Improving Preclinical to Clinical Translation in Alzheimer’s Disease: The MODEL-AD Preclinical Testing Pipeline

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Recommendations from 2015 NIA AD Summit
Increasing the Predictive Value of AD Animal Models and Enabling Transparent and Reproducible Preclinical Efficacy Testing

• Establish and implement guidelines for rigorous preclinical testing in LOAD models with the standards/rigor comparable to clinical trials in humans

• Provide a resource/facility for standardized therapeutic efficacy testing of preclinical drug candidates that prioritizes translational biochemical and physiological endpoints (e.g. PET/MR) over behavioral measures using best practices

• Develop a database of preclinical studies that would be available to the AD scientific community and incorporating experimental details as well as unpublished negative and positive data

NIA Funding Initiative
RFA AG16-04

MODEL-AD Consortium
Model Organism Development and Evaluation for Late-onset Alzheimer’s Disease
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
Intersection of the disease, drug mechanism of action, and biomarker properties yields region (A-C) represents potential false negative (-) or positive (+) readouts. Region D provides the optimal measure of drugs action on a disease process.

- The Disease $\cap$ Drug $\cap$ Biomarkers (D)
- An MOA relevant and translatable biomarker is available
- PET Biomarkers provide clinically relevant information on disease endpoints
- PET Biomarkers provide rapid clinical translation based on current clinical use
- Secondary confirmation via AutoRad ensures reliability of PET Biomarkers at higher resolution
- Tertiary confirmation via Immunopathology ensures target engagement independent of PET or AutoRad
Drug Selection Ranking Algorithm

\[ W(j) = \frac{1}{m} \sum_{i=1}^{n} \alpha(i) \beta(i,j) \gamma(i,j) \]

\[ \alpha = \begin{cases} 
0, & \text{if } \gamma = \text{None} \\
1, & \text{if } \gamma > \text{None} 
\end{cases} \]

\[ \beta \rightarrow [0.0, 1.0] \]

\[ \gamma = \{\text{none, poor, fair, good, excellent}\} \]

\[ \gamma: b \rightarrow [0, 1] \text{ as a sigmoid function} \]

- Candidates will be rank order will be based on a cumulative weighting scheme
  - Biophysical Characteristics
    - \textit{In vitro} and \textit{In vivo}
  - Pharmacokinetics Data
    - \textit{In silico}, \textit{In vitro}, and \textit{In vivo}
  - Toxicology Data
    - LD50
    - Acute
    - Chronic
    - Teratogenicity
  - Clinical Data
Drug Selection Ranking Algorithm - Analysis

- Donepezil (Aricept™)
  - Cholinesterase Inhibitors
  - 1 of 2 FDA approved medications for AD
  - Symptomatic Modifying Drug (SMOD)
- Levetiracetam (Keppra™)
  - Synaptic vesicle protein modulator SV2A
  - Atypical anti-convulsant medication
  - Disease Modifying Drug (DMOD) at 1/15th the anticonvulsant dose
- Verubecestat (MK8931)
  - Beta secretase 1/2 (BACE1/2) inhibitor
  - Phase 2/3 FDA EPOCH (suspended) APECS (ongoing)
  - Disease Modifying Drug (DMOD)
stopadportal.synapse.org
Welcome to the STOP-AD Compound Submission Portal

Screening the Optimal Pharmaceutical for Alzheimer’s Disease (STOP-AD) is a program that offers preclinical screening of compounds through the MODEL-AD Preclinical Testing Core.

APPLY FOR COMPOUND TESTING WITH THE MODEL-AD PRECLINICAL TESTING CORE

The Preclinical Testing Core (PTC) of the Model Organism Development for Late Onset Alzheimer’s disease (MODEL-AD) consortium supports preclinical screening of test compounds nominated by the greater research community. The PTC has established a streamlined preclinical drug testing strategy with go/no-go decision points that allow critical and unbiased assessments of potential therapeutic agents.

The PTC is accepting nominations for preclinical screening of test compounds in mouse models of late onset Alzheimer’s disease developed and validated by the disease-modeling project (DMP) of the MODEL-AD.

Compounds submitted for testing initiated via an application process through this web portal may be selected for evaluation through a preclinical testing pipeline funded by The National Institute on Aging U54 AG053435 and executed by the MODEL-AD PTC.

Submissions will be reviewed by a Steering Committee that evaluates and prioritizes nominations based on optimal drug-like properties and available experimental data that support the likelihood of success as a potential therapeutic for the treatment of Alzheimer’s disease. Compounds selected for screening will be conducted within the PTC labs at Indiana University and the University of Pittsburgh.
Welcome to the STOP-AD Compound Submission Portal

Screening the Optimal Pharmaceutical for Alzheimer’s Disease (STOP-AD) involves preclinical screening of compounds through the MODEL-AD Preclinical Testing Core (PTC) of the Model Organism Development & Evaluation for Lake-Orival Alzheimer’s Disease (MOOSEAD) consortium.

The PTC is accepting nominations for preclinical screening of test compounds nominated by the grants that support the disease-modeling project (DMP) of the MODEL-AD consortium. The PTC is committed to developing an optimized preclinical drug testing strategy with well-defined, informed, and unbiased go/no-go decision points that allow critical and unbiased evaluation of potential therapeutic lead compounds.

Compounds submitted for testing initiated via an application on submitted for evaluation through a preclinical testing pipeline funded by The National Institute on Aging and other cooperating institutions.

Submissions will be reviewed by a Steering Committee that evaluates and prioritizes nominations based on optimal drug-like properties and available experimental data that support the likelihood of success as a potential therapeutic for the treatment of Alzheimer’s disease. Compounds selected for screening will be conducted within the PTC labs at Indiana University and the University of Pittsburgh.
STOP-AD Compound Submission Portal

WELCOME!
Use the table below to submit a compound for consideration by the PTC core.

YOUR SUBMISSIONS

You have no submissions

ADD NEW COMPOUND
STOP-AD Compound Submission Portal

Your Submission

Naming

Submission Name
Enter a unique name for this compound submission
Give your submission a unique name that allows you to identify it.

First Name
Enter Contact First Name
Provide the name of the person who should be contacted about submission status.

Last Name
Enter Contact Last Name
Provide the name of the person who should be contacted about submission status.

Title
Enter Contact Title or Role

Validate

SAVE
STOP-AD Compound Submission Portal

YOUR SUBMISSION

- Required Data
  - Naming
  - Measurements
  - Basic Data
- In Vitro
  - Binding
- Pharmacokinetics
  - PK In Silico
  - PK In Vivo
- Toxicology
  - LD50
  - Acute Dosing

**Binding**

This form is currently included in the submission. Enter some data if you have it, or click "Skip".

**SKIP**

Start entering data by selecting "Add Data". If you have data from multiple cell lines, you can select "Add Data" again to add additional data.

- **Experiment Name**
  - Enter a unique name for this experiment.

- **What cell line was used for the binding assay?**
  - List the cell line used.

- **Binding assay details**
  - Describe the assay used to measure binding.

If this study has been published, please provide a reference.

[Next]
In Vivo Data

This form is currently included in the submission. Enter some data if you have it, or click "Skip".

Start entering data by selecting "Add Data". If you have data from multiple experiments, you can select "Add Data" again to add additional data.

- Experiment Name
  Enter a unique name for this experiment

- If this study has been published, please provide a reference.
  Enter reference

- Species*
  Select from list

- Model Strain*
  What strain of model was used?
PK In Silico

This form is currently included in the submission. Enter some data if you have it, or click "Skip".

**Drug Partition Coefficient (logP)**
- Enter the partition coefficient
  - Please provide the partition coefficient, which is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium.

**Acid Dissociation Constant (pKa)**
- Enter the pKa value
  - Please provide the pKa value, which is one measure used to indicate the strength of an acid.

**Molecular Weight (g/mol)**
- Enter the in silico molecular weight
  - Please provide the in silico molecular weight of the compound in grams per mole (g/mol).
Mouse models will be best matched to the compound of interest being evaluated in the screening pipeline based on both disease pathology and compound mechanism of action.
PTC: Building a Preclinical Testing Pipeline

**Pipeline Characteristics**
- 1-2 compounds per year (currently)
- Initial pipeline validation with well known model (5xFAD) and known compounds

**ARRIVE Guidelines and Best Practices**
- Drug QC & formulation stability
- N=10-12 per sex per dose
- Age-matched vehicle controls
- Blinded technicians
- Blinded data analysis
- Subjects randomized and counterbalanced for order of testing
- Raw data and SOPs to Sage/Synapse

PTC = Preclinical Testing Core
PTC: Building a Preclinical Testing Pipeline

Disease Modeling Project (DMP)
- Identification of Mouse Models

Steering Committee
- Triage of test compounds

1° Screen
Appreciable exposure in the target tissue in relevant model at pathological age

PK, PK/PD

Formulation Stability

Go/No Go Gate

2° Screen
Target engagement and confirmation of disease modification

PET/MRI

AutoRad
IHC

Go/No Go Gate

3° Screen
Functional activity – symptom modifying
Therapeutic index and biomarker confirmation

In Vivo
Functional Activity

Therapeutic Index

CPAC
Catalog #S8564,
Lot#S856401
1000ng on Column
RT: 9.013

JAX
Catalog #S8173,
Batch #01
1000ng on Column
RT: 9.722

PTC = Preclinical Testing Core
PET/MRI/AutoRad as a PD biomarker of:
- Glucose Metabolism (18F-FDG)
- Tissue Perfusion (64Cu-PTSM)
- Beta Amyloid Deposition (18F-AV45)
- Tau (3R/4R) Deposition (18F-AV1451)
PTC: Building a Preclinical Testing Pipeline

Effects of Test Compound on:
- Hippocampal working memory deficits
- Locomotor Activity
- Motor Coordination

PTC = Preclinical Testing Core
MODEL-AD PTC Educational & Training Resources

• Lecture Topics
  • Drug Discovery and Development Process
  • Pharmacokinetics and Bioanalytical
  • Pharmacodynamics and PD endpoints for AD
  • PK/PD Modeling
  • Behavioral Phenotyping & Pharmacology for AD mouse models
  • Translational Pharmacology (PET/MR)
  • Intersection of Clinical and Preclinical Genetics
  • MODEL-AD Consortium Resources and new AD mouse model Resources
  • Preclinical Biostatistics
  • Genetic Diversity
  • Featured Lecture: Ron Demattos, PhD – Eli Lilly, MODEL-AD EAB member
  • Town Hall Discussions

• 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
  • Executing experiments in line with ARRIVE guidelines
    • Blinding
    • Randomization
    • Counterbalancing
    • Controls
    • Sample size Analyses
  • Lunch & Learn Sessions: nanoString, Tissue Vision, CLIMB