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

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MODEL-AD
Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease
INDIANA UNIVERSITY
The Jackson Laboratory
Leading the search for tomorrow's cures
UCI University of California, Irvine
University of Pittsburgh
SageBionetworks

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studies that would be available to the AD scientific community and incorporating experimental details as well as unpublished negative and positive data

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),
U54 AG054349 (UCI)

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

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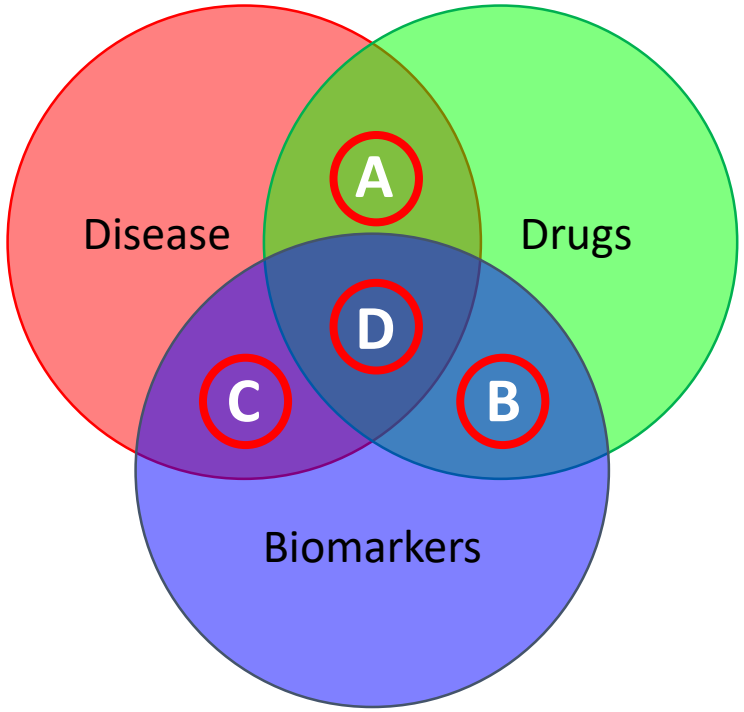
Disease/Drug/Biomarker Optimization

∩	Disease	Drugs
A	−	−
B	−	+
C	+	−
D	+	+



- The **Disease** ∩ **Drug** ∩ **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

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.

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Drug Selection Ranking Algorithm

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

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

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

$$\gamma = \{none, poor, fair, good, excellent\}$$

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

- Candidates will be rank order will be based on a cumulative weighting scheme
  - Biophysical Characteristics
    - *In vitro* and *In vivo*
  - Pharmacokinetics Data
    - *In silico, In vitro,* and *In vivo*
  - Toxicology Data
    - LD50
    - Acute
    - Chronic
    - Teratogenicity
  - Clinical Data

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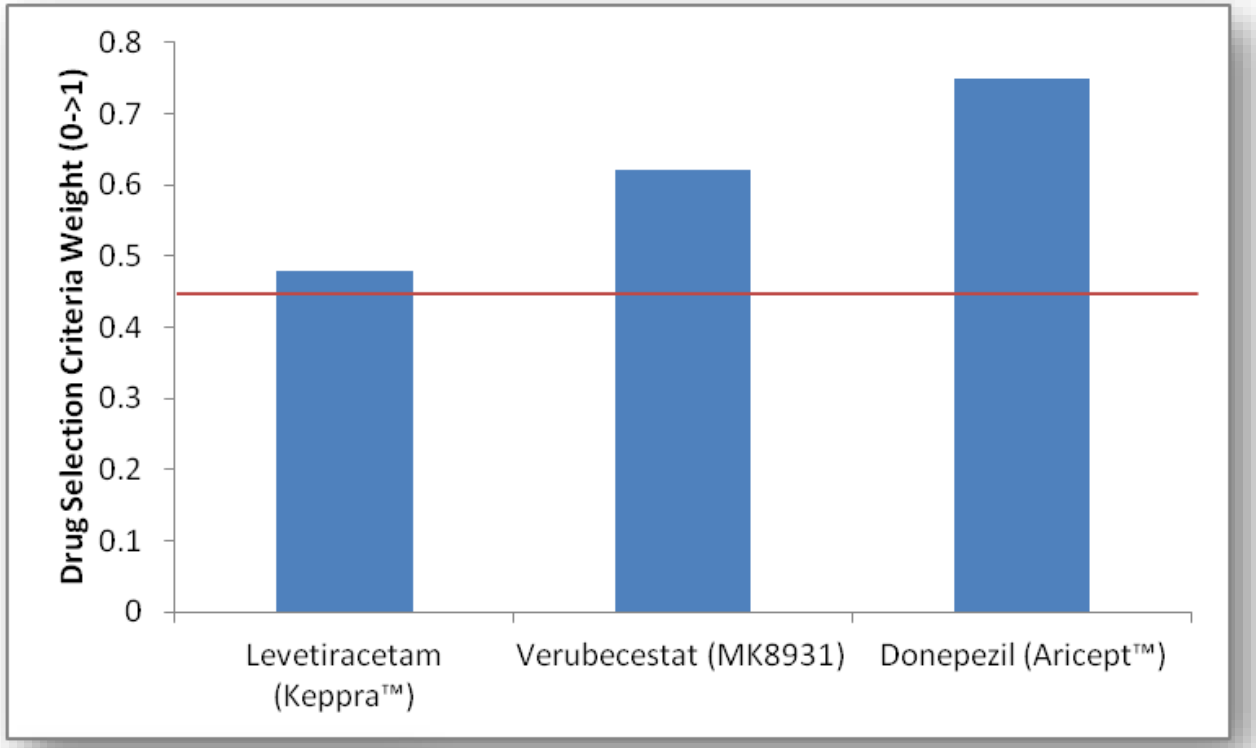
Drug Selection Ranking Algorithm - Analysis

- 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)



0.80-1.00	Excellent
0.71-0.80	Good
0.45-0.70	Moderate
0.35-0.44	Fair
0.00-0.34	Poor

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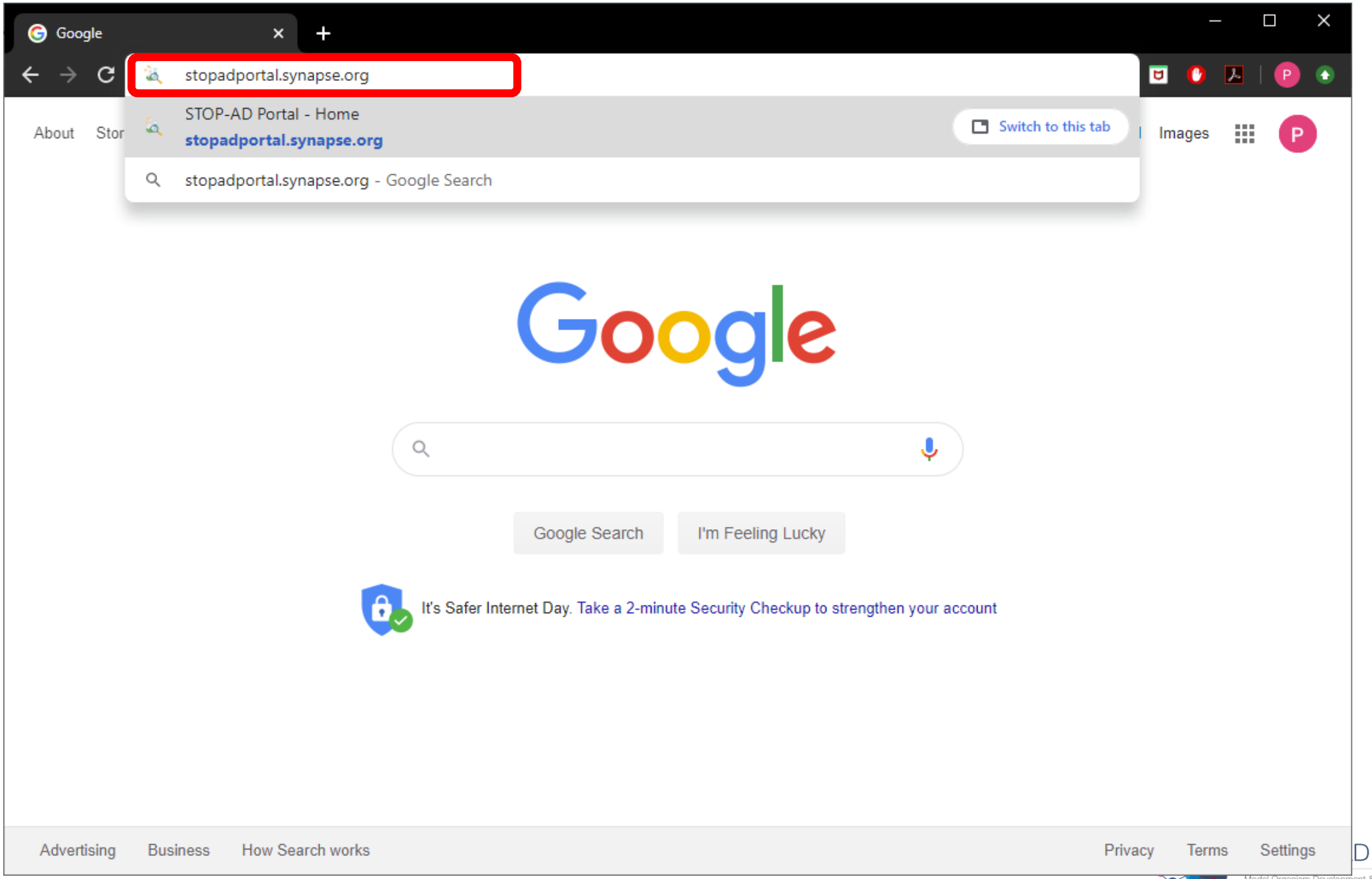

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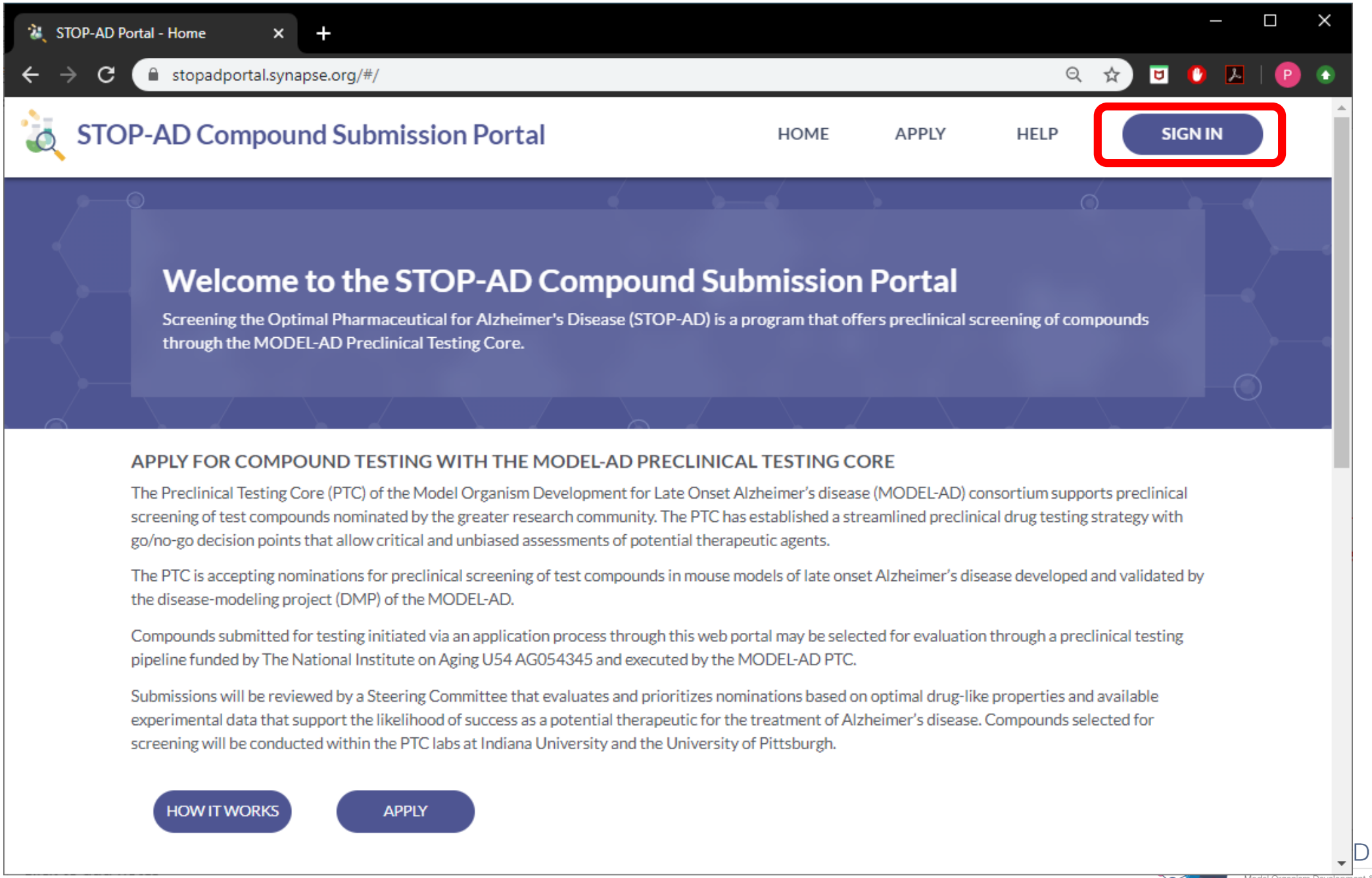
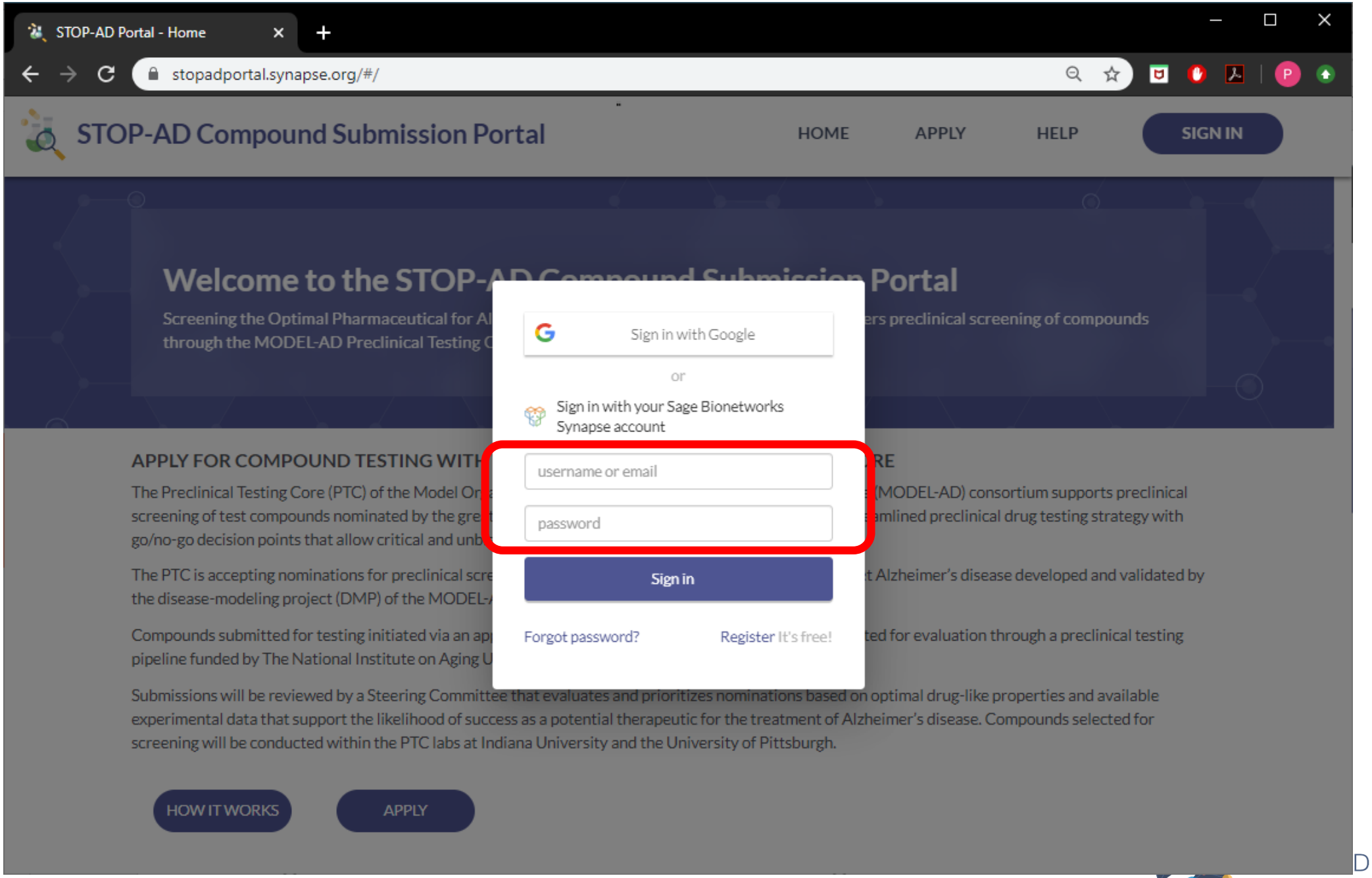

STOP-AD Portal - Home
stopadportal.synapse.org/#/
STOP-AD Compound Submission Portal
HOME
APPLY
HELP
SIGN IN
Welcome to the STOP-AD Compound Submission Portal
Screening the Optimal Pharmaceutical for Alzheimer's Disease (STOP-AD) is a program that offers preclinical screening of compounds through the 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 AG054345 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.
HOW IT WORKS
APPLY



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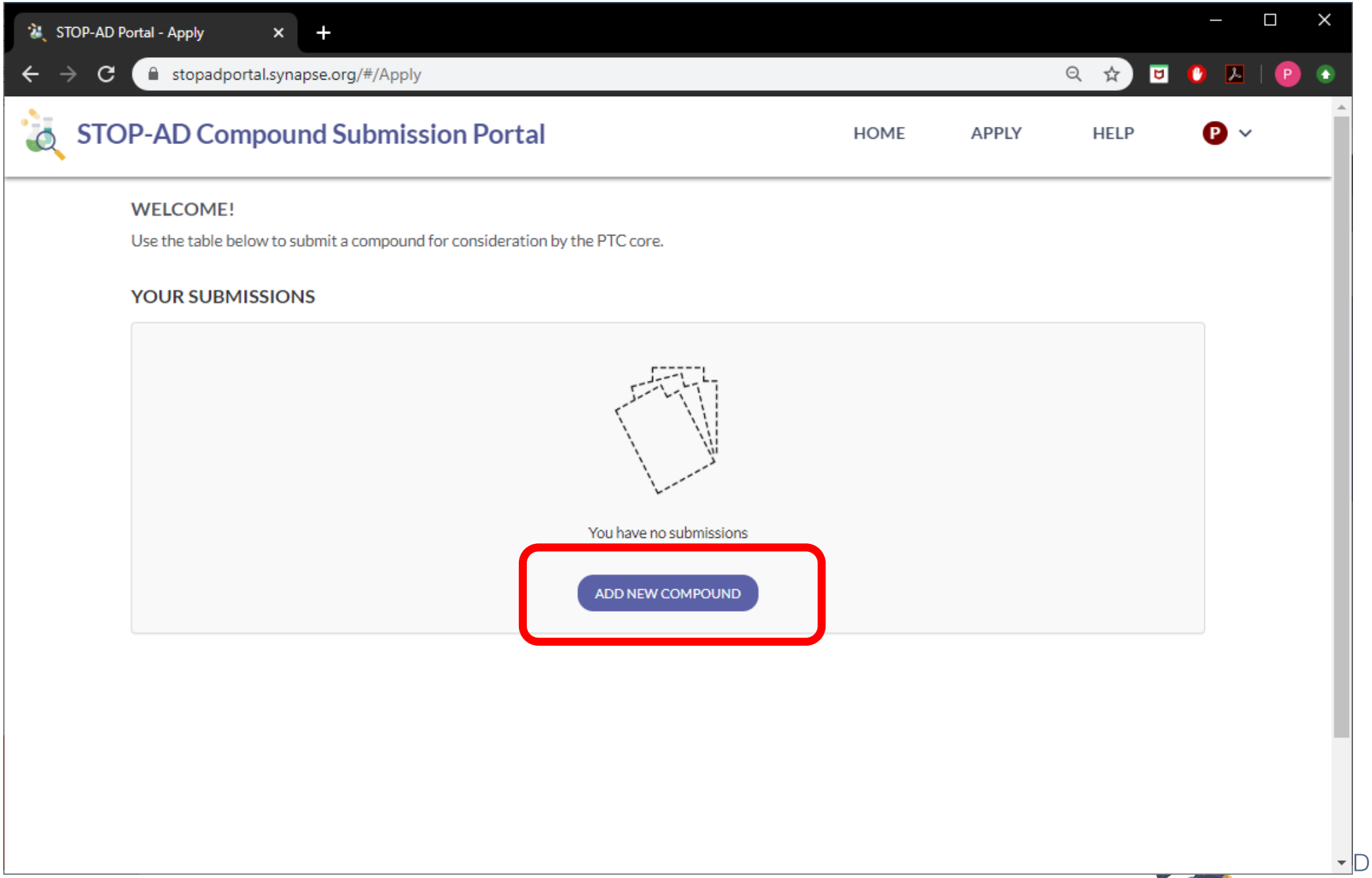

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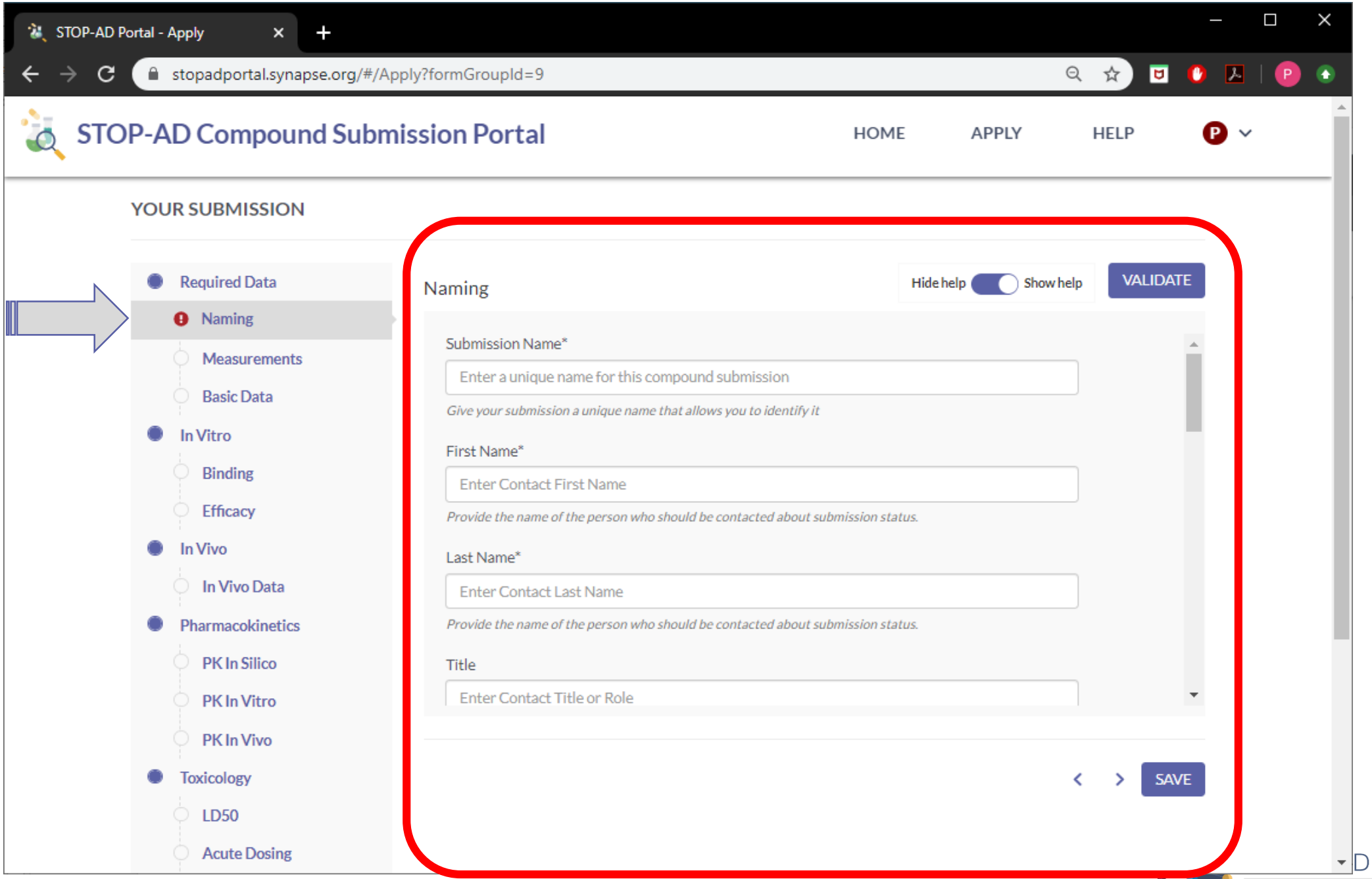
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Basic Data
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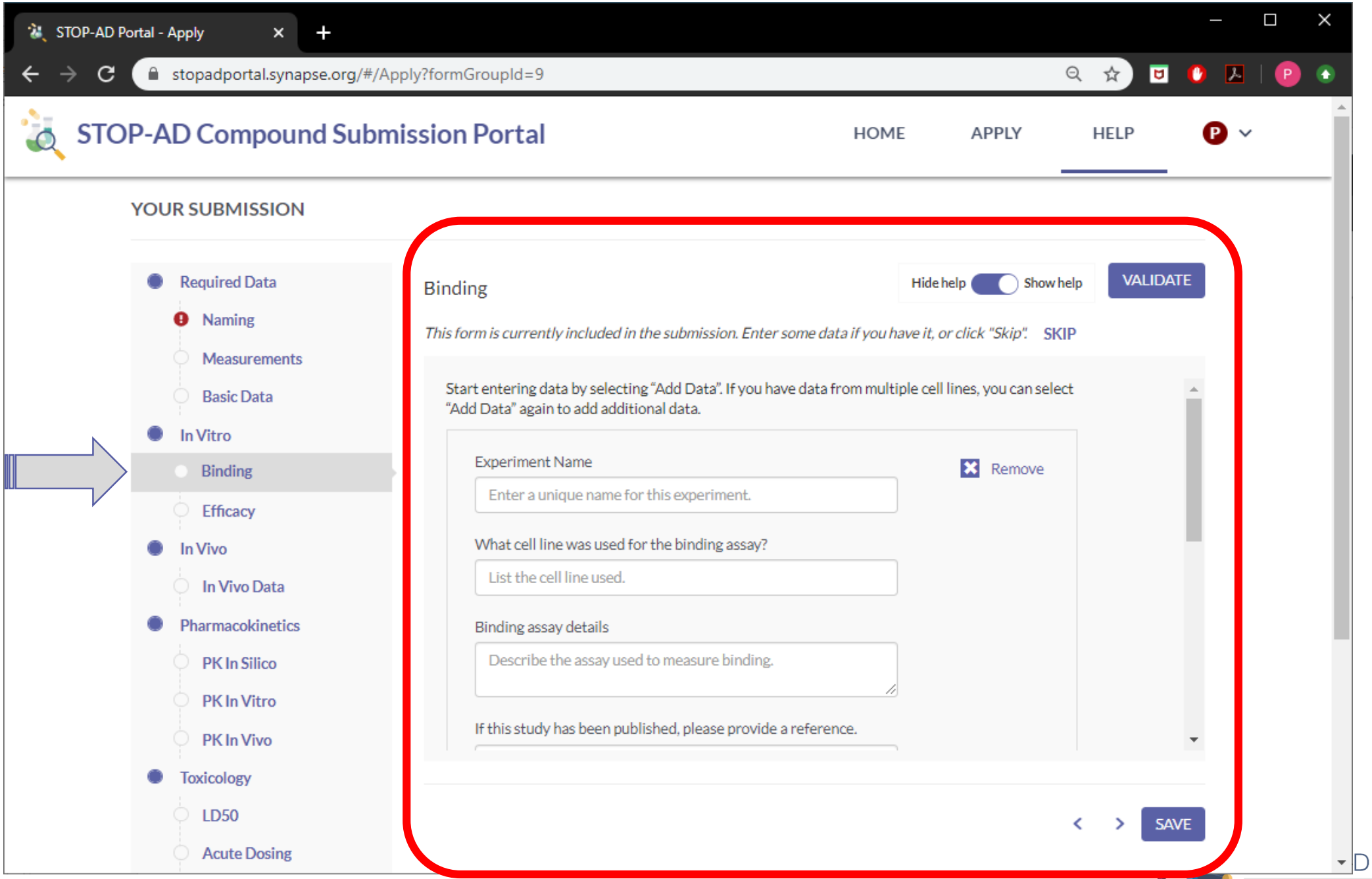
Efficacy
In Vivo
In Vivo Data
Pharmacokinetics
PK In Silico
PK In Vitro
PK In Vivo
Toxicology
LD50
Acute Dosing
Naming
Hide help
Show help
VALIDATE
Submission Name*
Enter a unique name for this compound submission
Give your submission a unique name that allows you to identify it
First Name*
Enter Contact 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
SAVE



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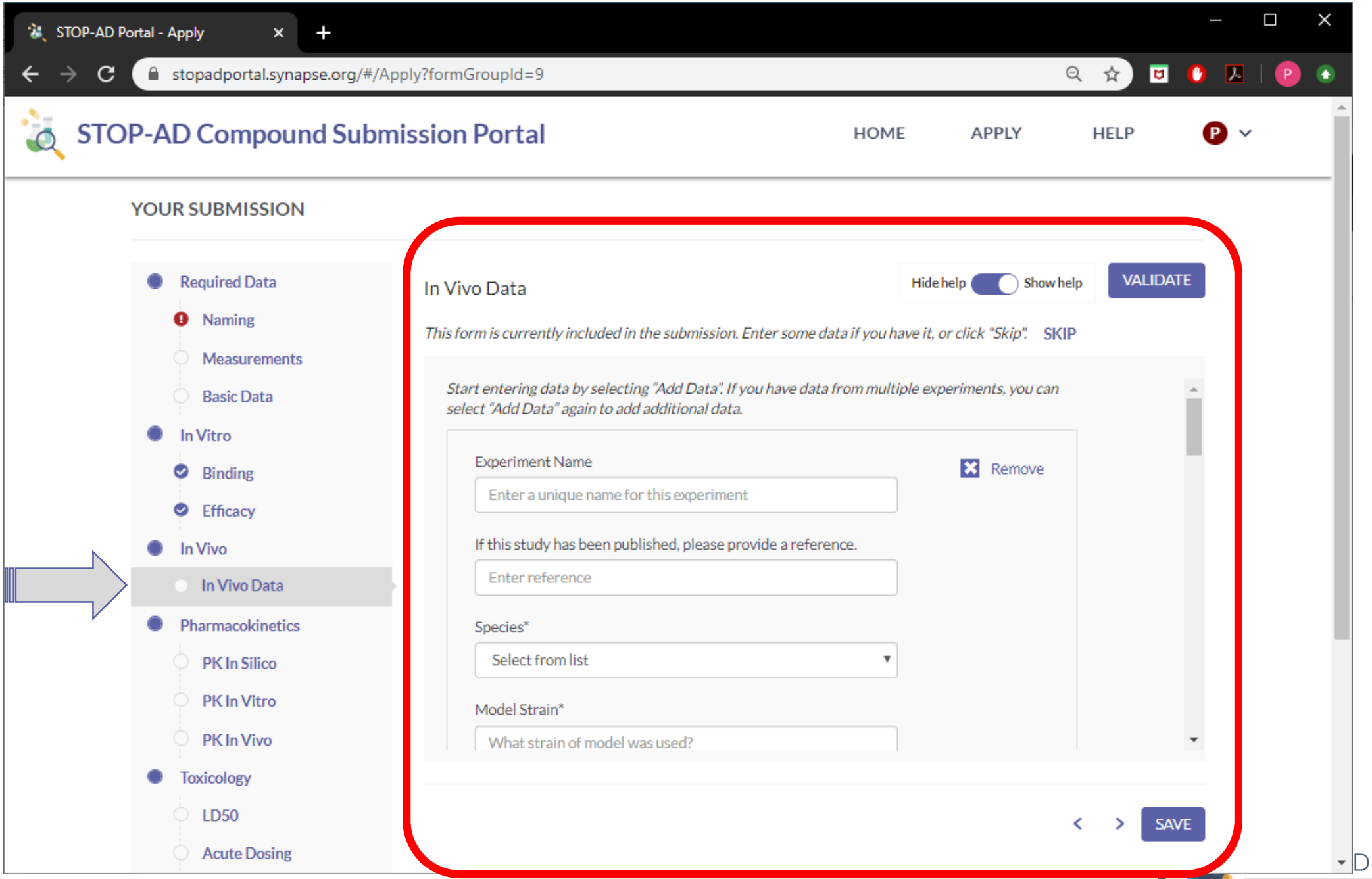
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Hide help
Show help
VALIDATE
This form is currently included in the submission. Enter some data if you have it, or click "Skip".
SKIP
Start entering data by selecting "Add Data". If you have data from multiple experiments, you can select "Add Data" again to add additional data.
Experiment Name
Remove
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?
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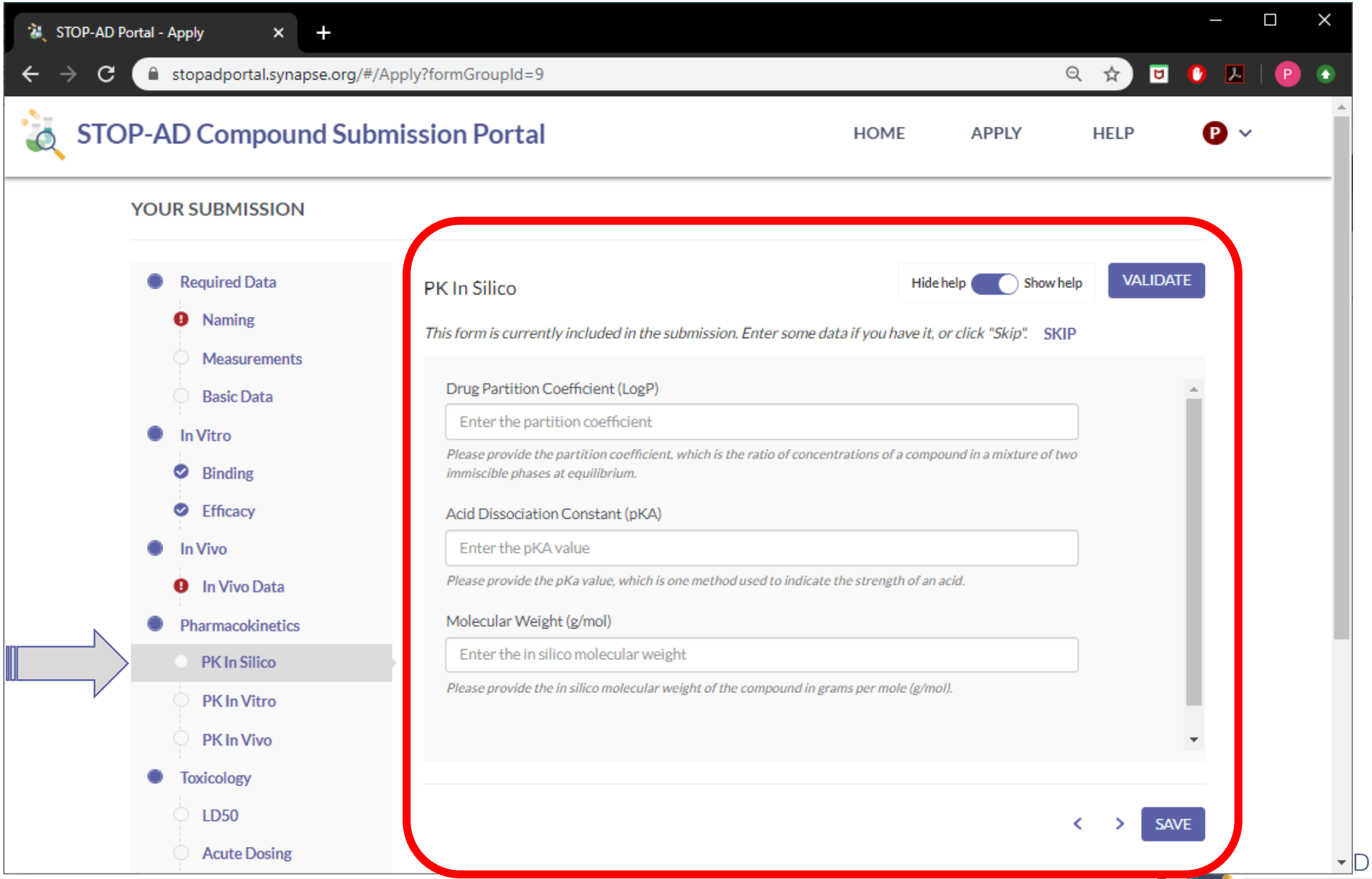
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PK In Silico
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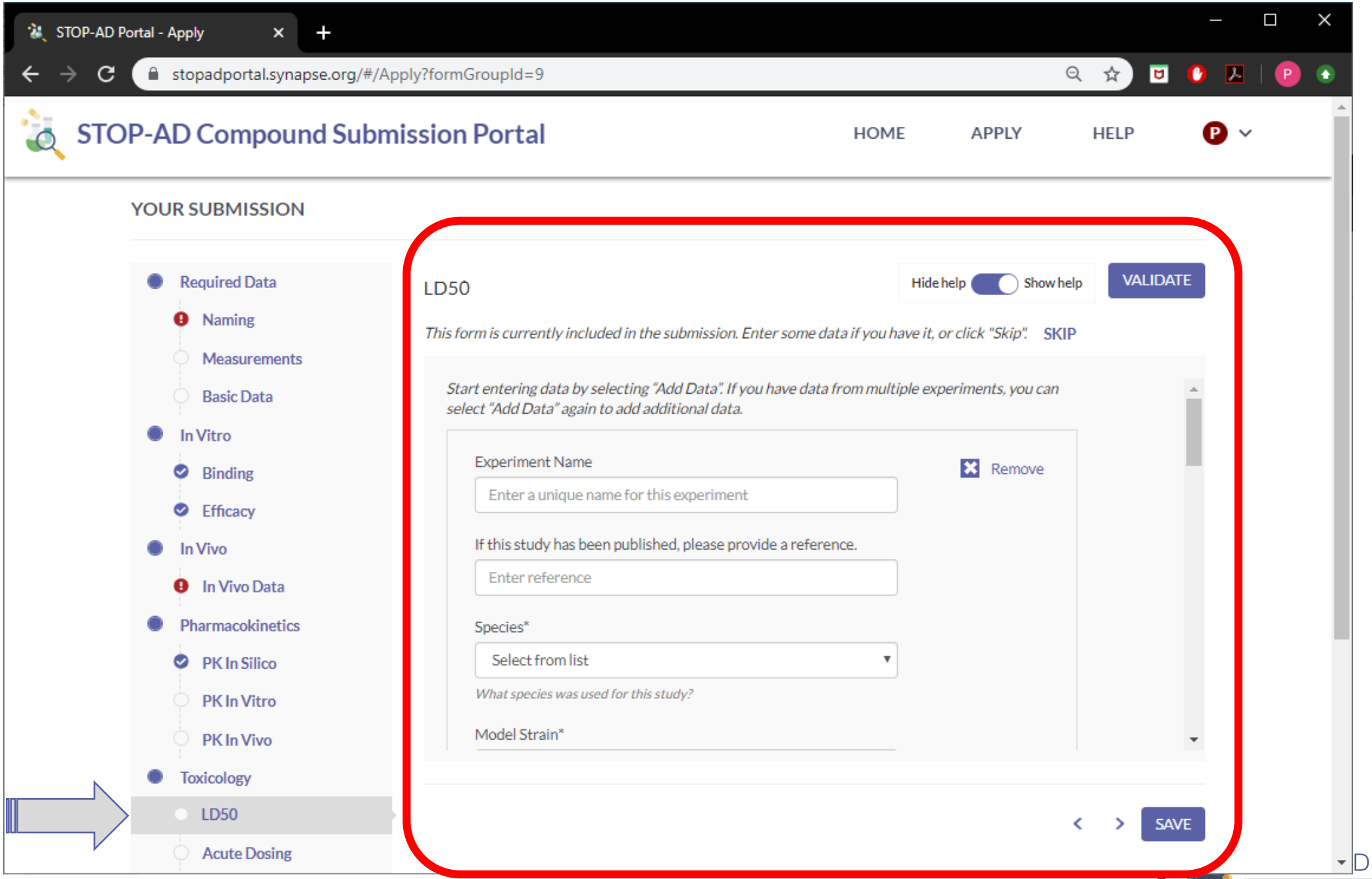
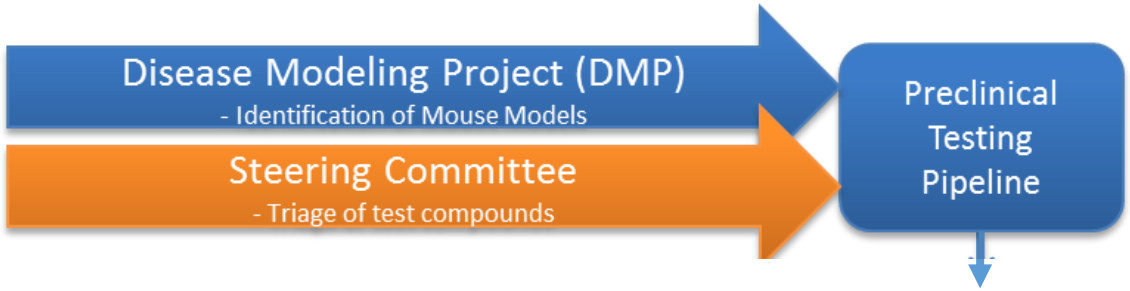
Show help
VALIDATE
This form is currently included in the submission. Enter some data if you have it, or click "Skip".
SKIP
Drug Partition Coefficient (LogP)
Enter the partition coefficient
Please provide the partition coefficient, which is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium.
Acid Dissociation Constant (pKA)
Enter the pKA value
Please provide the pKa value, which is one method 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).
SAVE



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

PTC: Building a Preclinical Testing Pipeline



- 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.

Mouse Model	Pathological Hallmark	Drug (Mechanism)	Primary Fluid Biomarker	Primary Biomarker	Secondary Biomarker	Primary Confirmation	Secondary Confirmation
			CSF/plasma	PET/MRI	PET/MRI	AutoRad	IHC
5XFAD	Abeta	BACE Inhibitor (Verubecestat)	AB40 AB42	AV45	FDG	AV45 FDG	Abeta
hTau	Tau	Tau Inhibitor	pTau	AV1451	PTSM	AV4151 PTSM	Tau
IL1RAP	Neuro-Inflammation	Anti-Inflammatory	Cytokines	PTSM	FDG	PTSM FDG	IBA1 GFAP

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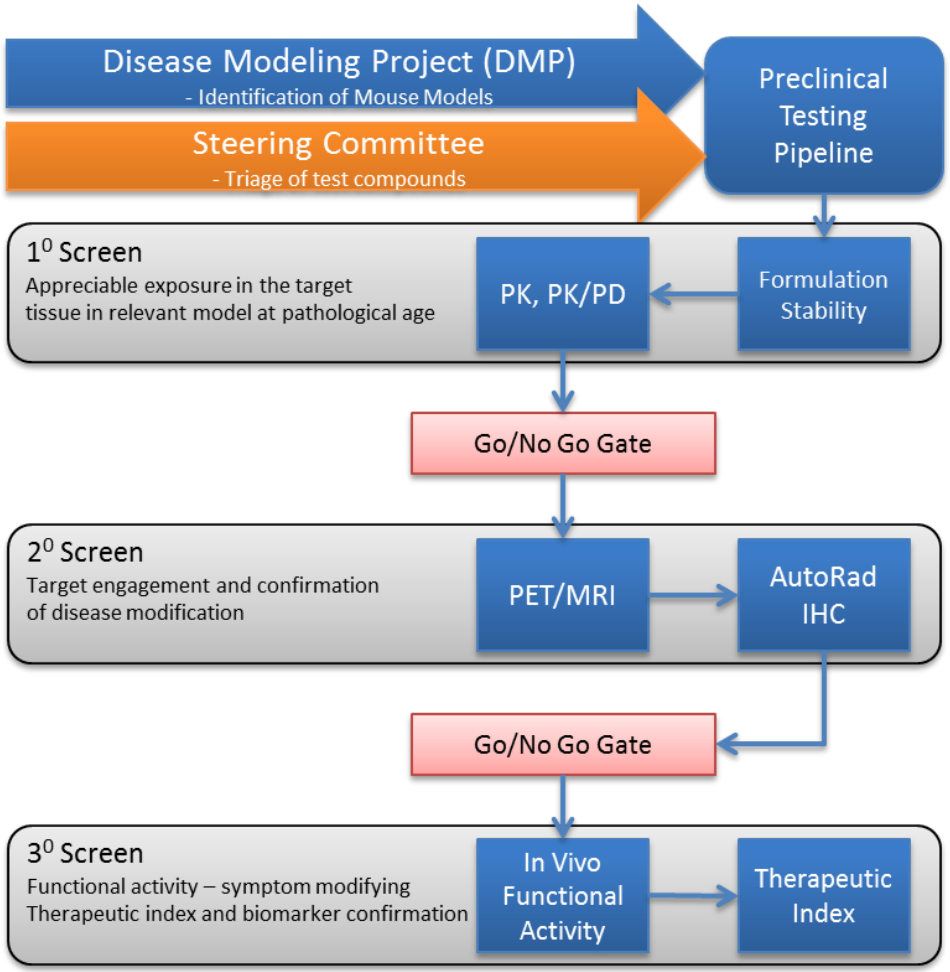

Pipeline Characteristics

- 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

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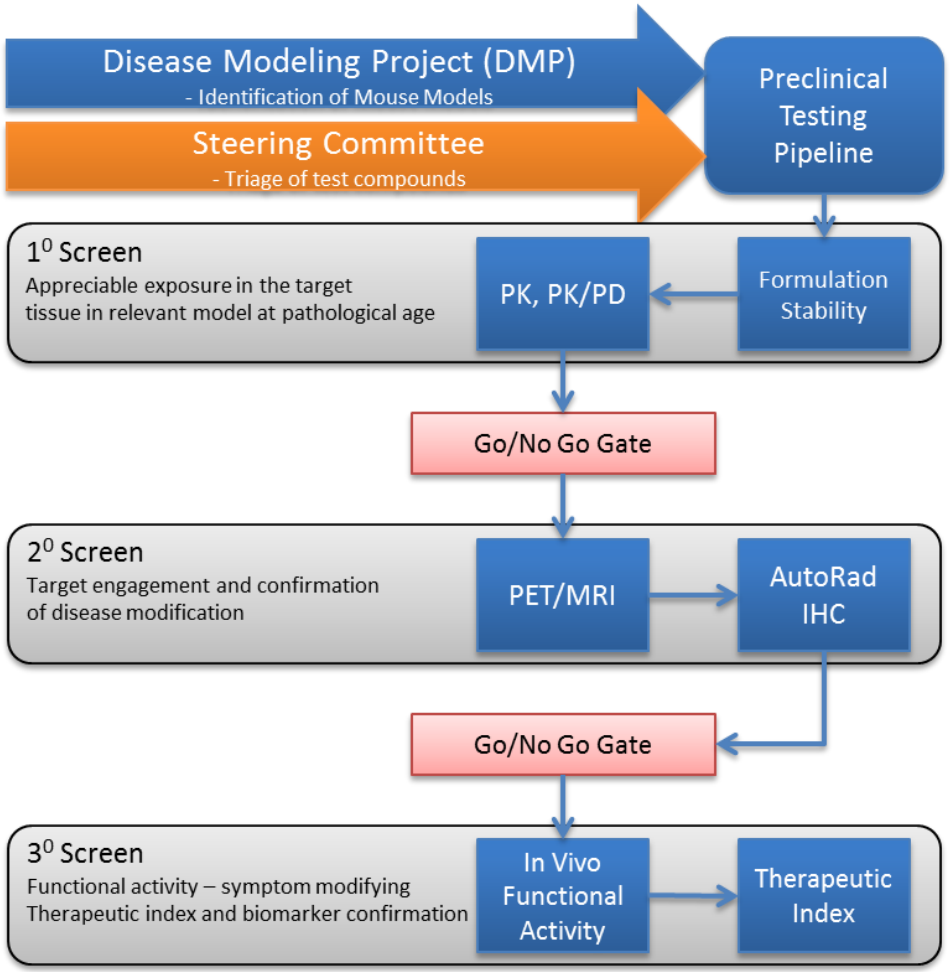

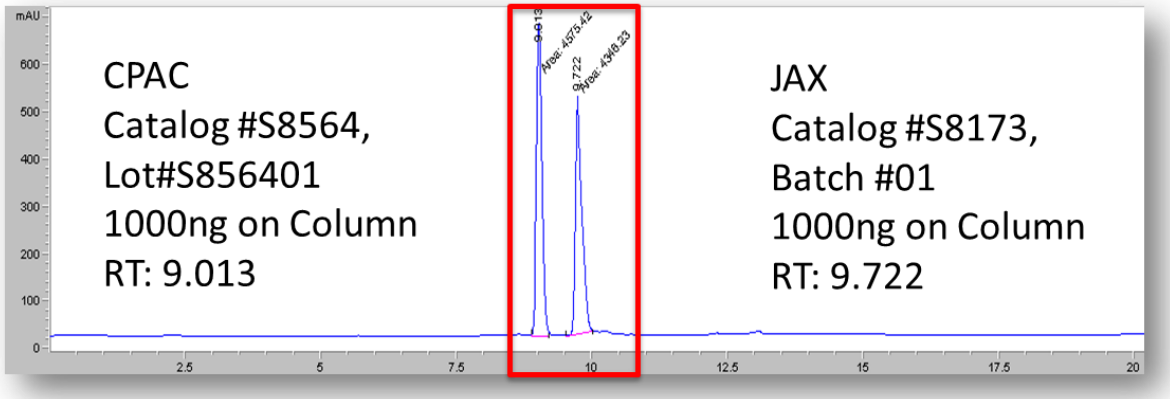

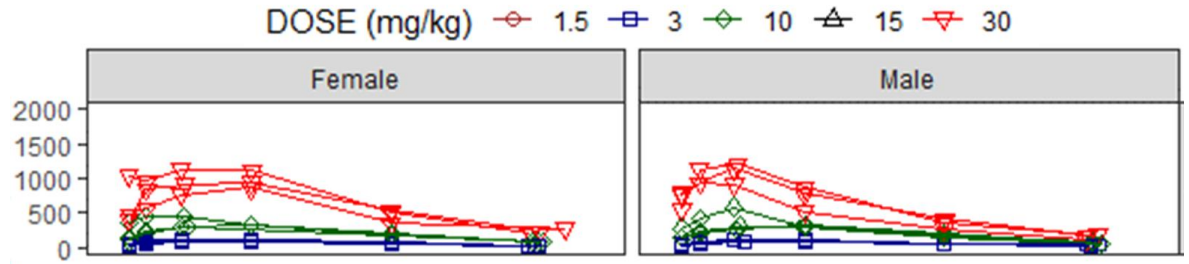

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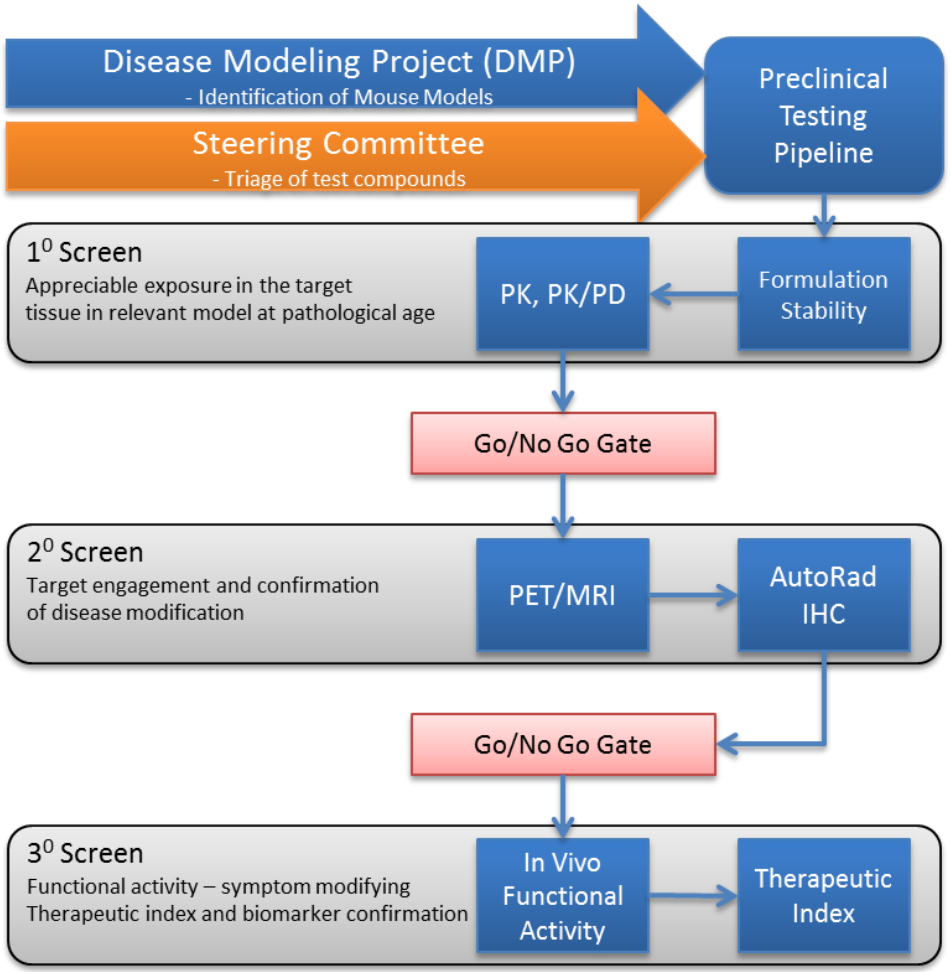
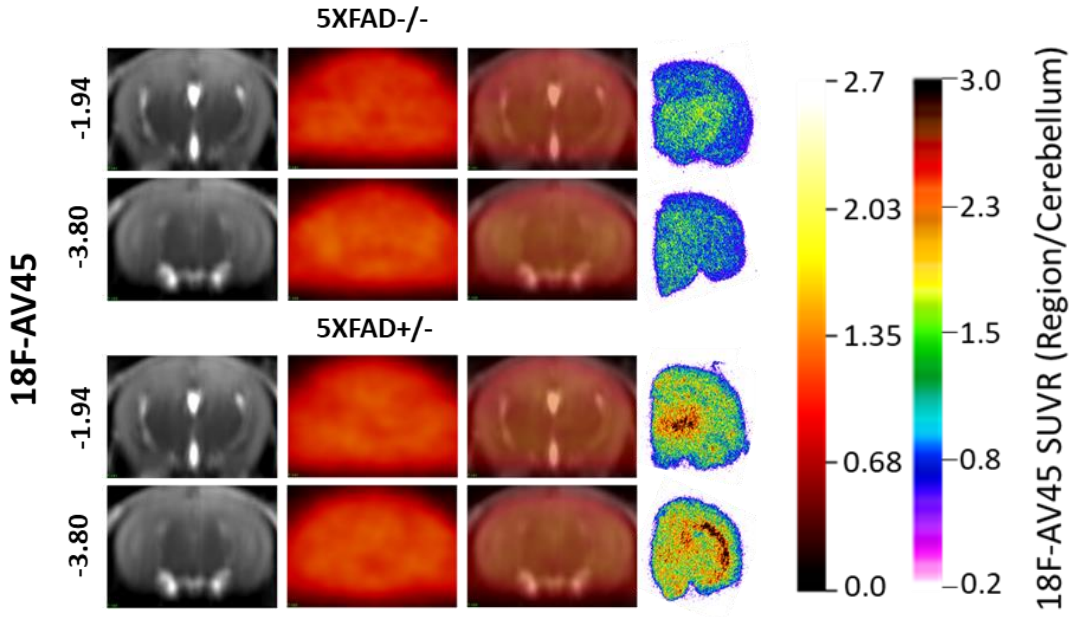


PET/MRI/AutoRad as a PD biomarker of:

- Glucose Metabolism (18F-FDG)
- Tissue Perfusion (64Cu-PTSM)
- Beta Amyloid Deposition (18F-AV45)
- Tau (3R/4R) Deposition (18F-AV1451)



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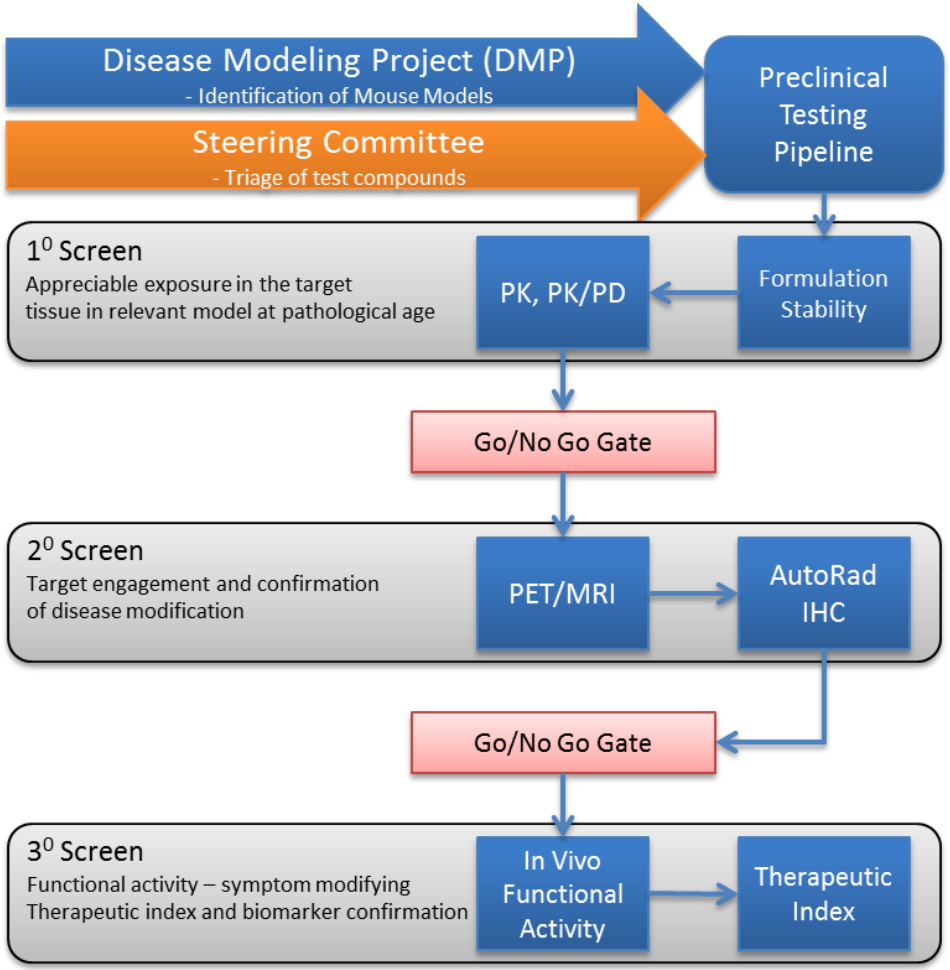
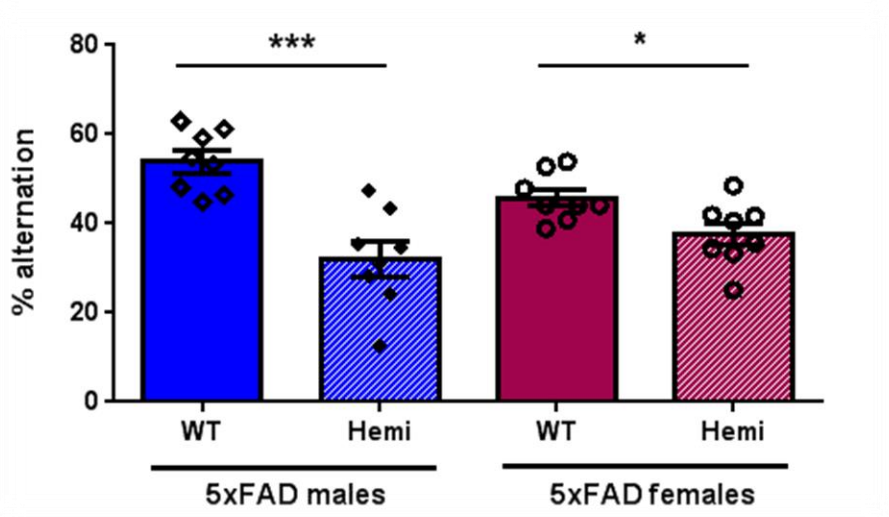


Effects of Test Compound on:

- Hippocampal working memory deficits
- Locomotor Activity
- Motor Coordination



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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

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