Utilization of Tracer Kinetic Data in Endogenous Pathway Modeling: Example from Alzheimer's Disease

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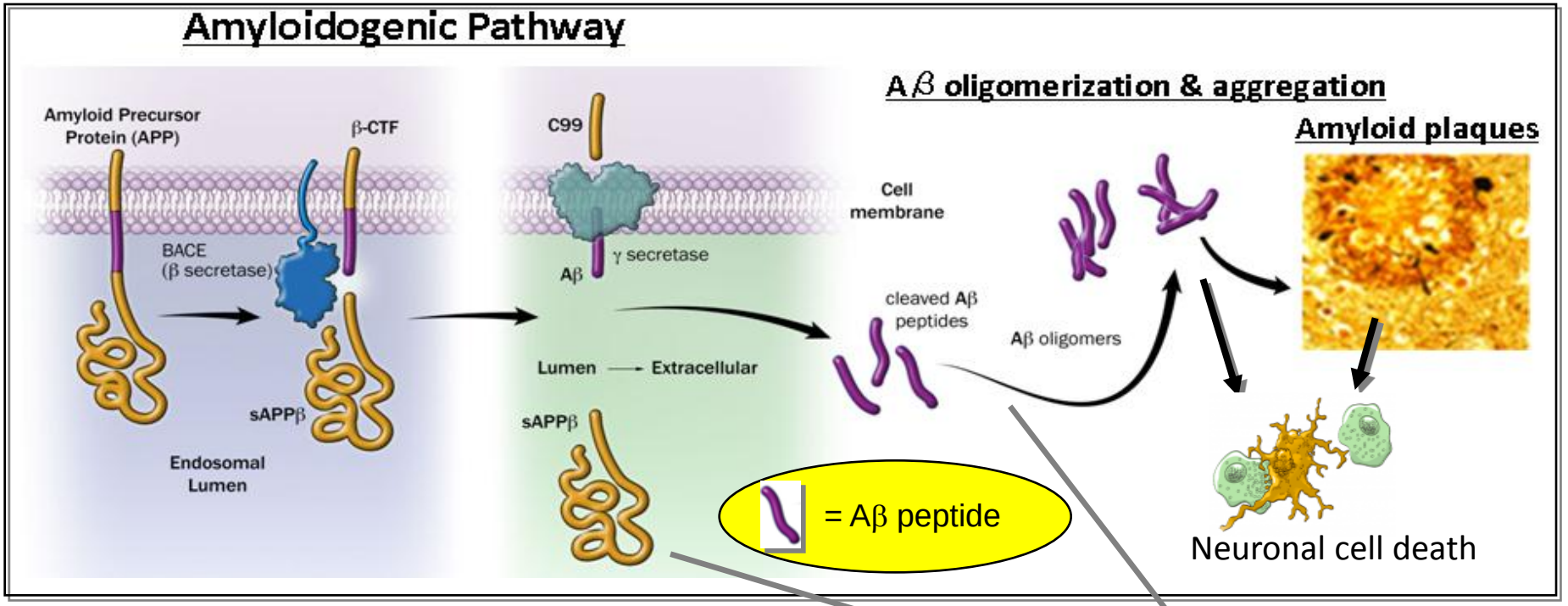
Background – Amyloid Hypothesis and Role of BACE

Amyloid Hypothesis: A**β** peptide levels are increased early in the disease process, forming toxic oligomers and plaques. These accumulate over time, leading to neuronal cell death and cognitive and functional decline over time



Site of measurement in humans studies

Cerebral Spinal Fluid (lumbar region)

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Stabile-Isotope Labeling of Aβ as a Kinetic Biomarker

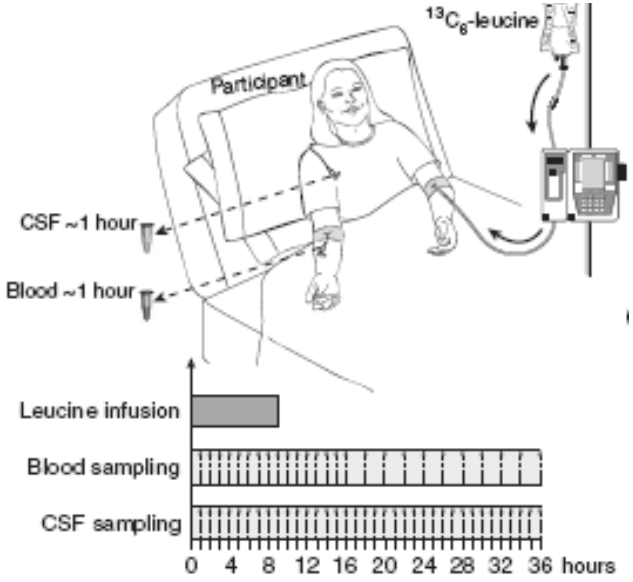
nature medicine

Bateman 2006 publication (+ 2007, 2009, 2010)

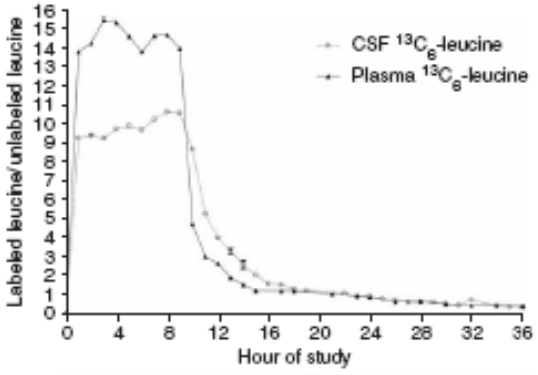
Method proposed to assess brain production and clearance

Human amyloid-β synthesis and clearance rates as measured in cerebrospinal fluid *in vivo*

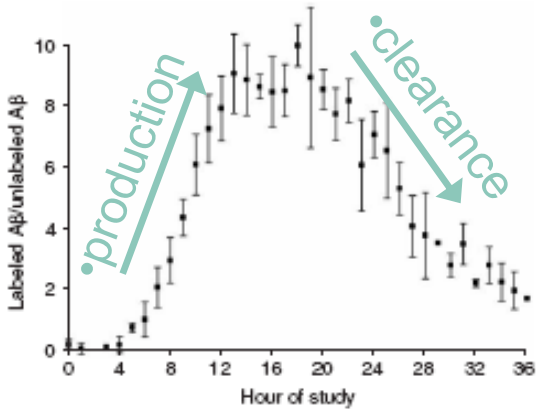
Randall J Bateman[1–3], Ling Y Munsell[4], John C Morris[1,2,5], Robert Swarm[6], Kevin E Yarasheski[4] & David M Holtzman[1–3,7]



Pulse of ^{13}C Labeled Leucine



Ratio of CSF Aβ Labeled



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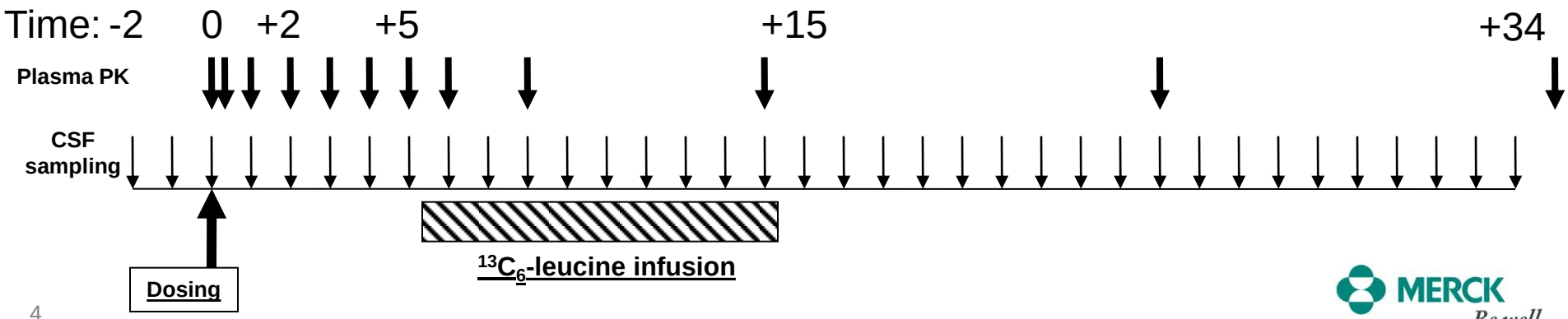
Clinical study design

- 15 healthy volunteer subjects
- Double blind, placebo controlled
- BACE inhibitor
- Single dose
- 3 parallel dosing arms:
  - Placebo
  - Low dose BACE inhibitor
  - High dose BACE inhibitor
- Restricted leucine intake

Sample Tube Preparation for 1 day – 5 subjects



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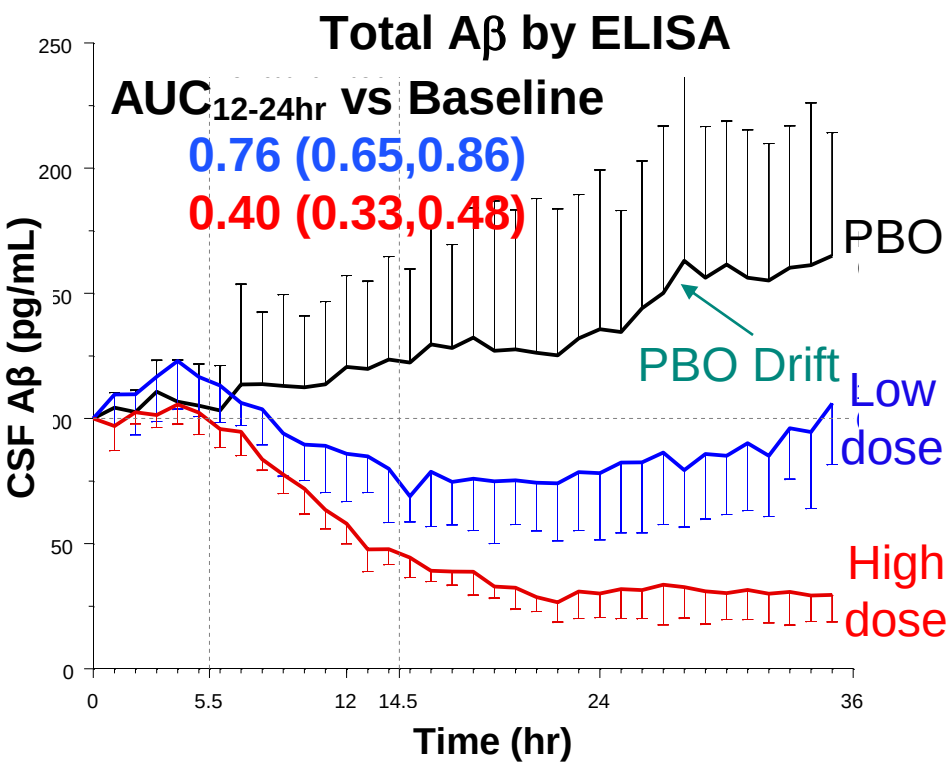
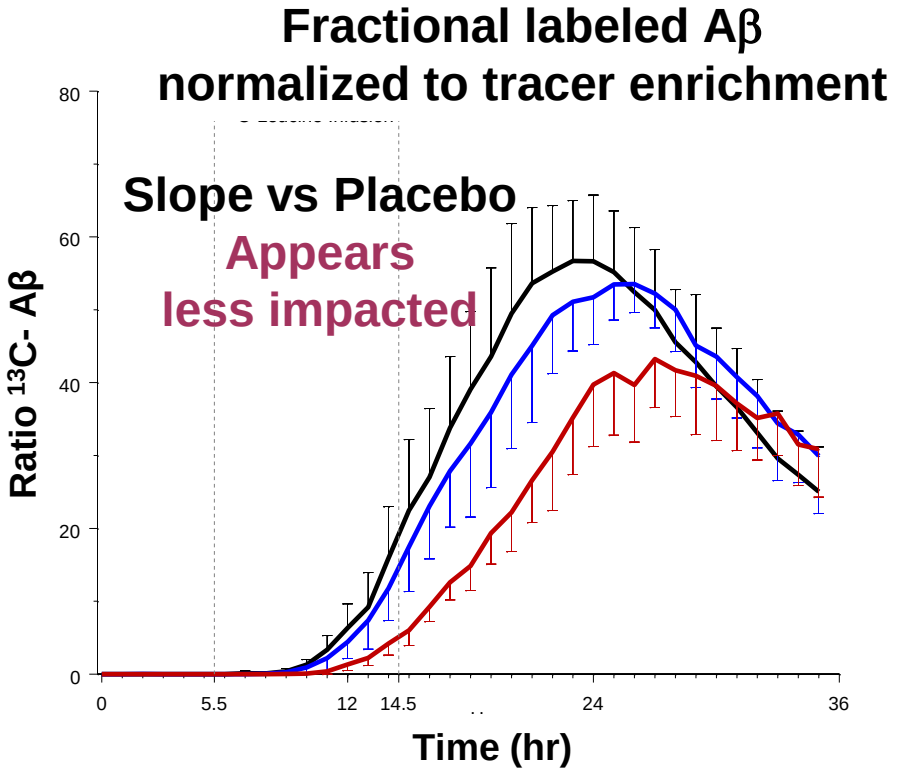
Single doses of BACEi elicit robust declines in CSF $A\beta_{total}$ and clear signal in labeled Aβ





- Larger effect size for Total Aβ
  - Placebo drift and variability → unclear interpretation for drug effect
- Fraction labeled Aβ – appears less impacted by drift and less variability on placebo
  - Does smaller effect mean that BACE drug effect on production is less than anticipated from Total Aβ?

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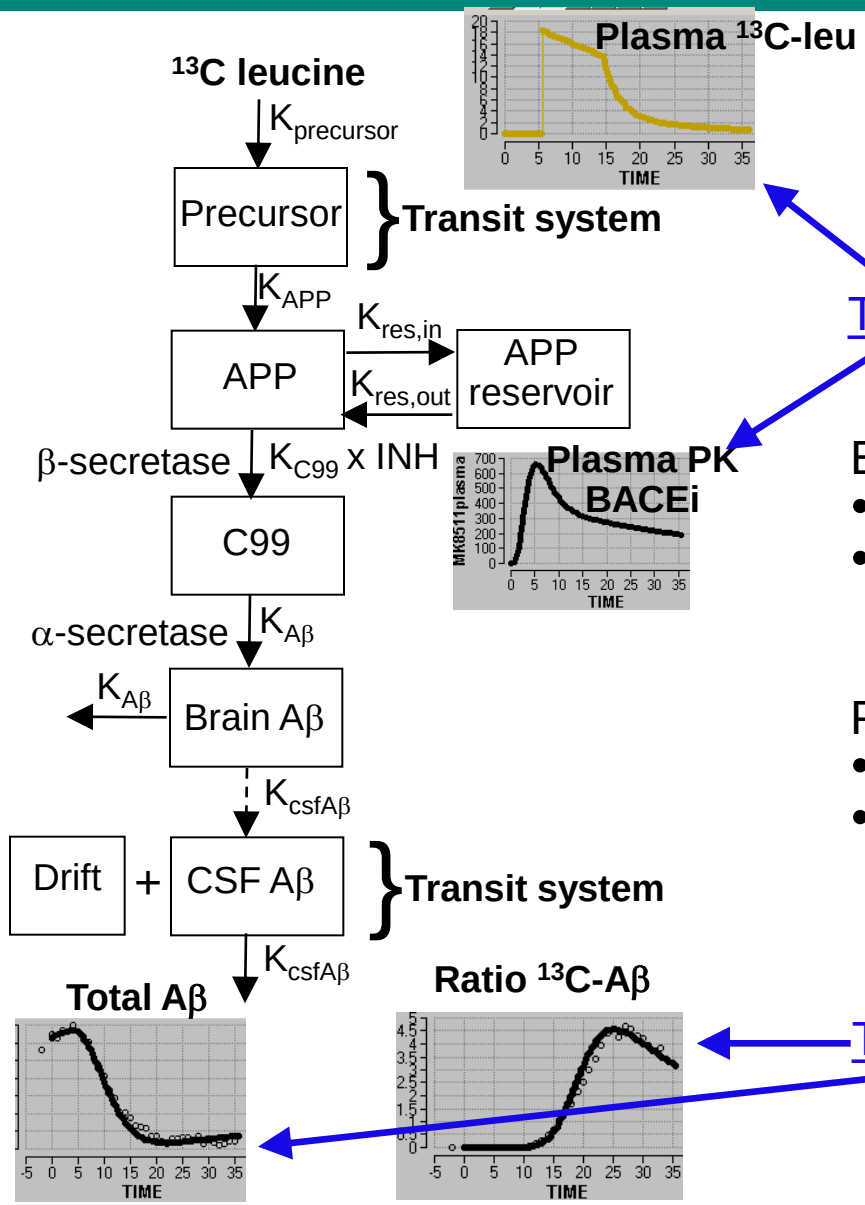
Model-based analysis enhances interpretation



Two independent inputs

Estimated

- Emax, IC50, Hill
- $K_{precursor}$, K_{app}, $K_{res,in}$, $K_{res,out}$, $k_{csfAβ}$

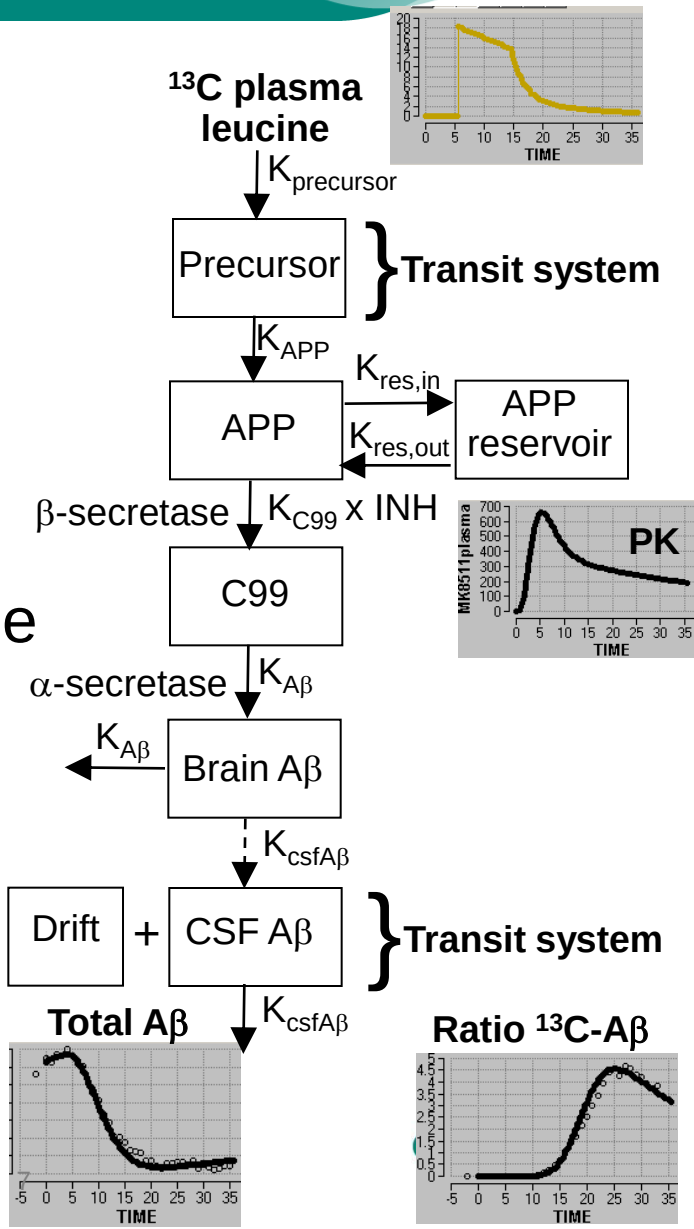
Predefined:

- $K_{APP} = K_{C99} = K_{Aβ}$
- Baseline + drift parameters as posthocs from total CSFAβ analysis (larger pooled analysis)

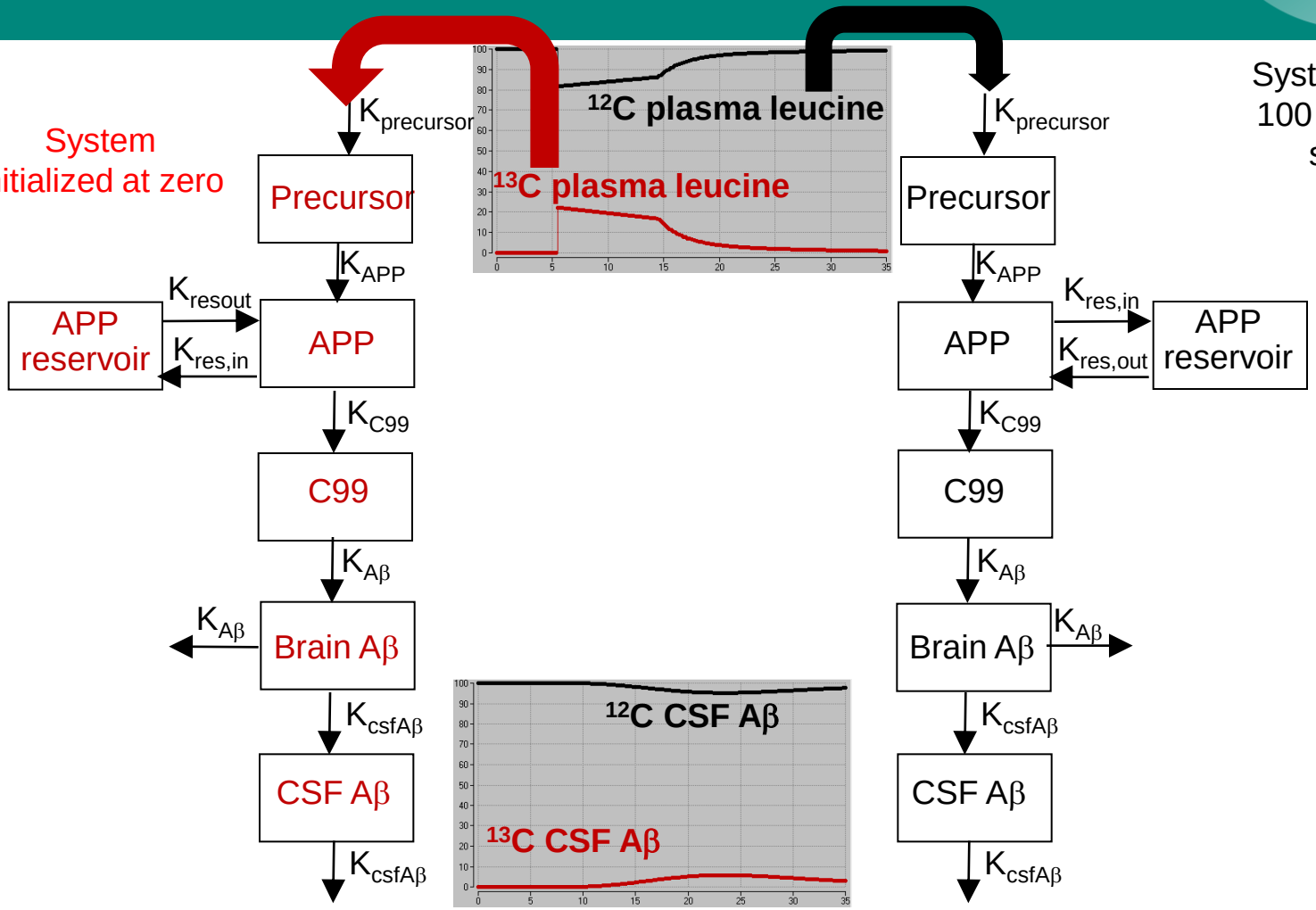
Two independent outputs

Assumptions

- Plasma ^{13}C-leu is better predictor than CSF ^{13}C-leu
- Plasma drug concentration is better predictor than CSF drug concentration (from other analysis on total Aβ)
- APP reservoir drives dilution of ^{13}C and addresses slow wash-out of ^{13}C from the amyloid pathway
  - No need for 'fudge' factor to scale plasma ^{13}C-leu to brain ^{13}C-leu
- No recirculation of ^{13}C-leu
- Placebo drift is local phenomenon, not reflecting brain total Aβ



Labeled and unlabeled parallel pathways



CSF Aβ = ^{13}C CSFAβ + ^{12}C CSFAβ

Ratio CSF Aβ = 100 x ^{13}C CSFAβ/^{12}C CSFAβ

Total CSF Aβ = Baseline Aβ x CSF Aβ/100 + DRIFT

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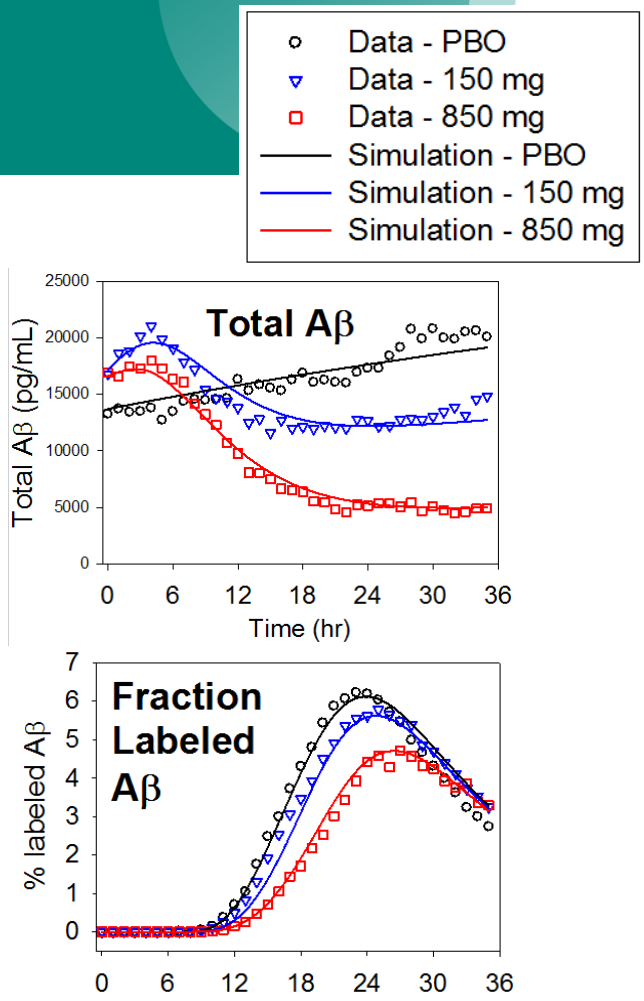
Results - parameter estimates + fits

Parameter	Estimate (90CI)	IIV (CV%)
MTT_{prec} (h)	1.68 (0.87-3.25)	
K_{app} (h)	0.25 (0.23-0.27)	10%
$K_{app,res,in}$ (h^{-1})	0.13 (0.12-0.15)	
$K_{app,res,out}$ (h^{-1})	0.0034 (0.0012-0.0097)	120%
$MTT_{CSF,A\beta}$ (h^{-1})	4.97 (3.96-6.24)	42%
E_{max}	0.97 (0.96-0.98)	
IC_{50} ($ng.mL^{-1}$)	0.41 (0.34-0.48)	
Hill	1.10 (0.87-1.24)	

NONMEM 7.2 FOCE; IIV total Aβ accounted for in baseline + drift



- Model representing major amyloid steps can account for joint data
- Single drug action (inhibition of BACE) can describe all data without disconnect in level of brain production inhibition implied by total Aβ and fraction labeled Aβ results
- Suggests that best interpretation of 13C data requires a kinetic modeling approach

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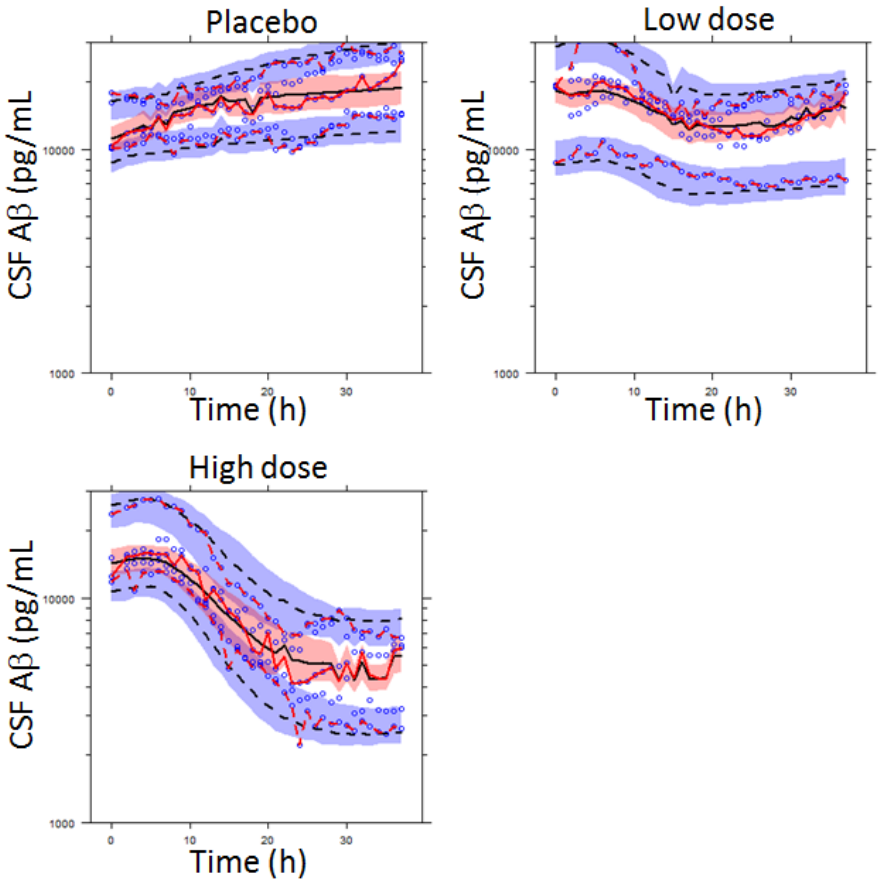
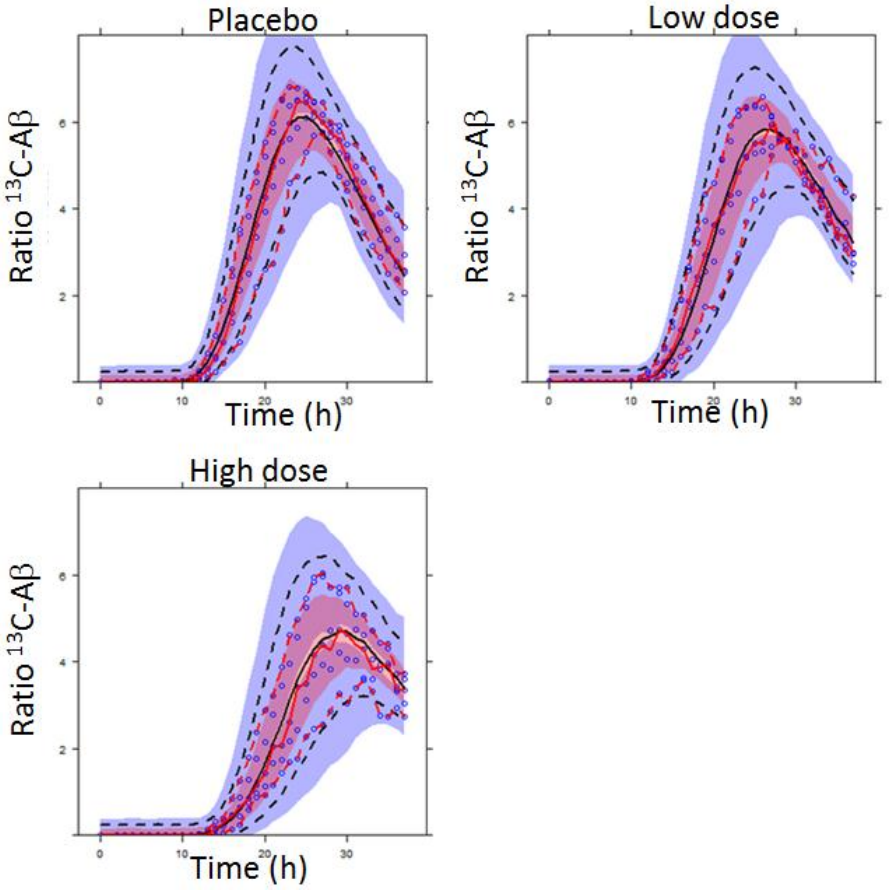
Results - VPCs

Total CSF Aβ



Ratio ^{13}C-Aβ



Solid red line: observed median; dashed red lines observed 10% and 90% quantile
Solid black line: predicted mean; dashed black lines predicted 10% and 90% quantile
Shaded areas: 90% confidence interval for predicted mean and quantile

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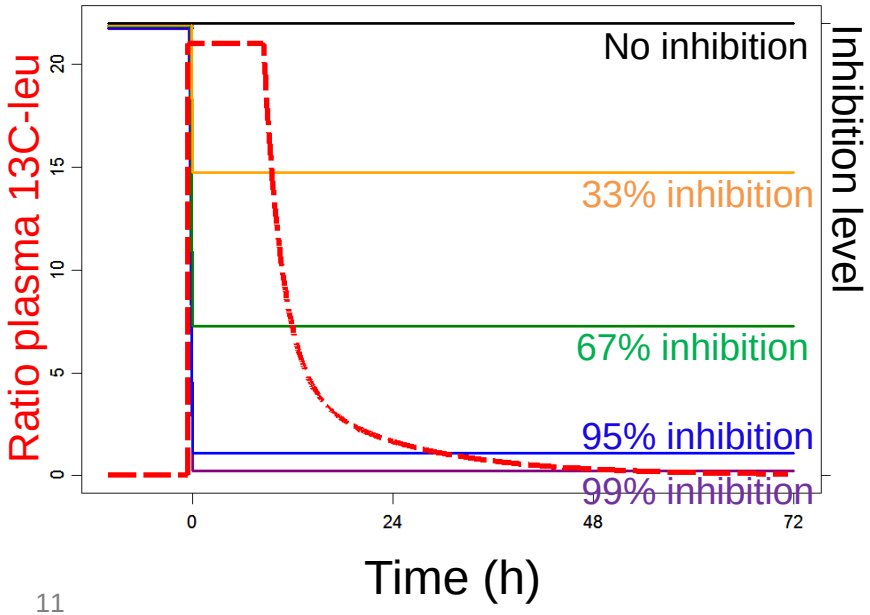
Understanding system behaviour to inform potential next trial design

- Alternative designs to identify BACE inhibitor and ^{13}C-Leu regimens that result in most valuable experiment. Variables to explore:
  - BACE inhibitor regimen (SD or steady state) relative to timing of 13C-leu infusion
  - Level of BACE inhibition

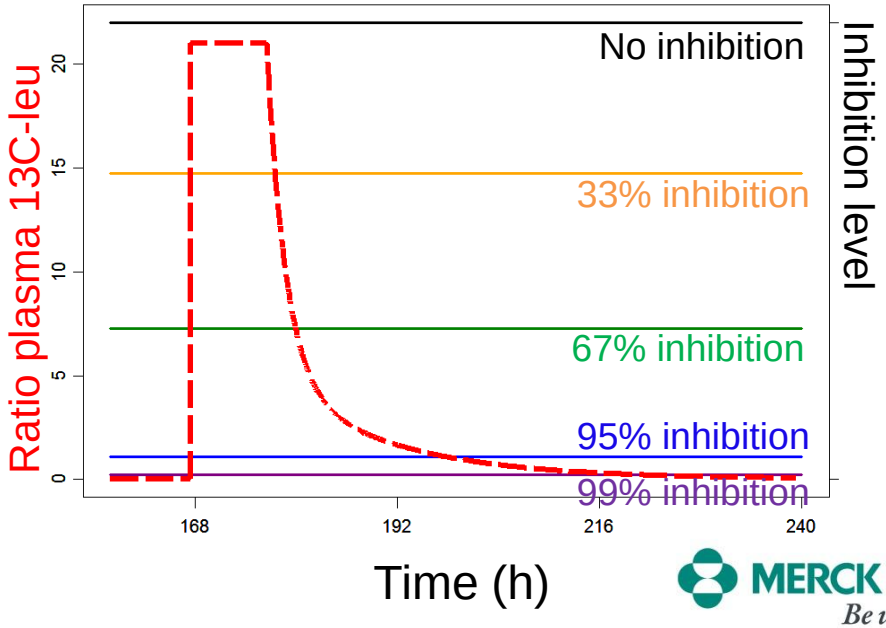
"Single dose"

System after sudden change in inhibition level



"Steady state"

System at stable level of inhibition



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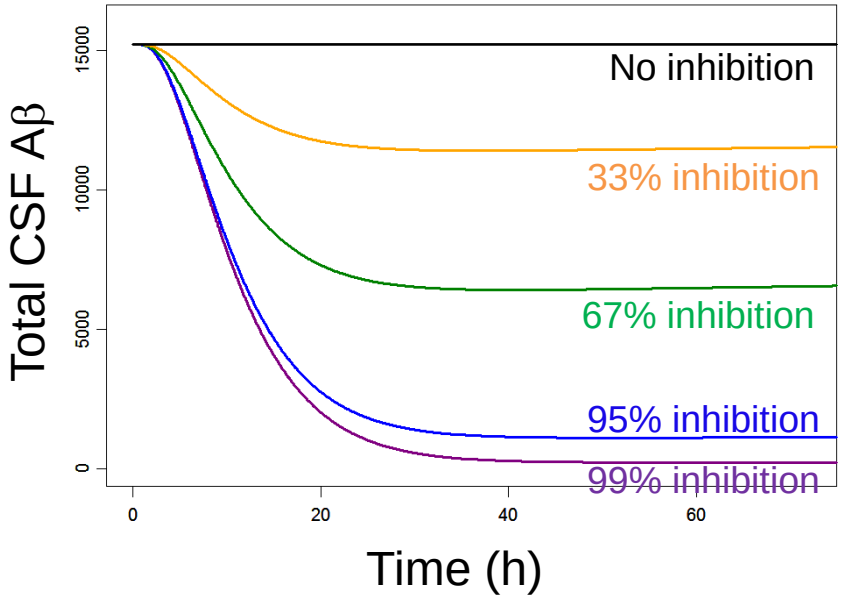
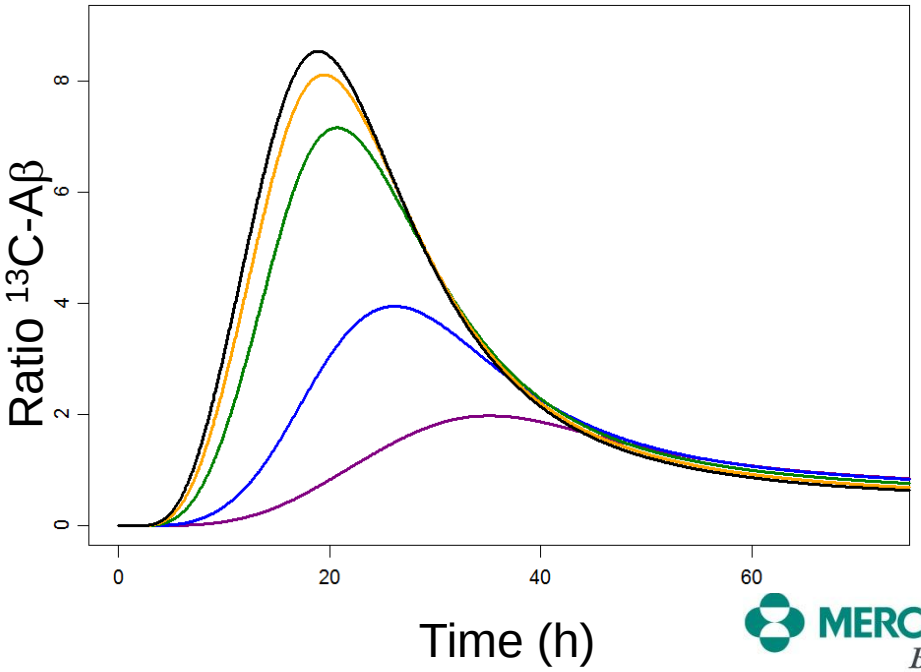
Single Dose Prediction – Dose-dependency in biomarker response if early 13C leucine infusion

- Total Aβ reflect the level of β-secretase inhibition
- Allows for estimation drug potency



- Information on level of inhibition and responsiveness amyloid pathway to adapt to induced level of β-secretase inhibition
- Allows for estimation underlying processes (pools, rate constants)



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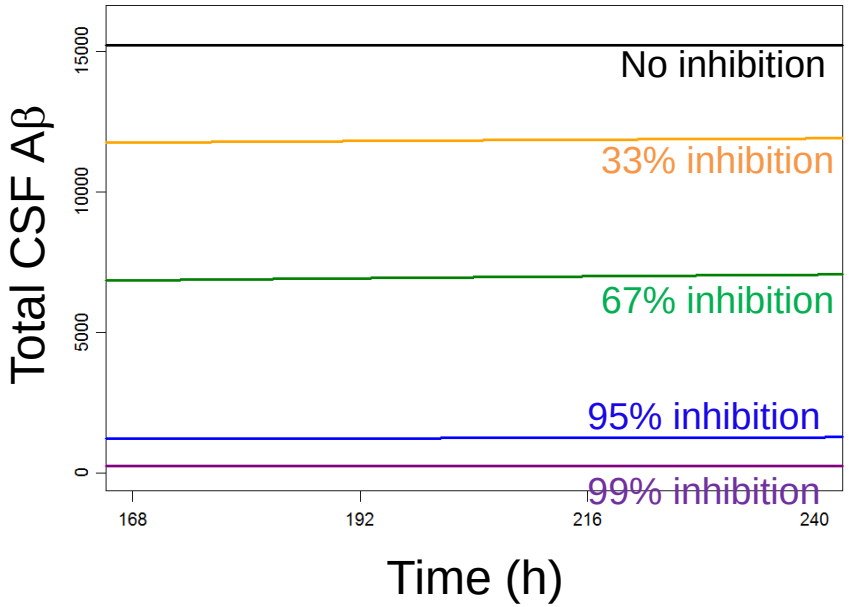
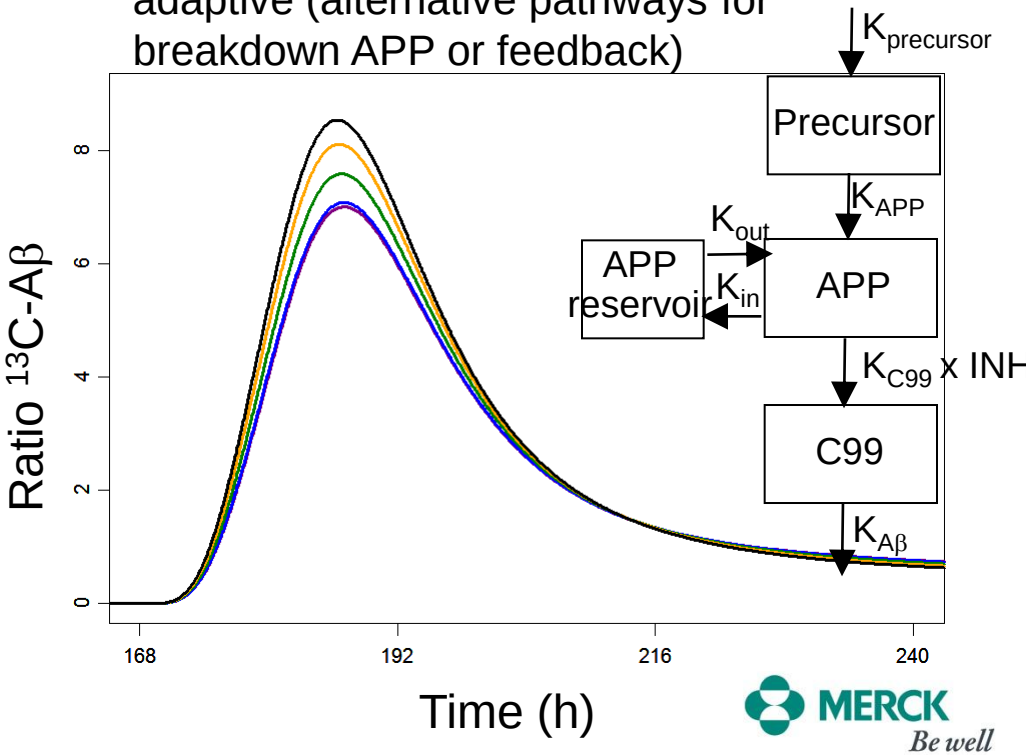
Steady-State Prediction – Little effect on fraction labeled Aβ, profound effect on total Aβ

- Total Aβ reflect the level of β-secretase inhibition
- Allows for estimation drug potency (in case also baseline is assessed)



- ^{13}C- Aβ potentially does not reflect the level of β-secretase inhibition.
- Separation of ^{13}C- Aβ profiles driven by APP pool. BACE inhibition can increase APP pool. Overlapping profiles indicate no change in APP reservoir, the system is adaptive (alternative pathways for breakdown APP or feedback)



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Timing of ^{13}C-leucine infusion relative to dosing of the BACE inhibito is key in obtaining informative data on the underlying system

- Fraction labeled Aβ predicted to be minimally altered if Aβ pool at steady-state
  - Occurs because the altered production rate under inhibition now matches the equilibrated total Aβ level – fractional addition of ^{13}C label into Aβ is then balanced (similar) to unaltered state
  - Separation at steady state, if any, is reflection of increased APP reservoir due to inhibition of APP elimination. No separation indicative for alternative APP elimination pathways or feedback mechanism
- Timing of the infusion is very influential in the magnitude of the ^{13}C signal in fraction labeled Aβ
  - Largest signal obtained when ^{13}C leucine infusion coincides with maximal dis-equilibrium at the very start of production inhibition. Effect size diminishes with later infusion start as the system is closer to equilibrated state with respect to production inhibition
- Modeling shows that a trial design that results in largest separation in fraction labeled Aβ profiles contains most information on underlying processes (pools, rate constants).

Conclusions

- Tracer kinetic approaches together with mechanistic modeling enhance the understanding of endogenous pathway dynamics.
- A model-based analysis enables distinguishing between steps in the amyloid pathway and distributional processes.
- This framework enables a more physiologically based approach to account for effects of Aβ oligomers and/or plaque pool in Alzheimer's disease.
- Finally, model-based simulations inform on improvements of the experimental design that will maximize derived knowledge on the underlying system pharmacology of the amyloid pathway.