CAMD and FDA 2015 Annual Scientific Workshop

Computational modeling for AD… where has CAMD come and where do we need to go?

Quantitative System Pharmacology

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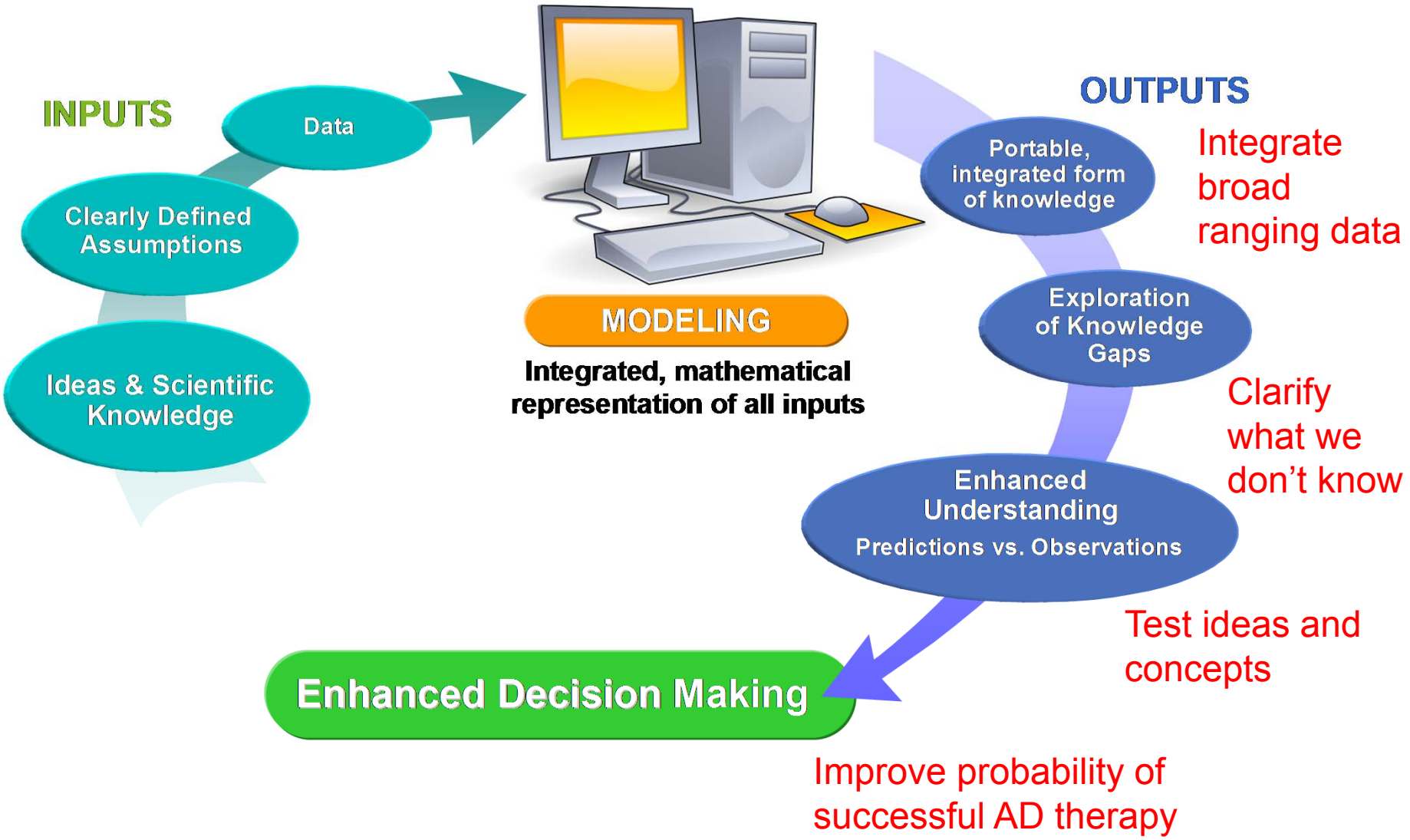
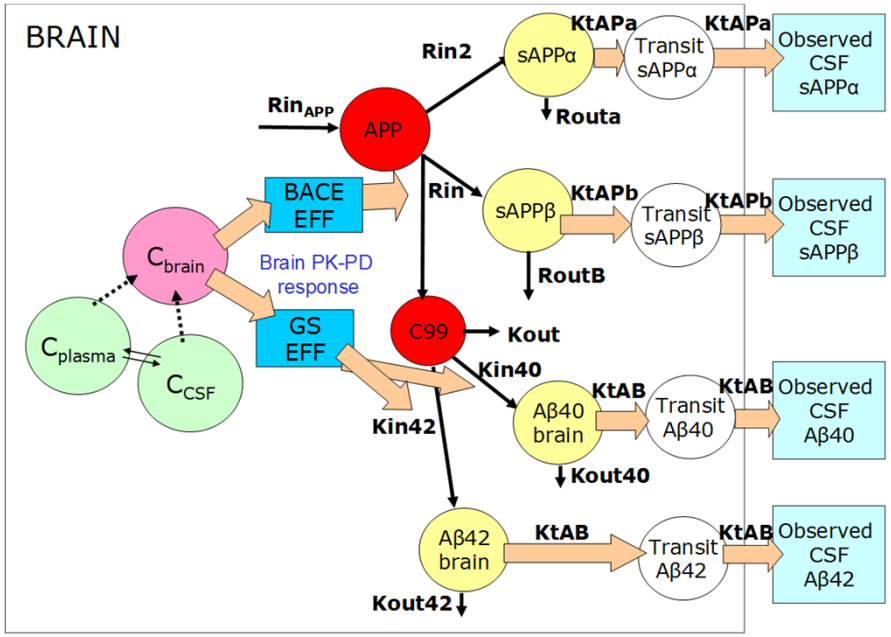
FDA White Oak Campus

Modeling and Simulation as a Tool to Enhance Understanding of Alzheimer's Disease



Enhanced Amyloid Pathway Model Platform Through Collaborative Rhesus Work

Collaboration among Merck (modeling, biomarker, pharmacology), Washington University, University of Leiden, and LAPP



- Integrates data for 4 biomarkers + tracer data from ported rhesus administered inhibitors of GSI/ BACE
- Model = Detailed map of brain amyloid production steps and distribution to CSF

Questions:

Utility of the 4 biomarkers

Relative effectiveness of BACE vs GS inhibition on brain production?

Interplay of Aβ kinetics with oligomers?

Role of alternate pathways in chronic BACE1 or GS inhibition?

Relative rates of turnover of brain pools vs rates of transit to CSF?

Platform development ongoing via PhD project at ULeiden

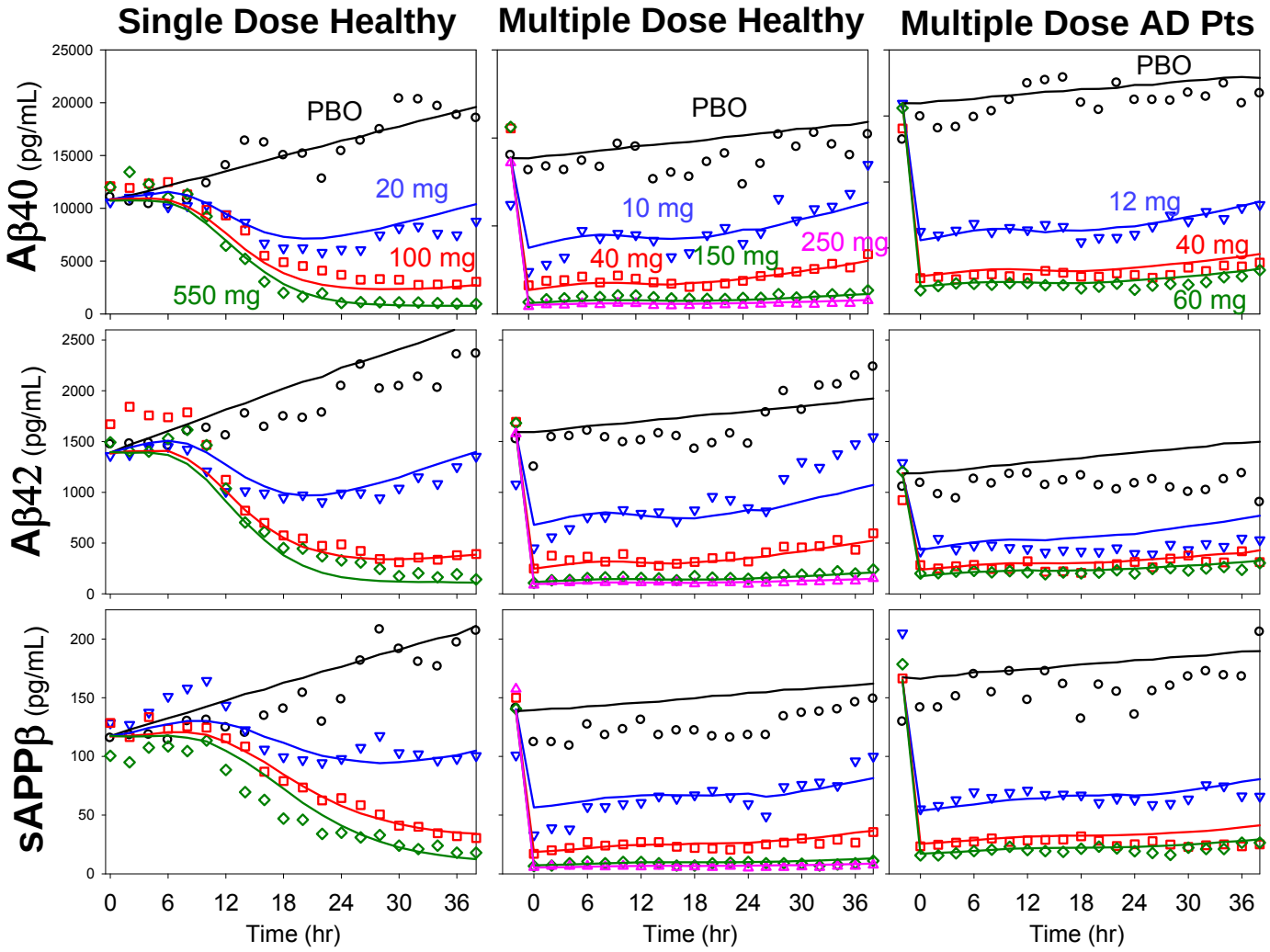
Three CSF biomarker Studies with MK-8931 Drove Phase 2/3 Study Planning and Initiation

Biomarker PK/PD from 3 Phase 1 studies informed Phase 2/3 dose:

- Initial Ph2/3 dose selection based on healthy subject data
- Later confirmed Ph2/3 doses in AD biomarker study; also provided unique data to understand impact of disease

Design Features	Single Dose Healthy Young	Multiple Dose Healthy Young	Multiple Dose AD Patients
Population (ages)	Healthy (19-45 yr)	Healthy (19-45 yr)	Mild-to-Mod AD (52-84 yr)
MK-8931 doses (n)	Placebo (6) 20 mg (6) 100 mg (6) 550 mg (6)	Placebo daily (10) 10 mg daily (5) 40 mg daily (5) 150 mg daily (8) 250 mg daily (8)	Placebo daily (6) 12 mg daily (8) 40 mg daily (8) 60 mg daily (8)
Lumbar catheterization for CSF sampling	Day 1	Day -1 baseline LP Day 14	Day -1 baseline LP Day 7

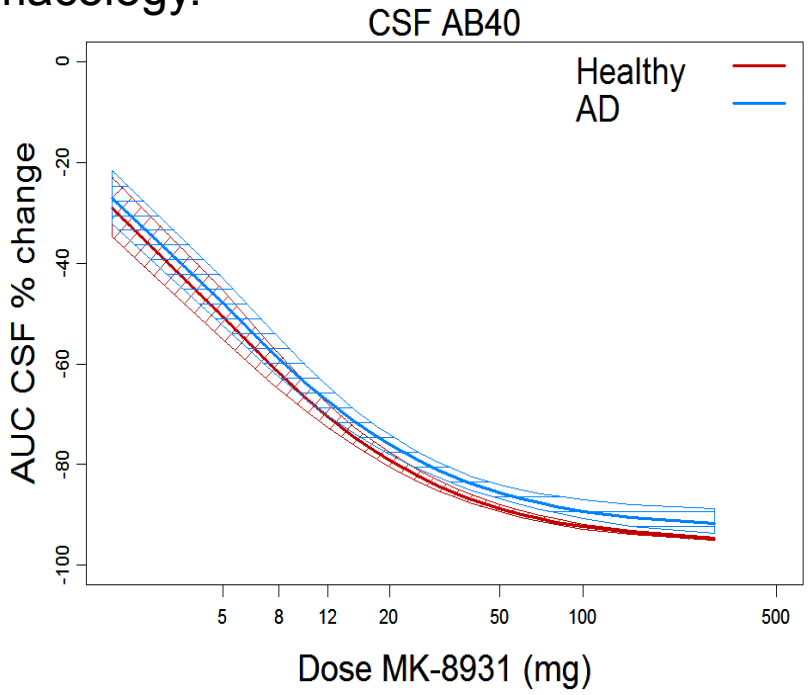
Model-based Integration of Data from all 3 Studies
- median observed (symbols) vs model (lines) values

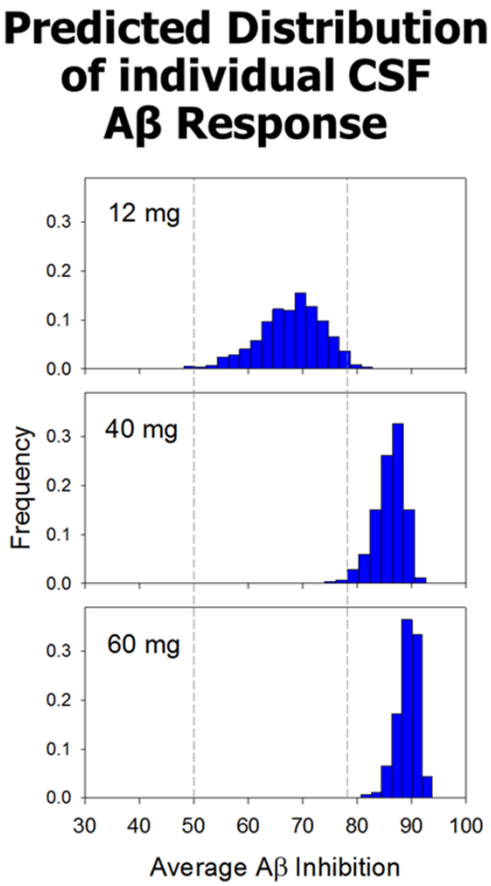


- Simultaneously fit Aβ40, Aβ42 and sAPPβ individual time course data
- Single drug action (i.e., inhibition of BACE) describes all data

MK-8931 Model Predicted Steady-State Response with Daily Dosing

- Simulation of individual patient Aβ reduction distributions indicates:
  - At 12 mg MK-8931 QD >95% in 60-75% range
  - At 40 mg MK-8931 QD >95% in 80-90% range
- Ongoing trials of MK-8931 provide a unique opportunity to test the amyloid hypothesis and enhance the understanding of the underlying systems pharmacology.



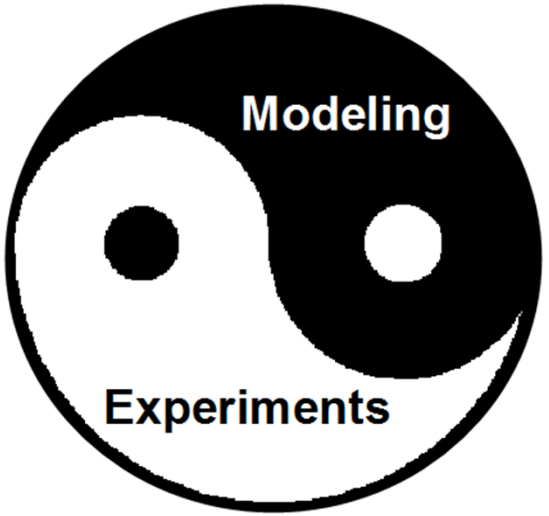


Start with Identification of Key Questions which Systems Pharmacology may be able to inform

- A wide variety of drug development questions are amenable to being informed by Systems Pharmacology approaches. Examples include:
  - **Go/no go decisions** – Does the compound have sufficient promise to advance to next stage?
  - **Dose selection** – What doses, regimens, schedules will maximize efficacy and minimize adverse events? Be informative to study in next trial?
  - **Development molecule choice** – Which candidate has best probability-of-success? Will it differentiate from existing therapies?
  - **Discovery target choices** – Which pathway target has most promise to yield a novel therapy in an indication? What level of modulation is needed for a clinically meaningful effect?
  - **Polytherapy** - What are the optimal combinations of compounds? How might a novel mechanism molecule be used with existing therapies?
  - **Regulatory Interactions** – Questions from regulators during development or review
- M&S modelers and leaders and discovery/development teams need to synthesize wide ranging input to focus in on key question
  - Requires wide engagement

Qualification of Systems Pharmacology Models

- The usual: robustness and precision of parameter estimates, diagnostic plots, individual fits and predictive checks



- Critical to further evaluate:
  - consistency of model with physiology
  - sensitivity to poorly informed parameters, terms and assumptions
- Robustness of complex models tied closely with experimental data. Confidence enhanced by:
  - Integration of multiple inputs and measures
  - complex designs with rich timecourse data
  - ability to prospective predict a non-obvious response
  - consistency of model through additional roll-outs of new data

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