MODEL-AD

Preclinical Efficacy Testing Pipeline and Training Resources

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

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NIH AD Research Summits 2012/2015 Recommendations Aimed at:

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 AD Tg 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 biochemical and physiological endpoints
- Preclinical efficacy testing of *selected* candidate AD therapeutics using standardized 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studies that would be available to the AD scientific community and incorporating experimental details as well as unpublished negative and positive data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 **O**rganism **D**evelopment and **E**valuation for
Late-onset **A**lzheimer's **D**isease

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PTC Aims and Milestones

- **Years 1-2**
  - **Establish and validate processes and procedures**
    - Testing protocols (SOPs), exclusion/inclusion criterion, subject identification, logistics (e.g. sample shipment JAX to IU)
  - **Recruit and Train staff**
    - Staff are required to reproduce data validation sets under blinded conditions
      - Develop training protocols and provide this resource to the community
  - **Establish preclinical testing pipeline**
    - Validate pipeline with BACE inhibitor in well characterized mouse model (5xFAD)
    - Determine Go/NoGo criterion
    - Refine processes and procedures
    - Test preclinical pipeline with drug currently in clinic
  - **Develop and implement process for vetting potential drug candidates nominated by the greater AD research community**
    - Establish a publically accessible web mechanism to submit drug candidates
- **Years 3-5:** Evaluate 2 novel compounds per year in MODEL-AD LOAD mouse models

All raw data, methods, and analyses published via Synapse/Sage portal and AlzPED for community access

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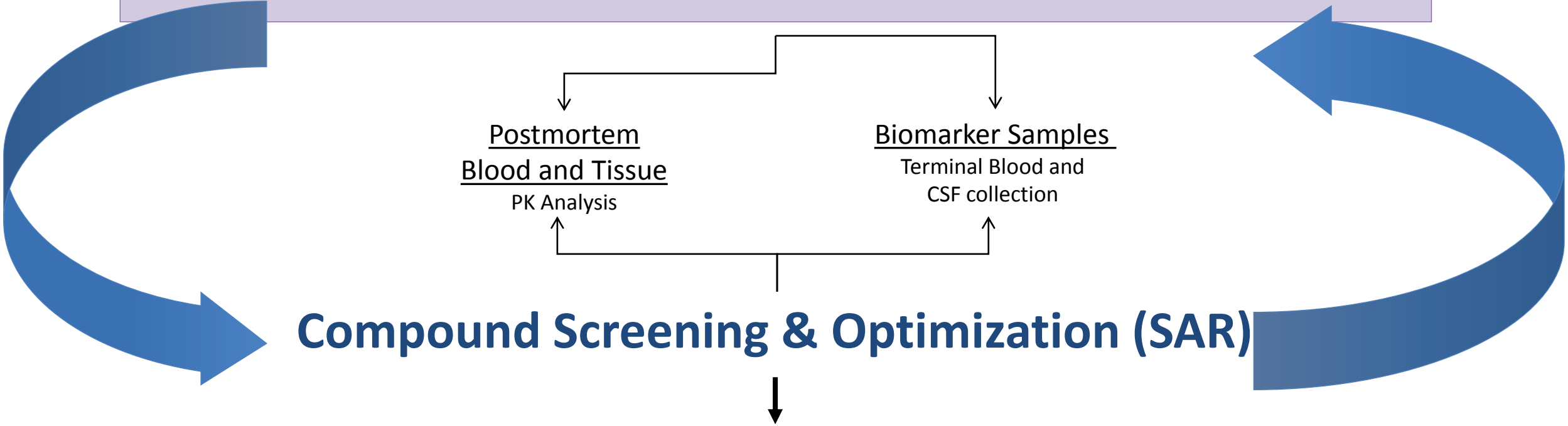
Historical Drug Discovery

Primary Screen: **Behavioral Testing in Rodent Models**

- Reversal of a scopolamine/MK801 induced cognitive deficit in normal *young adult males*
- Reversal of a "*cognitive deficit*" in Tg mice (often limited to males only)
- *Under-reported: dose response relationship; misinterpretation of behavioral confounds; ARRIVE guidelines?*



PK/PD Modeling (Mouse <---> human)

Young adult male (WT) C57BL/6J male mice for safety/tolerability/toxicology

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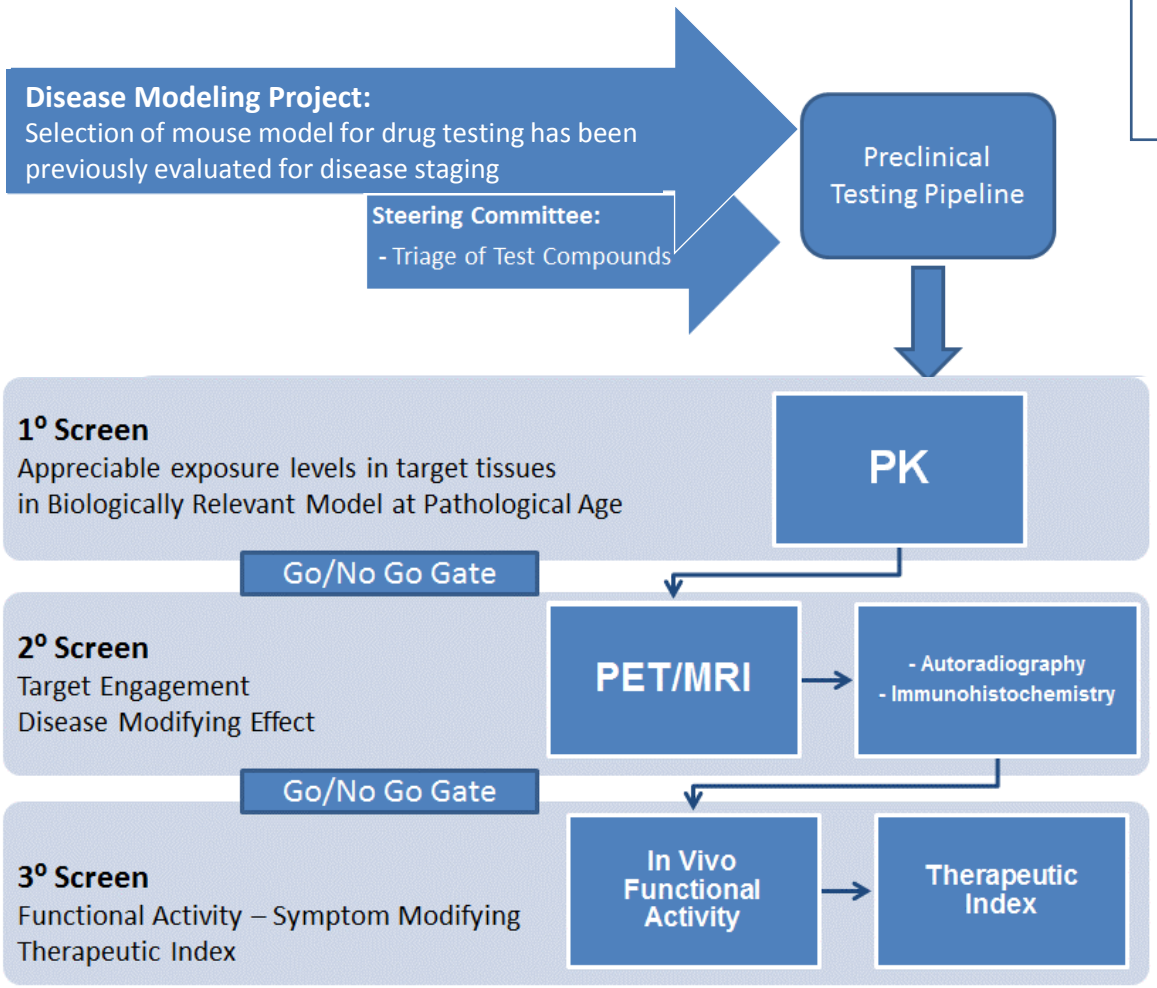
MODEL-AD Preclinical Testing Core (PTC)

- Emphasis on prioritizing pharmacokinetic and translational pharmacodynamics over behavior as a primary screen for preclinical efficacy



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

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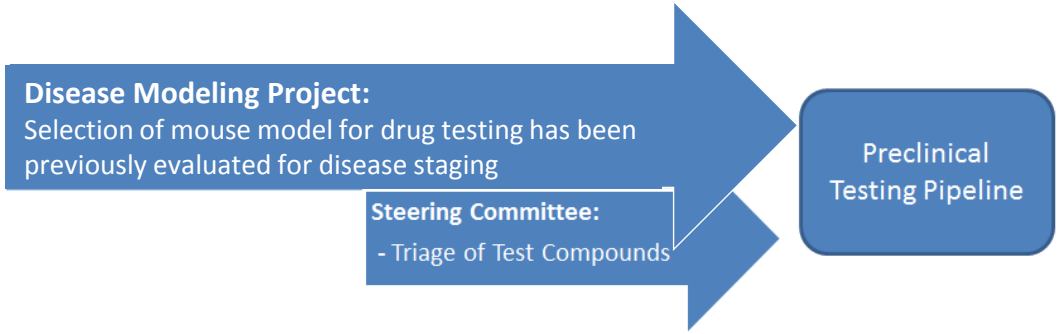

- Mouse models will be best matched to the compound of interest being evaluated in the screening pipeline based on both disease pathology and compound mechanism of action.

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)	AB42	AV45	FDG	AV45 FDG	Abeta
hTau	Tau	Tau Inhibitor	pTau	AV1451	PTSM	AV1451 PTSM	Tau

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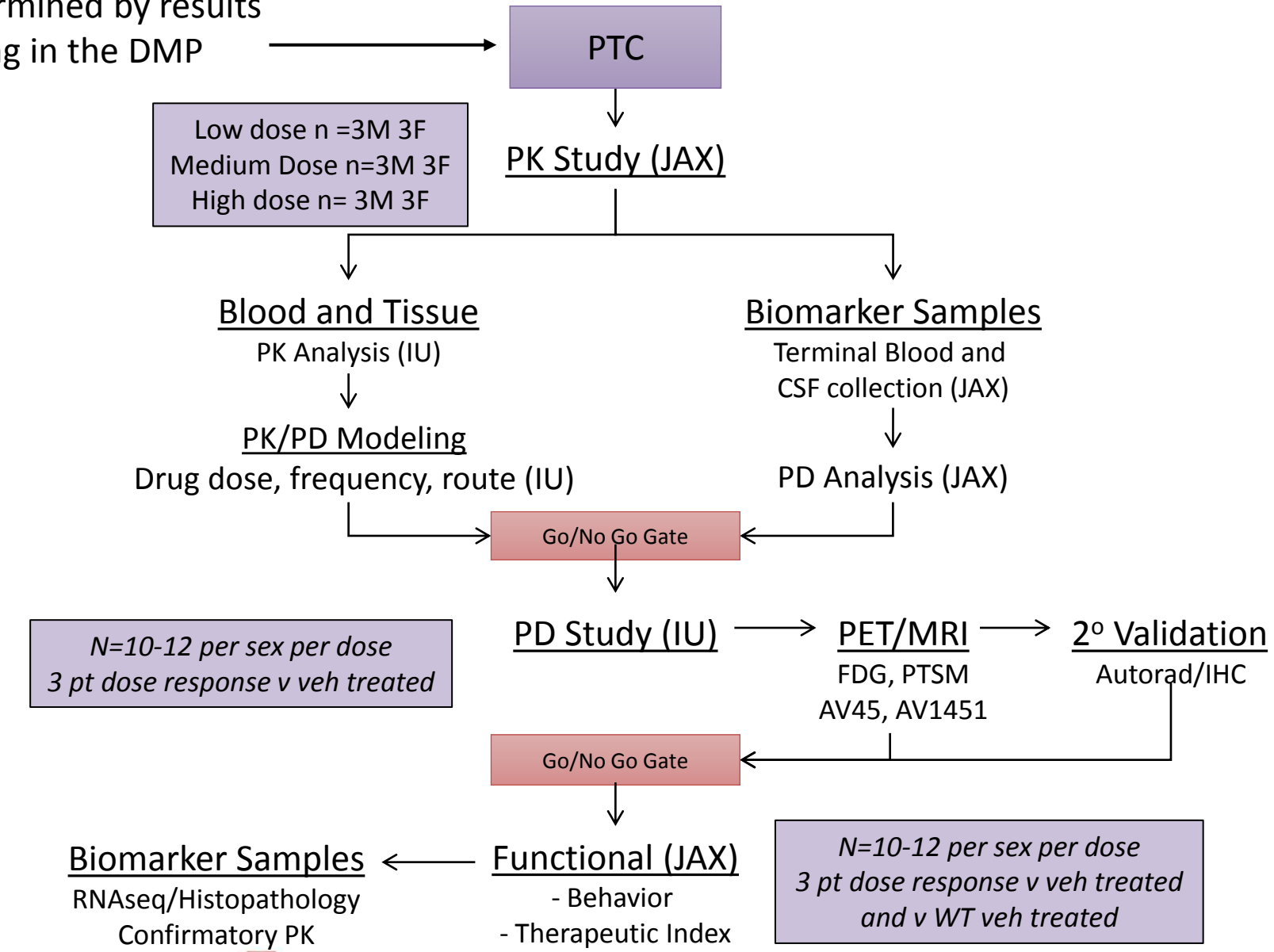
Age of dosing determined by results from disease staging in the DMP



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PTC: Therapeutic Strategy

- **Our goal is to develop a testing strategy that maximizes the therapeutic potential of all drug candidates by initiating the dosing strategy prior to the onset of disease relevant biomarker readouts.**
  - To do this, our strategy in the 5XFAD mouse is to initiate dosing at 3mo with a duration of 3mo, thus maximizing the neuroprotective effects of the candidate.

Evaluation of Verubecestat in 5xFAD

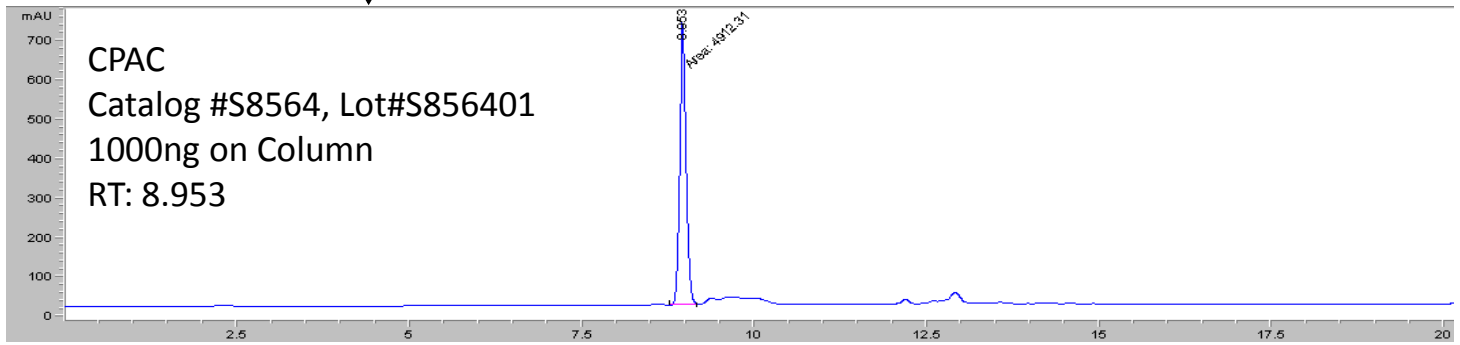
3 mg/kg PO n =3M 3F
10 mg/kg PO n=3M 3F
30 mg/kg PO n= 3M 3F

PK Study (JAX)

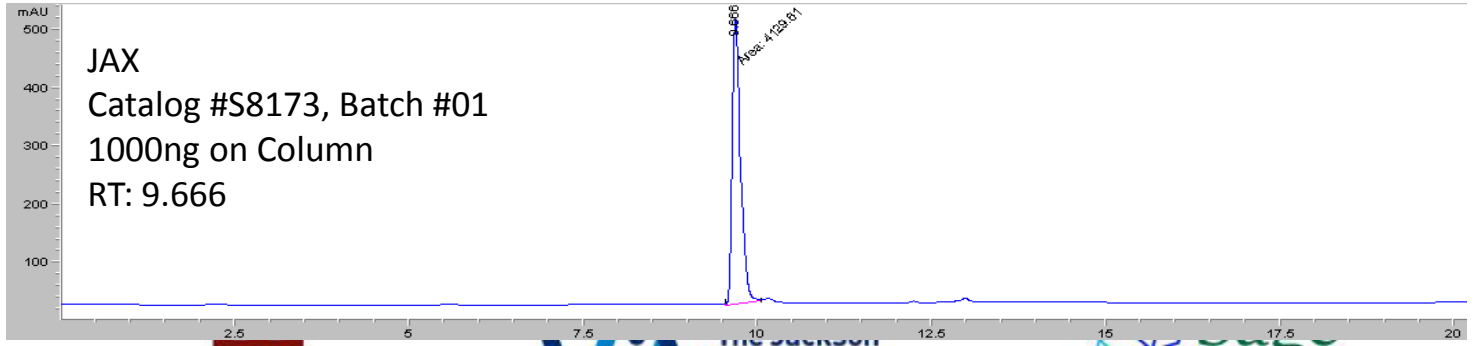
Serial Blood Samples:
0.25,0.5, 1, 2, 4, 8,
24hr(T)

Blood and Tissue
PK Analysis (IU)

Biomarker Samples
Terminal Blood and
CSF collection (JAX)



CPAC
Catalog #S8564, Lot#S856401
1000ng on Column
RT: 8.953



JAX
Catalog #S8173, Batch #01
1000ng on Column
RT: 9.666

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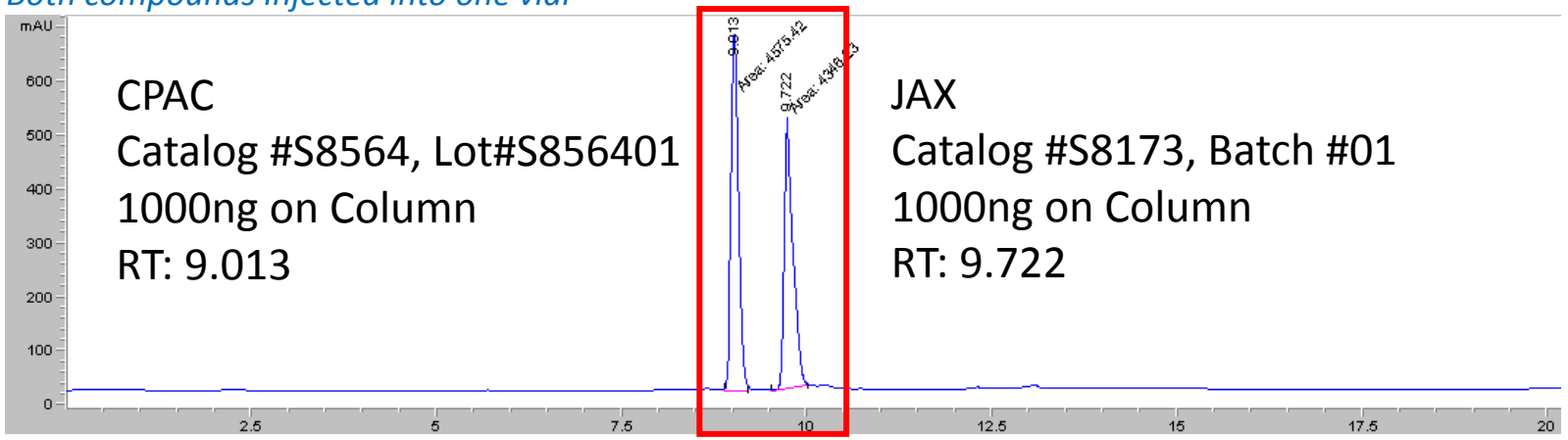
QC process for confirming test compounds prior to initiating studies is a critical component of the PTC

Both compounds injected into one vial



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

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

- PTC Bioanalytical Team (CPAC @ IU)
  - LC/MS/MS analysis of Standards + Test compound
  - Compound is <u>not</u> Verubecestat
  - Vendor replacement of drug lot
  - Verubecestat PK and Imaging studies were swapped with the Levetiracetam studies to conserve time and resources.

These data highlight the importance of validating the test compound prior to full study conduct, and as a result saved the PTC, MODEL-AD, and NIA $$$$$

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Evaluation of Levetiracetam in 5xFAD

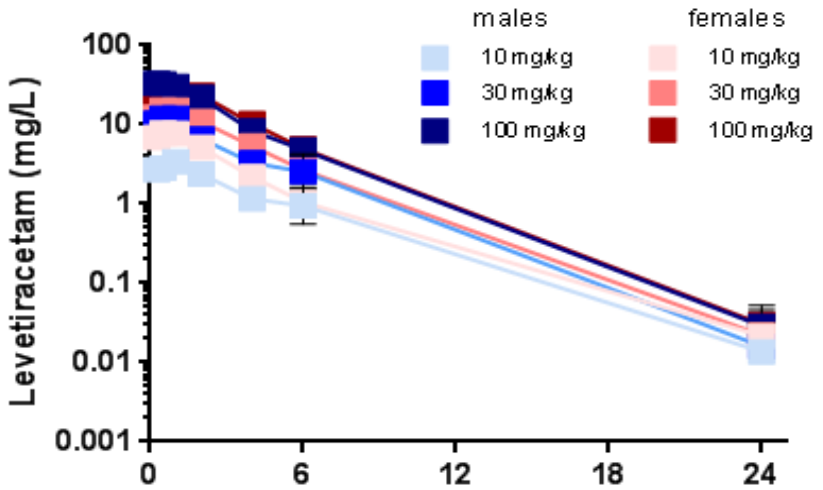
10 mg/kg PO n =3M 3F
30 mg/kg PO n=3M 3F
100 mg/kg PO n= 3M 3F

PK Study (JAX)

Test compound QC and 7+day formulation stability

Serial Blood Samples:
0.25,0.5, 1, 2, 4, 6hr(T)

Blood and Tissue
PK Analysis (IU)



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Evaluation of Levetiracetam in 5xFAD

10 mg/kg PO n =3M 3F
30 mg/kg PO n=3M 3F
100 mg/kg PO n= 3M 3F

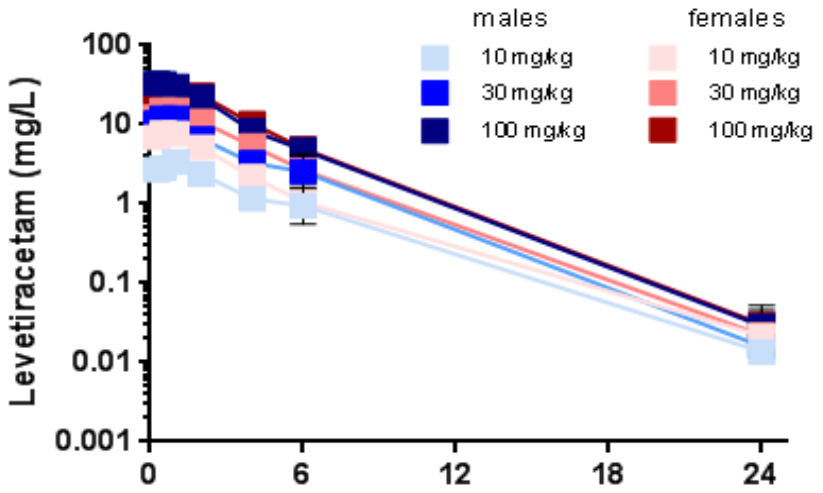
PK Study (JAX)

Test compound QC and 7+day formulation stability

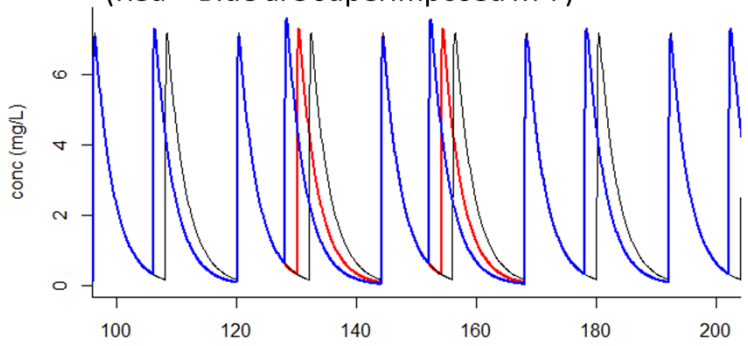
Serial Blood Samples:
0.25,0.5, 1, 2, 4, 6hr(T)

Blood and Tissue
PK Analysis (IU)

PK/PD Modeling
Drug dose, frequency, route (IU)



Black = every 12 hours
Red = 10 + 14 hour intervals
Blue = 10 + 14 M-F; 8 and 16 on weekends
(Red + Blue are superimposed M-F)



BID dosing preferred. Additional simulations carried out to explore variations in daily dose intervals.

Dosing Schedule	Cmax	Cmin
Q12 hours	7.16	0.18
10 hours	7.1	0.1
14 hours	7.3	0.1
8 hours	7.05	0.55
16 hours	7.6	0.05

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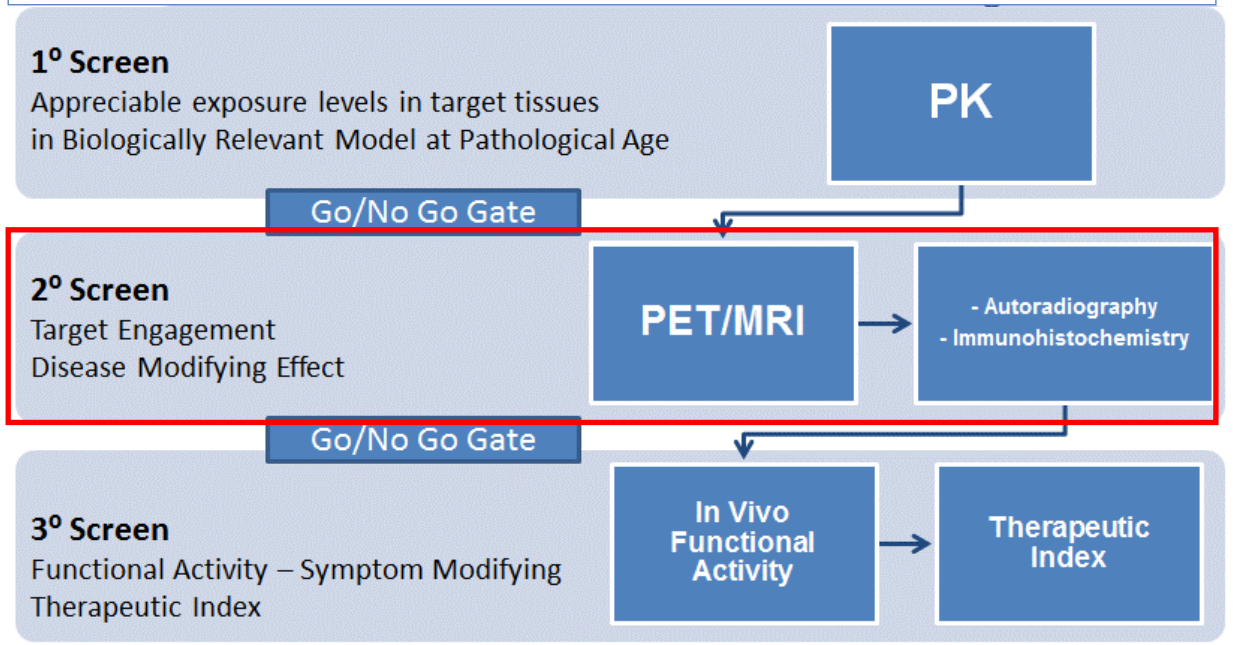
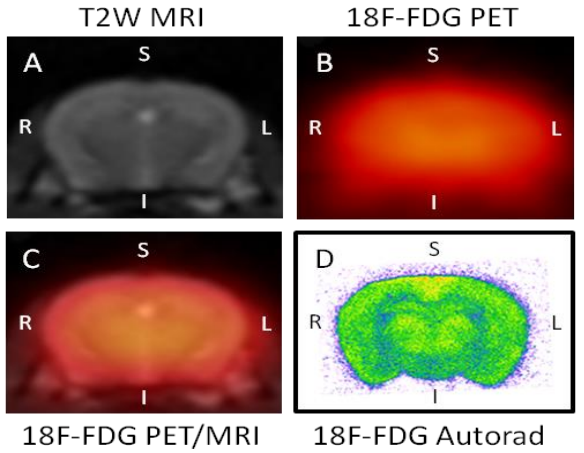
MODEL-AD Preclinical Testing Core (PTC)

Prophylactic Strategy

- Dosing initiating before the onset of disease progression
- 5XFAD male and female mice chronic administration from 3 months of age through 6 months of age
  - Levetiracetam (PO, BID, 0, 10, 30, 56 mg/kg)
  - Verubecestat (TBD – PK in progress)



- PET/MRI/AutoRad as a PD readout of cerebral changes in:
  - -Regional Metabolism (18F-FDG)
  - -Beta Amyloid deposition (18F-AV45)



IndyPET3 scanner and Siemens 3T Prisma scanner co-registered to Paxinos-Franklin atlas

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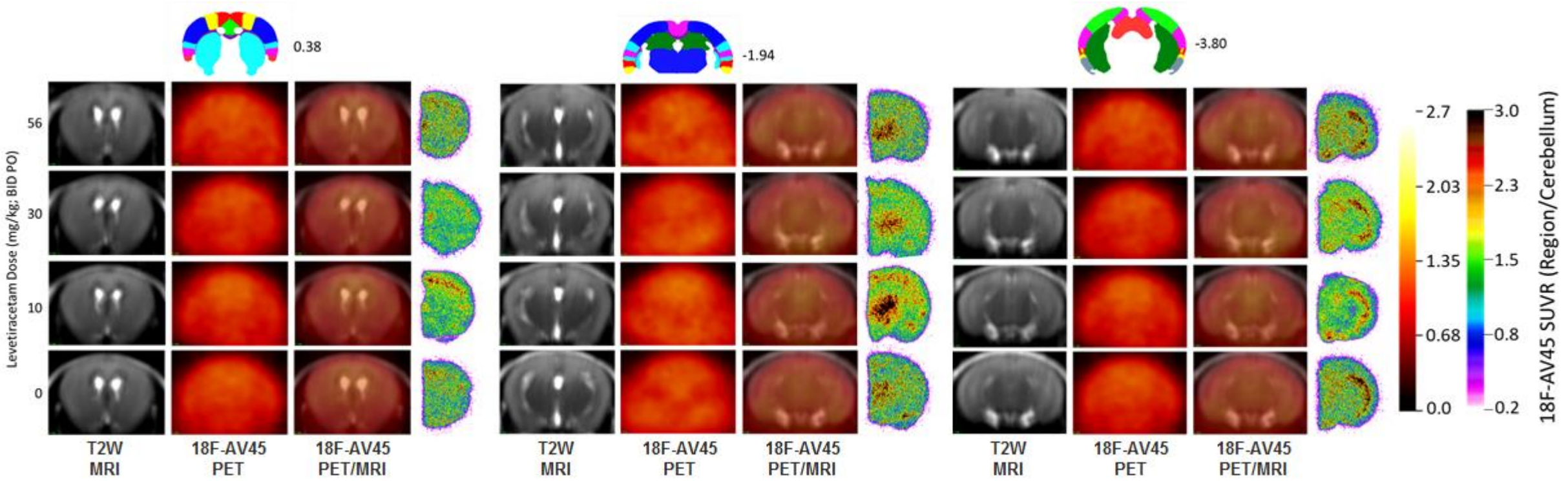
18F-AV45 PET/MRI/Autoradiography: Prophylactic treatment of LEV in 6 mo aged 5xFAD mice

- No alteration of amyloid deposition as measured at 6 mo of age in male and female 5xFAD treated prophylactically with LEV
  - N=73 6mo old 5XFAD mice (n=32 female; n=41 male; N=7-11 per sex per dose level) with 56 brain regions per subject (N=4088 total regions; 1792 females, 2296 males) extracted from co-registered to Paxinos-Franklin atlas
  - Post mortem 18F-AV45 autoradiography in 16 brain regions per subject (N=7008 total; 3936 males, 3072 females) at 3 bregma targets according to Paxinos-Franklin.

FDG-PET and behavioral cohorts prophylactic dosing in progress



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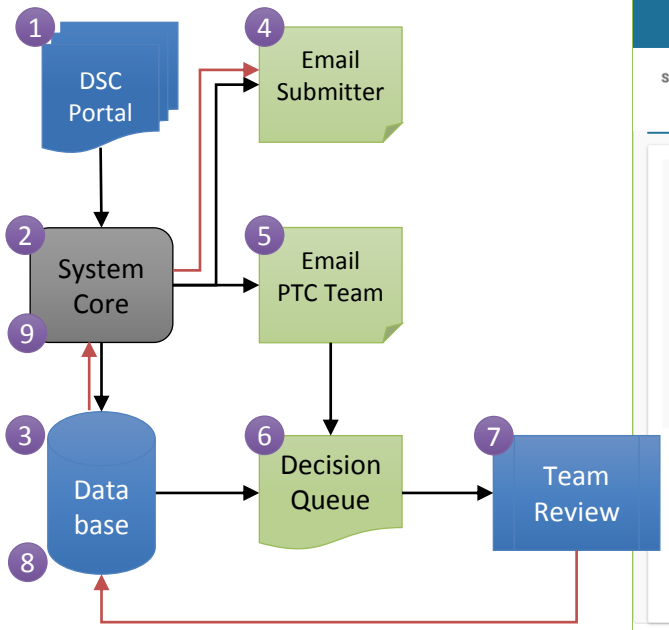
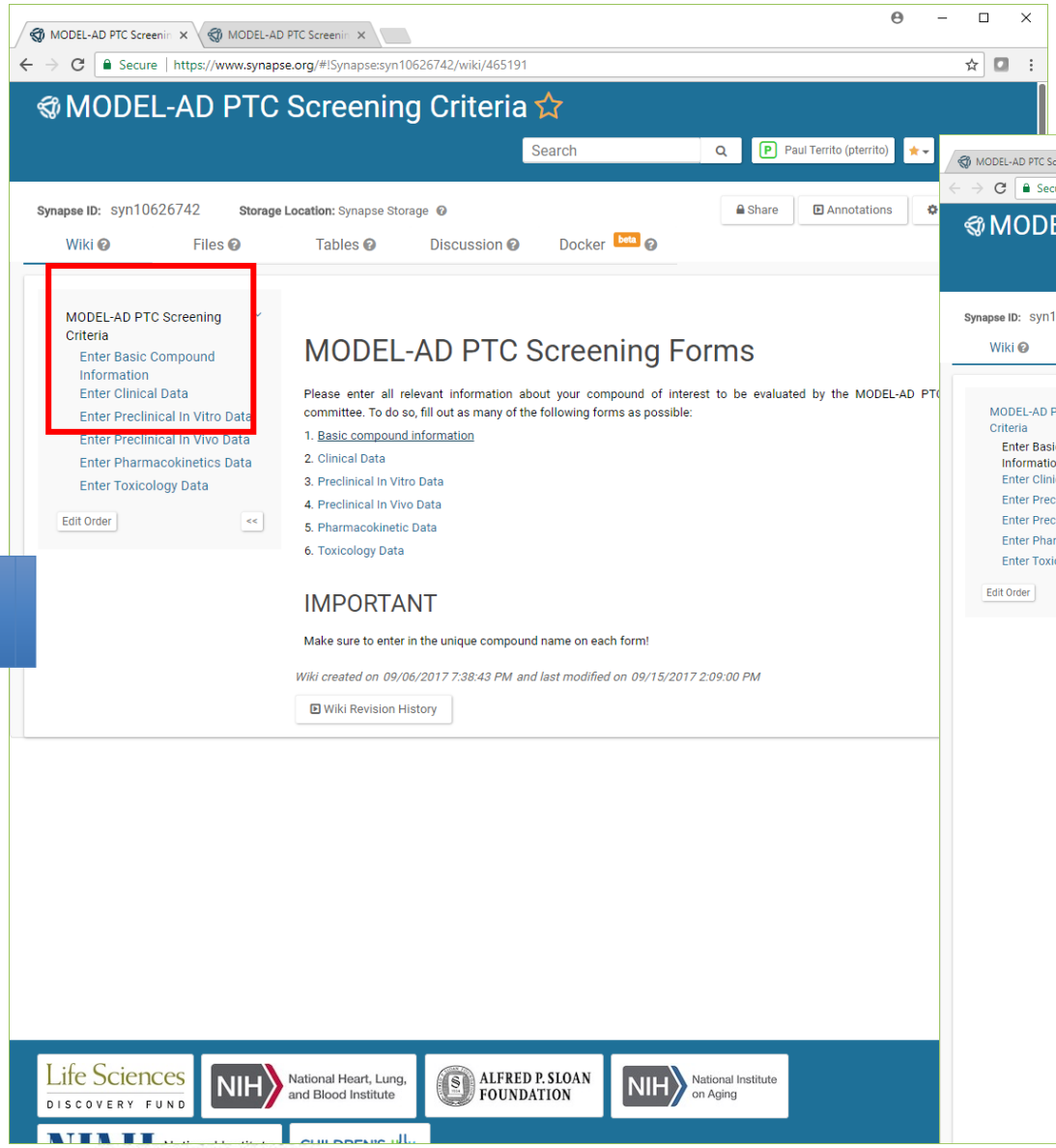
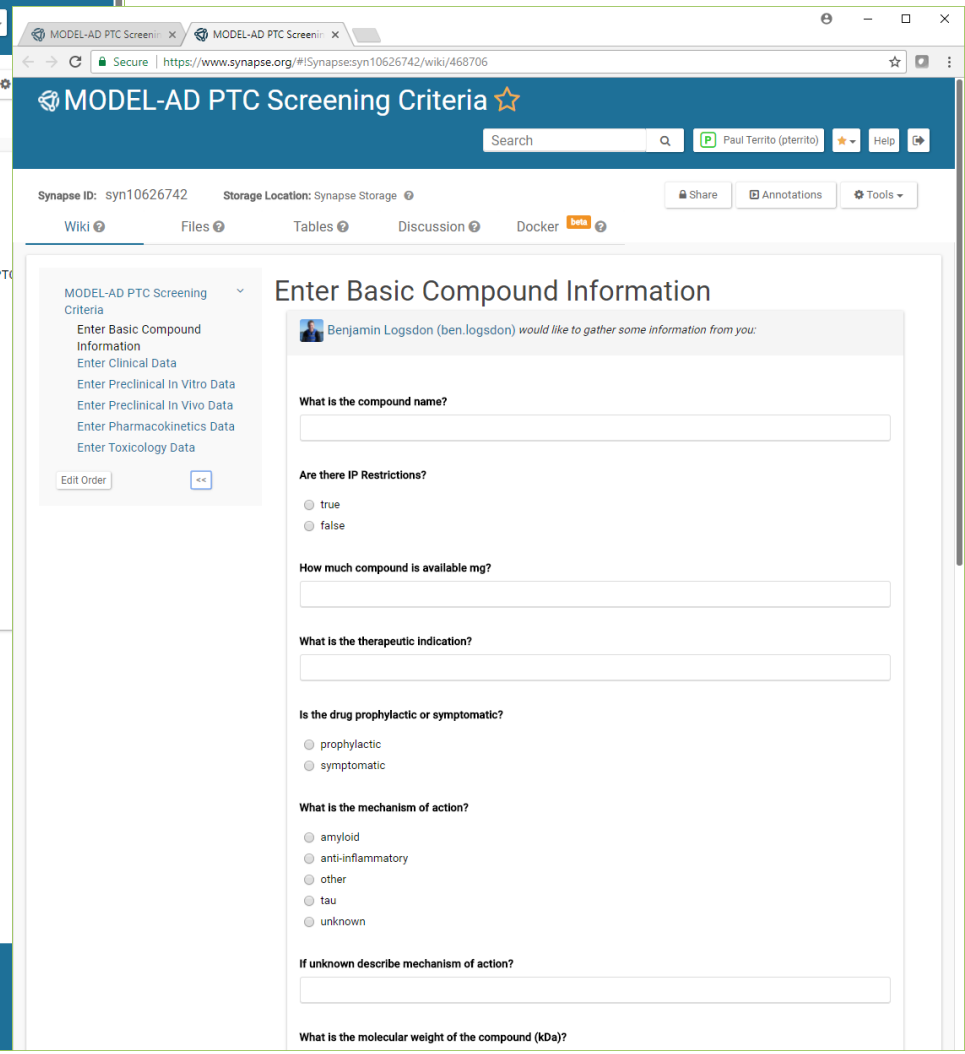
PTC: Candidate Drug Submission Portal – *In Development*

Process Model – PTC DSC







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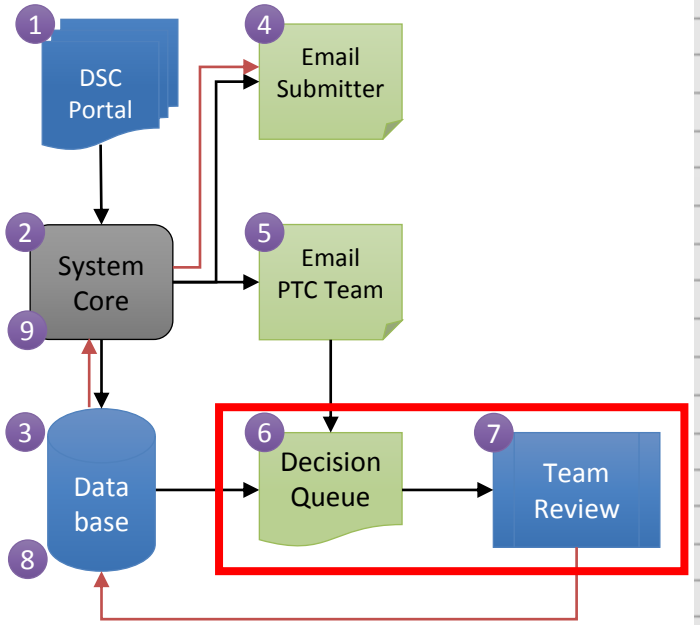
PTC: Drug Selection Criteria – *In Development*

Process Model – PTC DSC



To use this workbook for a drug of interest, perform the following:

1) Enter the drug name/compound information along with source above.
2) For each factor that the drug contains, select a Fuzzy term from the list for the gamma value
3) Once completed for all factors review weight below (see M119)
4) Interpretation:
   a) W < 0.45, drug failed to meet minimum threshold
   a) 0.45 > W < 0.69, drug may need more information to proceed
   c) W > 0.7, drug meets minimum threshold

Drug Name:

* Alpha values can only be 0 or 1 as integers (automatically set when selecting Gamma weights)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
13	Assay									Alpha	Beta	Gamma	Total	Notes
14	(#)									(0,1)*	[0,1,0]**	(Quality)		
15	1	Must not have IP restrictions which would prevent dissemination of data								0	1	None	0	
16	2	Must have a defined TID								0	1	None	0	
17	3	Must have a well characterized MOA								0	1	Poor	0	
18	4.a	Clinical (Phase 1-4 or OLU) compounds (1.0)										Fair		
19	4.a.i	Within species (i.e. mouse data within a mouse model)										Good		
20		(nested values carry 0.67 of total weight)										Excellent		
21	4.a.i.1	Disease model (nested values carry 0.45 of total weight)												
22		ED50 or EC50 (0.33)								0	0.33	None	0	
23		Kx (Kd or Ki or Km) (0.22)								0	0.22	None	0	
24		IC50 (0.11)								0	0.11	None	0	
25	4.a.i.2	Control model (nested values carry 0.22 of total weight)												

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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 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

- **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

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