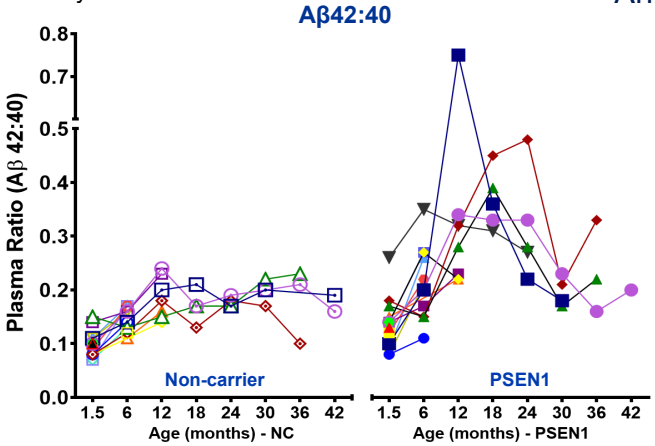
✓ **Cognitive and Behavioral Assessments**
- Touchscreen-based cognitive tasks
- Neurodevelopment, motor, fine motor, circadian, social behavior, anxiety, motivation (NPS)

✓ **Multi-omics analysis**
- WGS, RNAseq, proteomics
- Longitudinal signatures from direct reprogramming of fibroblasts annually to iNSCs

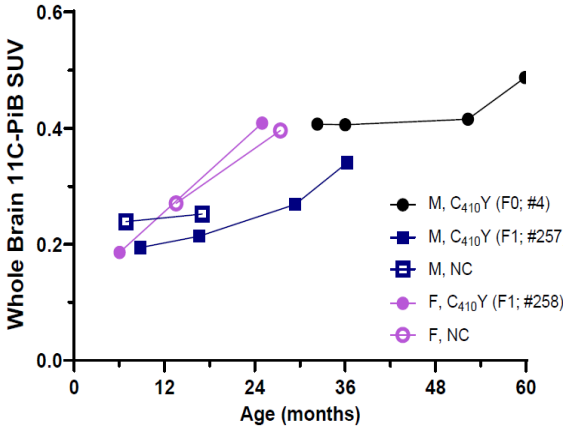
Marmoset *is the patient* Approach



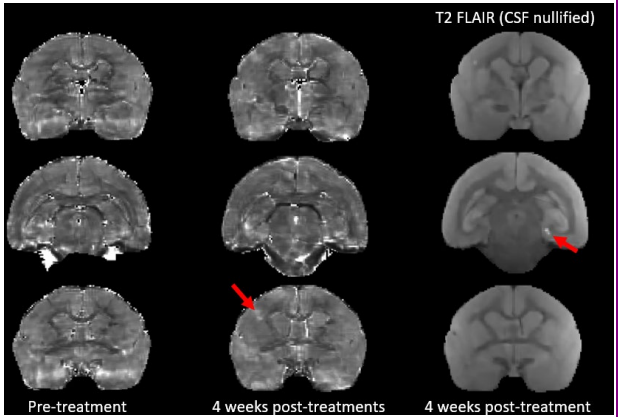
N=17 F1/F2 Germline age/sex-matched non-carrier yoked controls



Neuroimaging Battery
- Awake restraint training
- Annual PET, MRI, fMRI



Enrolled 1st Patient – Lecanemab MAD study
- PiB+ subject enrollment criteria
- ARIA observed 5 weeks post



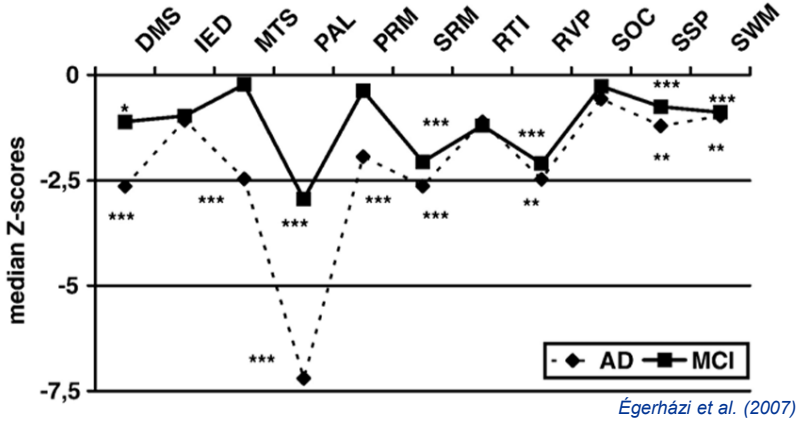
1. Sukoff Rizzo et al 2023 Alz & Dementia Translational Research and Clinical Interventions
2. Homanics, Park, Bailey et al, 2024, Alz & Dementia

Laurel Dieckhaus, PhD
Silva Laboratory

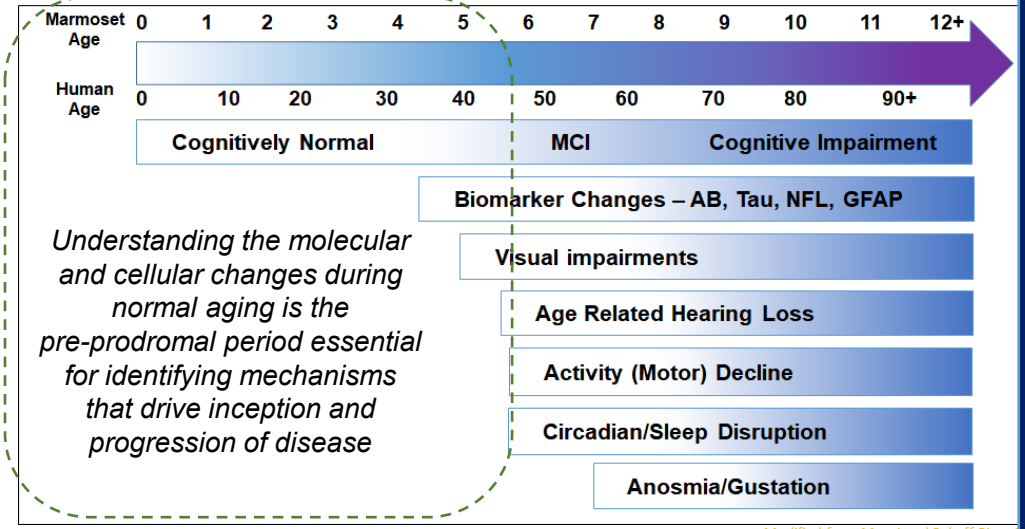
MARMO-AD
Marmosets as Research Models of Alzheimer's Disease

Marmosets are an ideal NHP species for studying ADRD

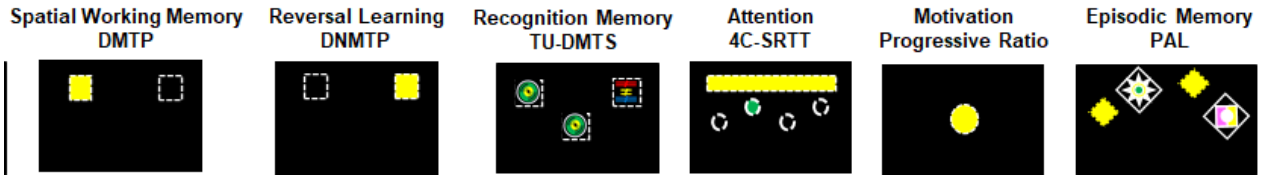
CANTAB



Égerházi et al. (2007)



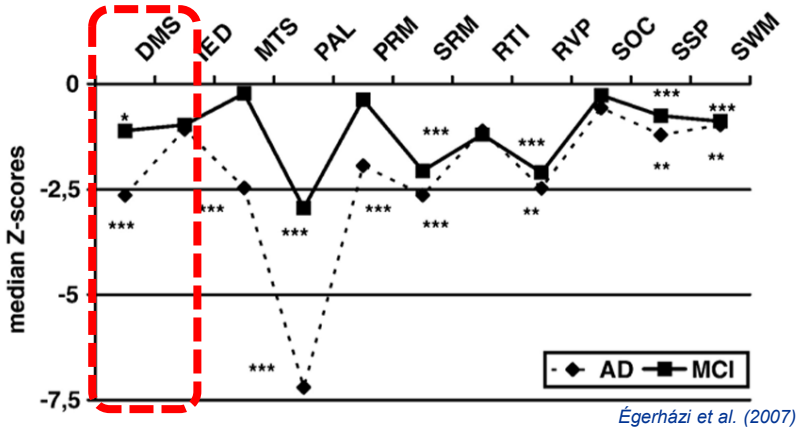
Modified from Murai and Sukoff Rizzo



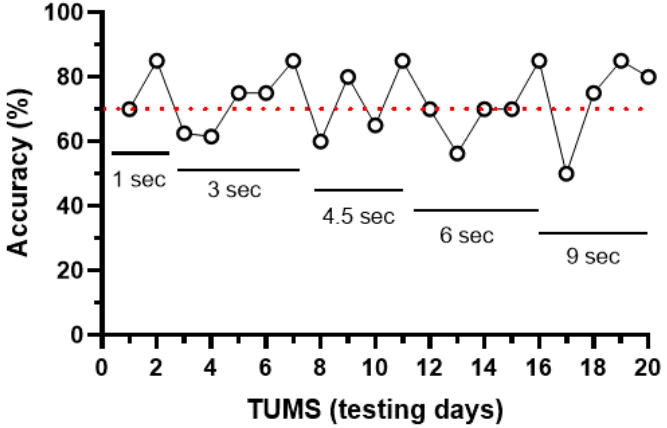
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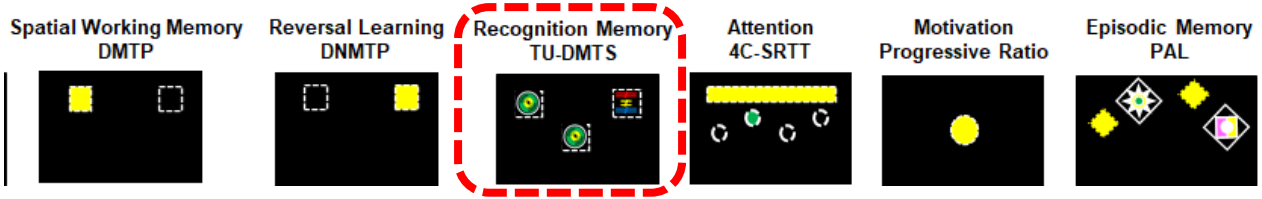
Marmosets are an ideal NHP species for studying ADRD

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Égerházi et al. (2007)

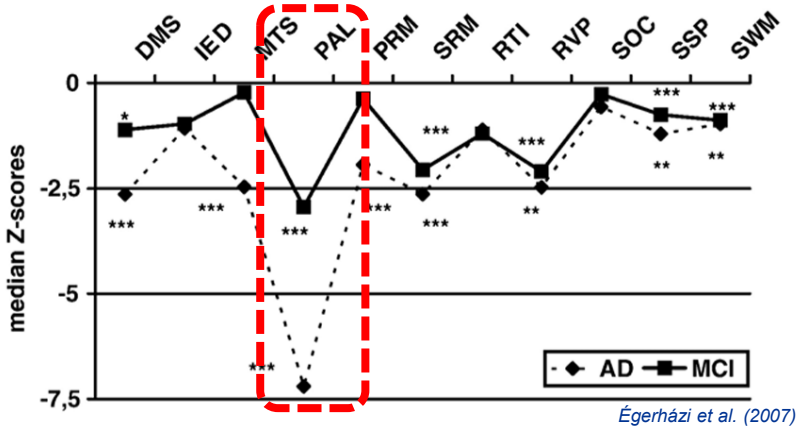




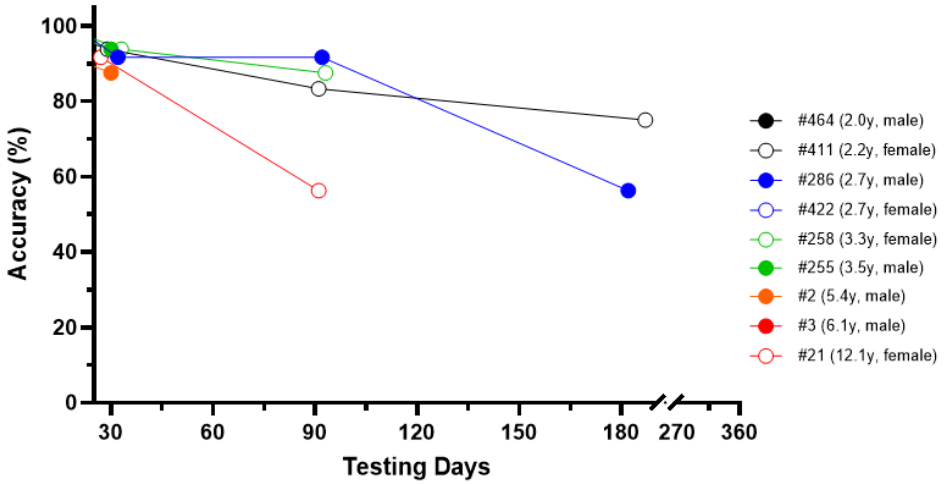
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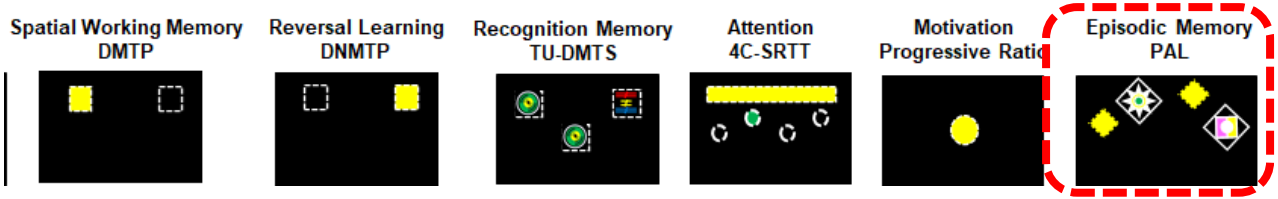
Marmosets are an ideal NHP species for studying ADRD

CANTAB



Égerházi et al. (2007)





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Combinatorial Problem Solving Task For Evaluating Executive Function

- A nonspatial combinatorial optimization task that evaluates the ability to choose the most valuable reward outcomes when provided choices of lesser reward outcomes

- Subjects are trained to associate reward values with different stimulus combinations
  - Combinations **= 7** → high value (150uL)
  - Combinations **<7** → low value (20uL)
  - Combinations **>7** → null value (no reward)

- Each trial consists of 3 phases:
  1. Trial Initiation
  2. Sample Phase
  3. Choice Phase

MARMO-AD
Marmosets as Research Models of Alzheimer's Disease

Precision Medicine Approach for Preclinical Translational Studies



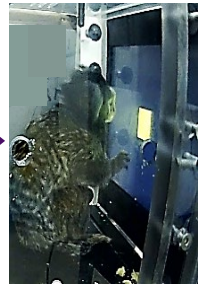
Proposed Novel Therapeutic Intervention



- Mice do not express target
- Poor sequence homology

iPSC Screening

- Match Mouse Model with MOA
- Recapitulation of Human Disease Signature
- Prioritize PK and PK/PD, In vivo Target Engagement
- Use Behavior to De-risk (side-effect profile)



MARMO-AD

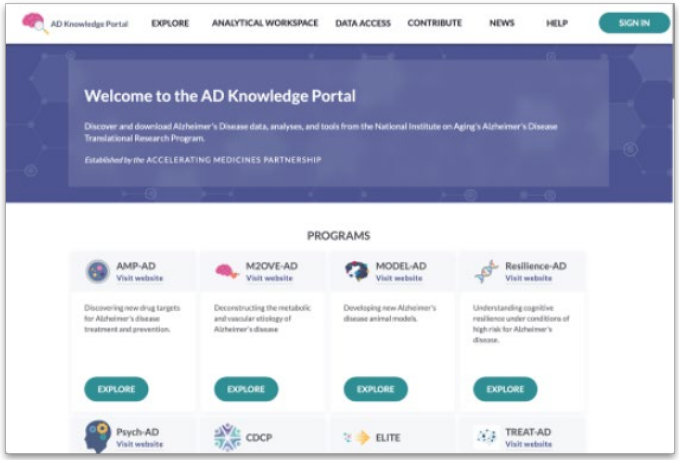
- Confirm and Extend PK/PD
- In vivo Target Engagement
- Awake PET/MRI
- Cognitive Assessments
- Neuropsychiatric co-morbidities

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MODEL-AD Resources Available to the Research Community

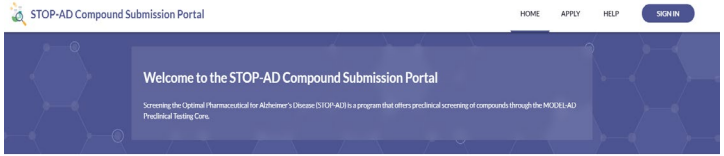
AD Knowledge Portal

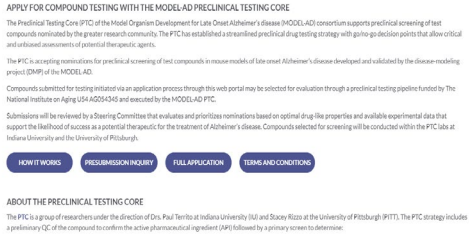
Catalog of all raw data and protocols

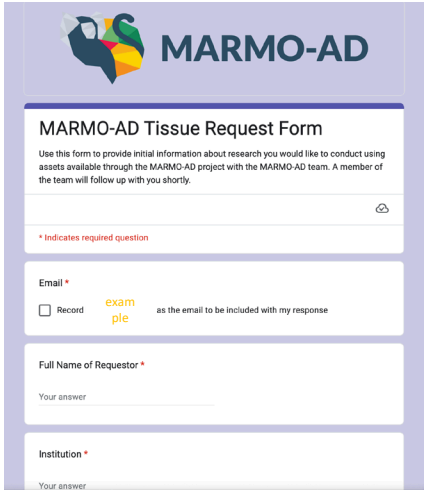


https://adknowledgeportal.org/

https://stopadportal.synapse.org/







Principles and Techniques for Improving Preclinical Translation in Alzheimer's Disease — NIA R13AG060708

Upcoming Event

PRINCIPLES AND TECHNIQUES FOR IMPROVING PRECLINICAL TRANSLATION IN ALZHEIMER'S DISEASE

Location: Bar Harbor ME

May 4-8 2026

Scholarships Available *www.jax.org*

NIA R13AG060708

- **Lecture Topics**
  - Drug Discovery and Development Process
  - Pharmacokinetics and Bioanalytical
  - Pharmacodynamics and PD endpoints for AD
  - In vivo Target Engagement
  - PK/PD Modeling
  - Behavioral Phenotyping for AD mouse models
  - Translational Pharmacology (PET/MR)
  - Intersection of Clinical and Preclinical Genetics
  - New MODEL-AD Mouse Models & Resources
  - Preclinical Biostatistics
  - Genetic Diversity
- **Hands On Training & Practicums**
  - *in vivo* PK studies
  - Drug formulation
  - Routes of administration (PO, IP, SC, etc)
  - Serial blood sample and terminal CSF and tissue collections
  - Frailty index assessment
  - Executing experiments in line with ARRIVE guidelines
    - Blinding
    - Randomization
    - Counterbalancing
    - Controls
    - Sample size Analyses

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  - Gareth Howell (JAX)
  - Greg Carter (JAX)
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NIH National Institute on Aging

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  - Bruce Lamb (IU)
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MARMO-AD MODEL-AD TREAT-AD

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