

# Cross-Species Scaling of CNS Aβ40 Response to a Gamma Secretase Inhibitor Through Semi-Mechanistic PK/PD Modeling and Application to Early Decision Making

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## Background and Objectives

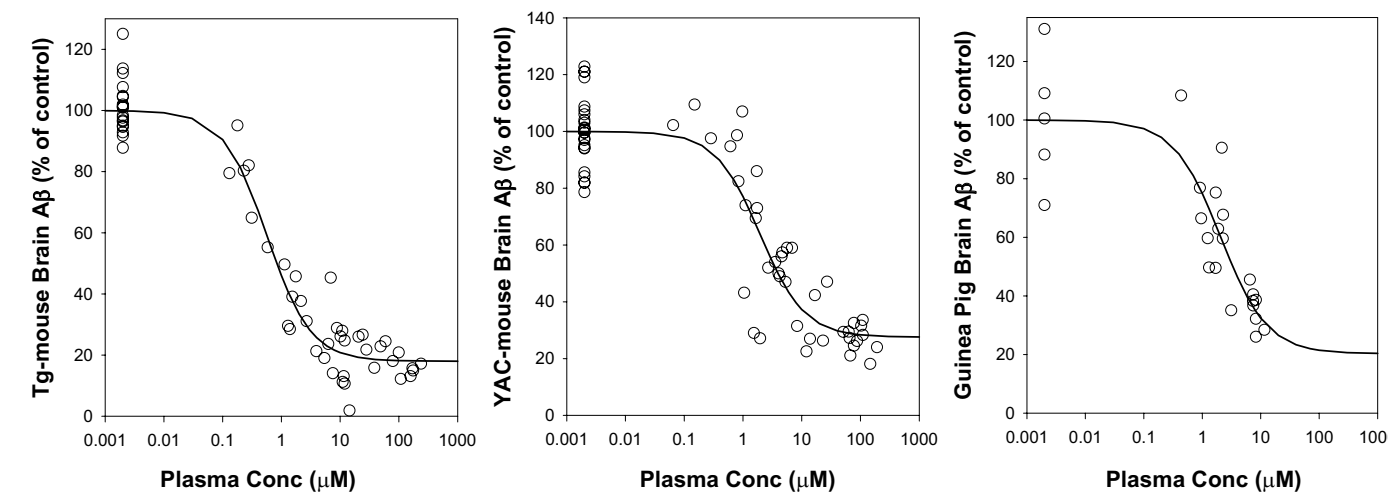
- The amyloid hypothesis contends that build-up of Aβ and its associated plaques in brain tissue leads to development of Alzheimer's disease.
- The γ-secretase inhibitor, MK-0752, can acutely and significantly lower CSF Aβ40 concentrations in humans [1].
- The objectives of this work were to develop PK/PD models of CNS Aβ40 response to MK-0752 in 5 different species (3 rodent, monkey, and human) and to develop methods for cross-species scaling of the PK/PD relationship

## PK/PD Model Development Non-human Species

Data were obtained as follows: In the rodents (Tg-mouse, YAC-mouse, and guinea pig) brain tissue and plasma were obtained at approximately 4 hours post-dose and analyzed for Aβ40 and MK-0752 concentrations. In CMP-porated rhesus monkeys serial plasma and CSF samples were obtained following single-dose administration and were analyzed for Aβ40 and MK-0752 concentrations. All models and simulations were conducted using ASCL software (AEgis) and utilized naive pooling approaches to obtain mean parameter estimates.

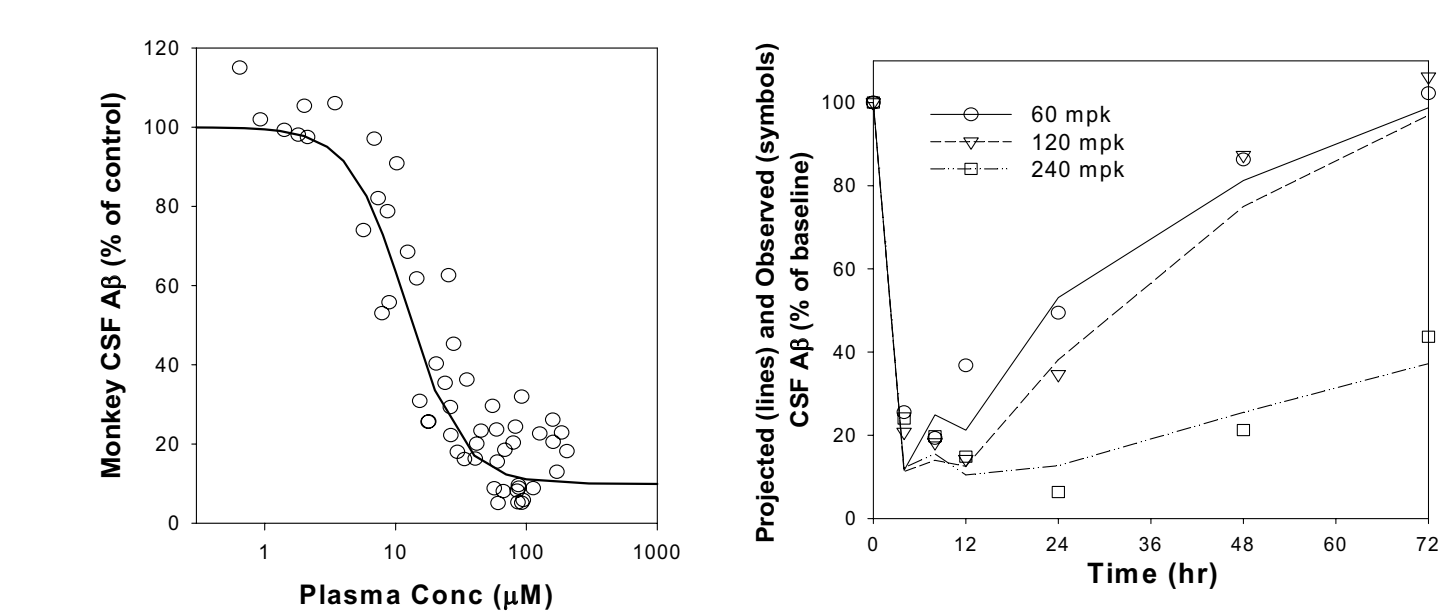
Data in the 3 rodent species were well described by a sigmoid Emax relationship. Data from the monkey were also well described by a sigmoid Emax relationship and the serial sampling allowed for confirmation of minimal hysteresis in this species. Across the 4 non-human species, there was reasonable agreement on the estimates for Emax and the hill coefficient; however there was a ~20-fold variation in IC50 estimates, that may have been related to protein binding differences.

## Sigmoid Emax PK/PD Relationship Characterized Tg-Mouse, YAC-Mouse, and Guinea Pig Data Well



$$A\beta \text{ level} = 100\% - E_{max} * \frac{C^n}{(C^n + IC_{50}^n)}$$

## Sigmoid Emax PK/PD Relationship Characterized Monkey Data Well



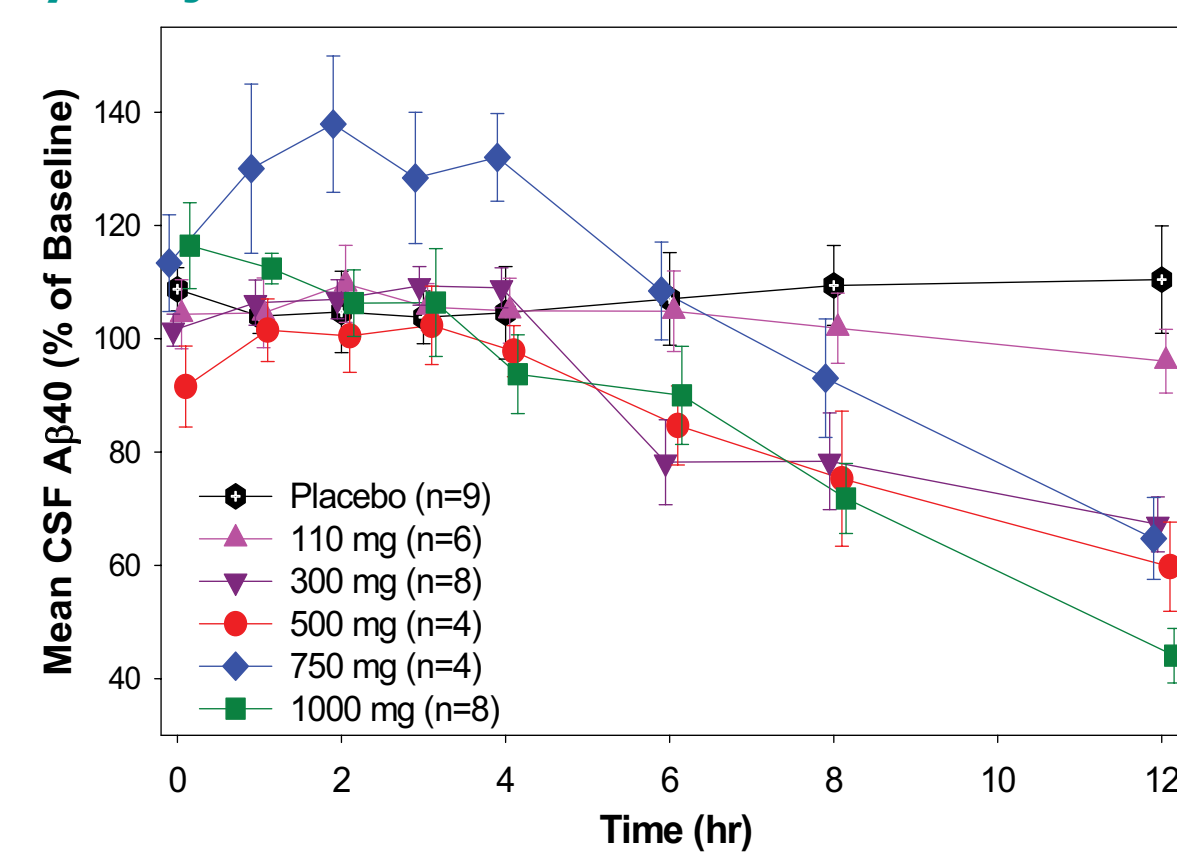
- Serial CSF data in CMP-porated rhesus allowed for test of lack of hysteresis (time delays)

## PK/PD Model Development – Human

In human clinical studies, serial plasma and CSF samples were obtained in healthy subject over 12-30 hours following a single dose through a lumbar spine catheter. Inconsistencies in the presence or absence of time delays between PK and PD endpoints dictated differing PK/PD model structures across the species, but the core equation for impact of MK-0752 on brain Aβ was kept consistent across all models. All models and simulations were conducted using ASCL software (AEgis) and utilized naive pooling approaches to obtain mean parameter estimates.

In humans, a substantial time-delay was noted between peak drug concentrations in CSF (3-4 hr) and peak Aβ reduction in CSF (~12 hr) and application of the sigmoid Emax model used in animals was judged inappropriate. A semi-mechanistic PK/PD model was developed that incorporated time delay in drug reaching the CNS and in the brain Aβ response reaching the location of lumbar CSF sampling. This model well described the plasma and CSF PK data and the CSF Aβ data and produced the dose and time-dependent variations in the 4 analytes/anatomical sites tracked, consistent with the data. Because the model kept the core sigmoid Emax equation to describe drug effects on brain Aβ response, the parameters from this model could still be compared to those obtained in animals.

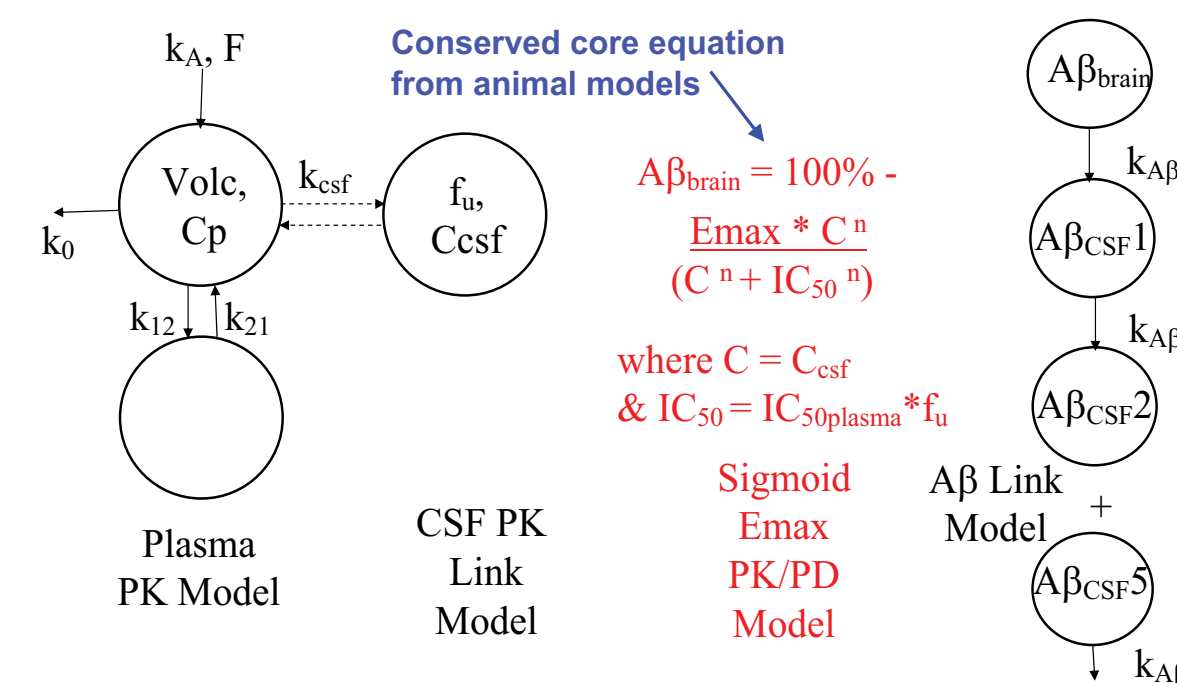
## Mean (SE) Aβ Profiles in CSF Following Single Doses in Healthy Subjects



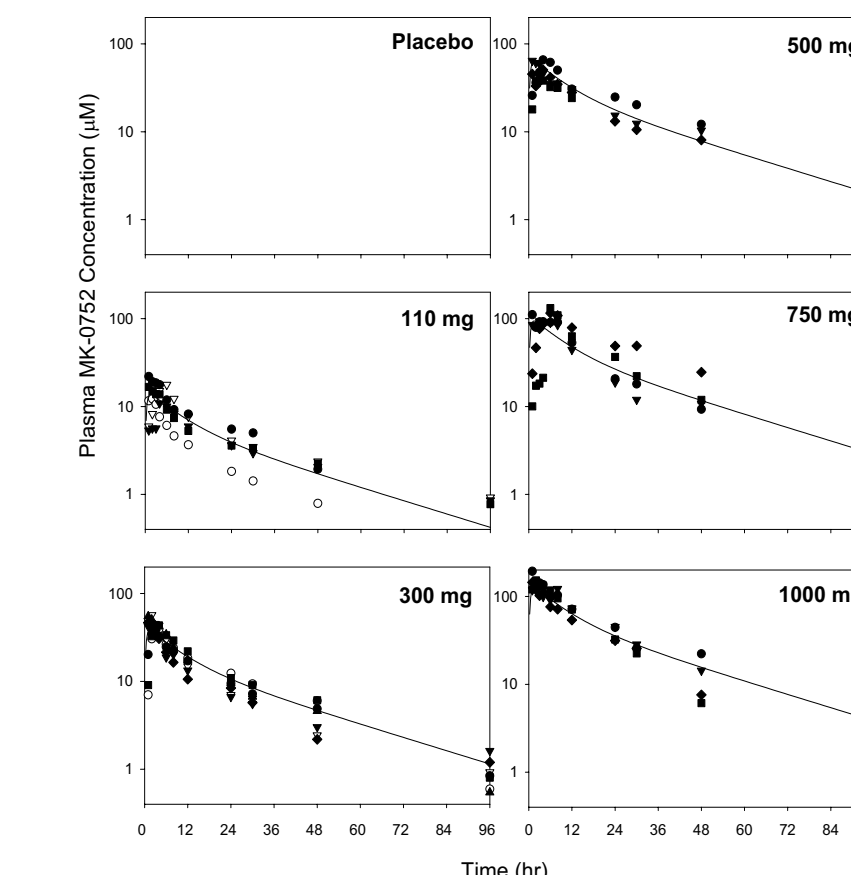
\*excludes 1 outlying subject in 300 mg group

- A substantial time-delay noted between peak drug concentrations in CSF (3-4 hr) and peak Aβ40 reduction in CSF (~12 hr)

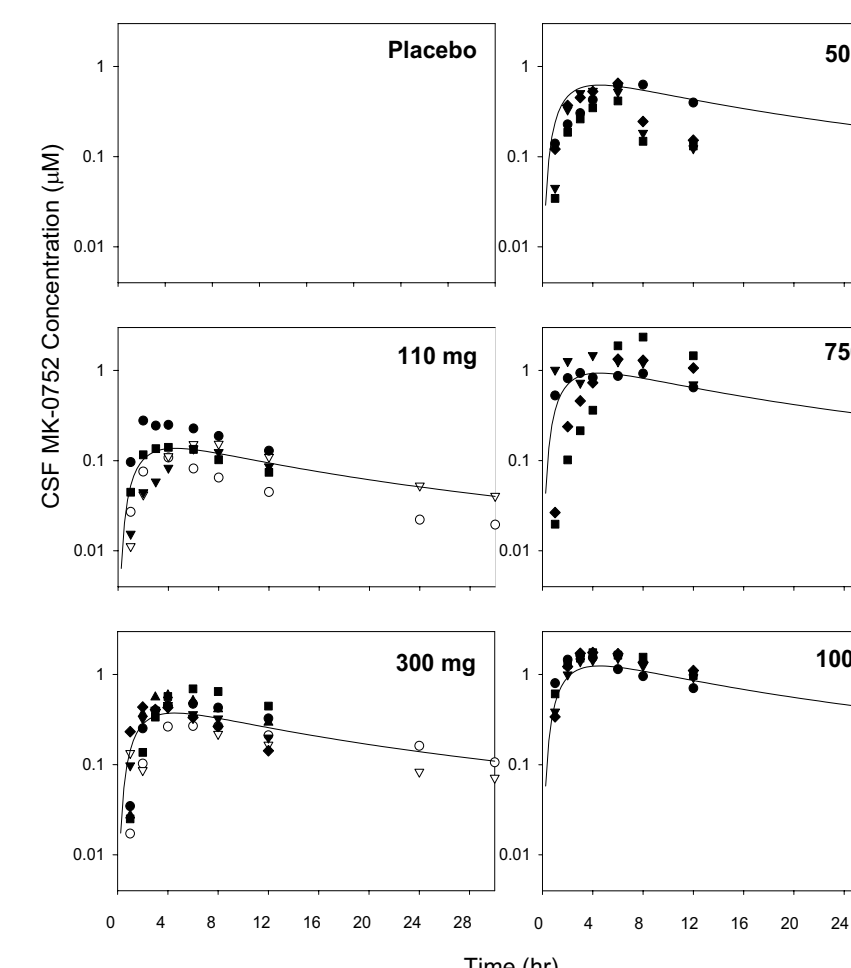
## Human PK/PD Model - Time -Delays in Drug Distribution and CSF Flow to Lumbar Region



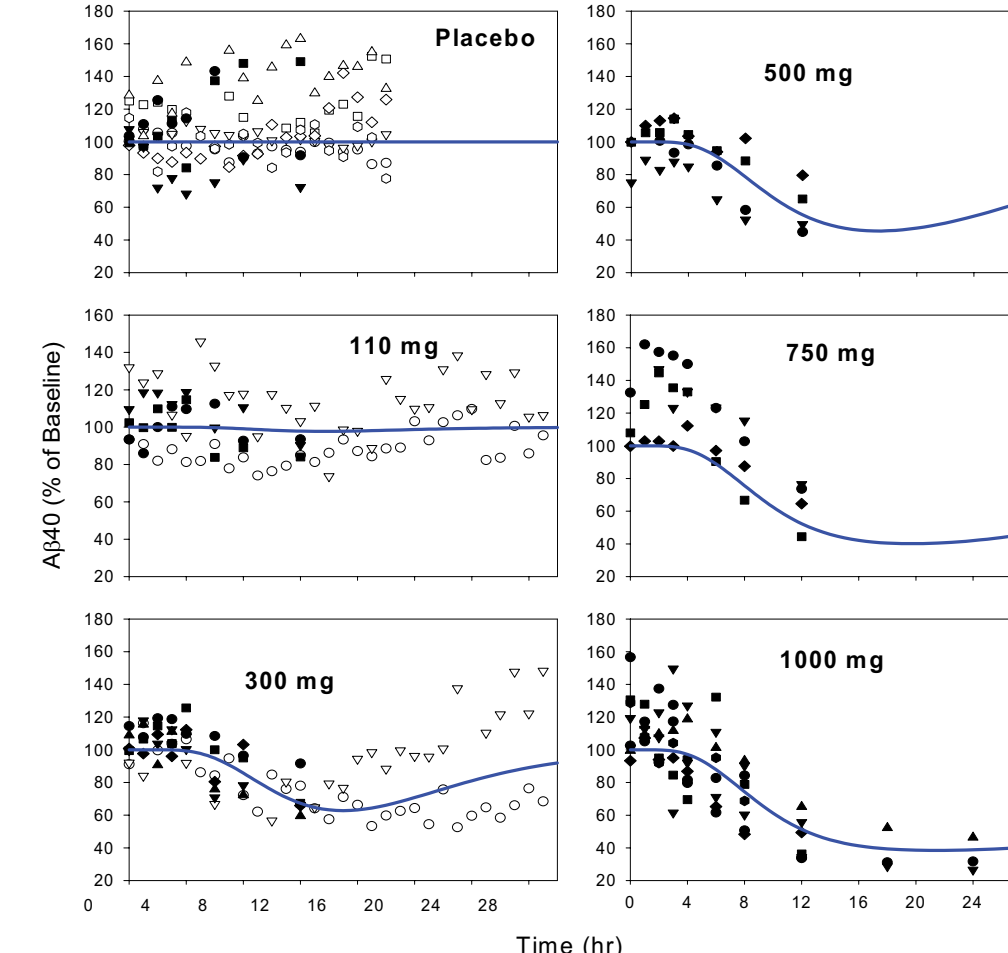
## Naïve Pool Fit of PK Profiles in Plasma to Model



## Naïve Pool Fit of PK Profiles in CSF to Model



## Naïve Pool Fit of Aβ



## Cross-Species Scaling Approach

The IC50 values from the core equation for impact of MK-0752 on brain Aβ varied considerably across the species in a manner consistent with differences in plasma protein binding. Therefore, a cross-species scaling approach was developed to relate IC50 across species utilizing a protein binding correction, that assumed that the equivalent free IC50 values would be similar across all species ( $IC_{50} = 0.055 / f_u$ ). As shown in the following figure the IC50 values in all 5 species were within 3-fold (illustrated by the dashed lines) of this predicted relationship (solid line).

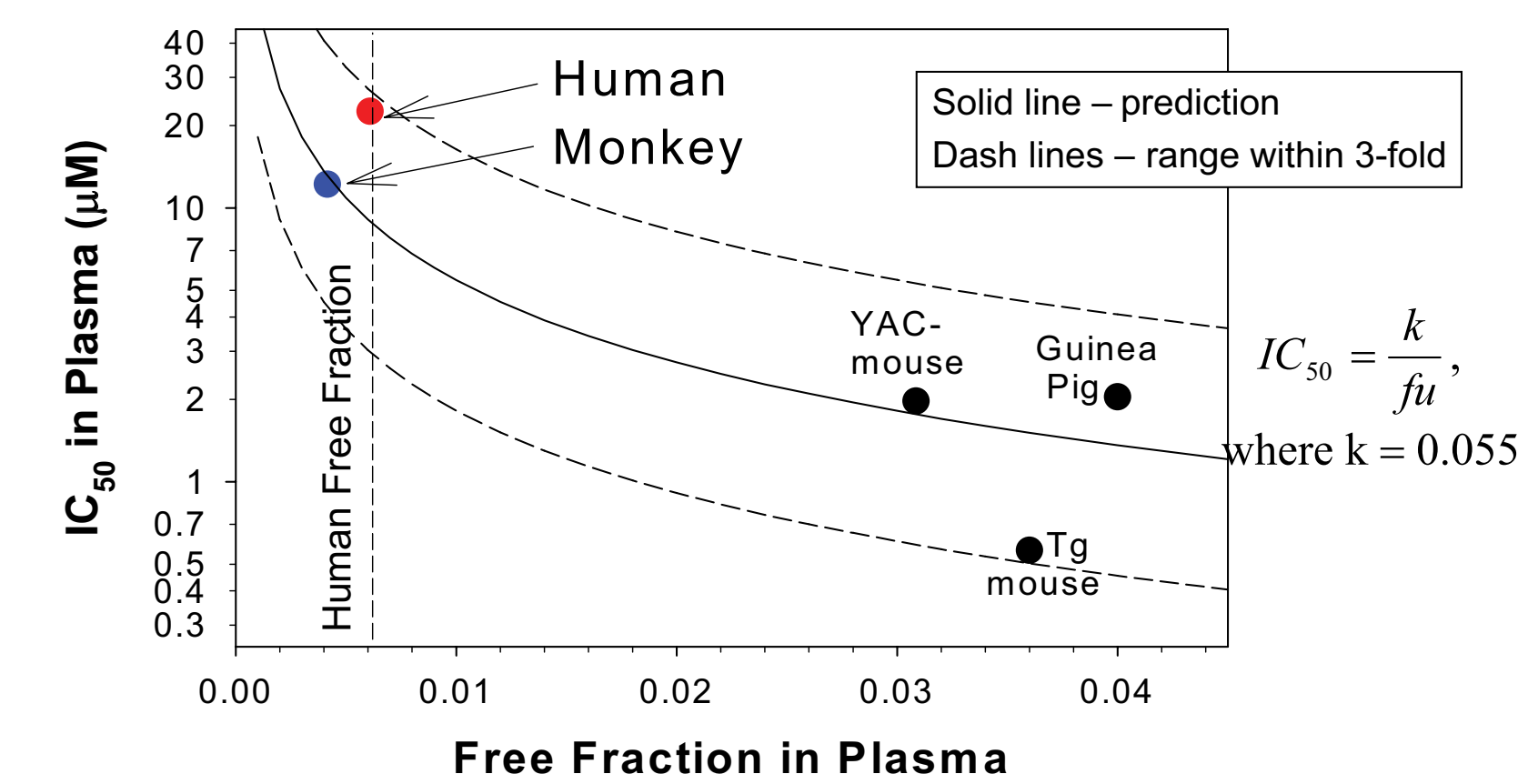
## Approach for Scaling PK/PD Relationship Across Species

Species	Model Parameter Estimate			Plasma Free Fraction
	IC50 (μM)	Emax (% reduction)	n	
Drug plasma conc / brain Aβ level				
Tg mouse	0.57	82.0	1.17	0.036
YAC mouse	1.96	72.4	1.14	0.031
Guinea Pig	2.06	79.7	1.08	0.040
Drug plasma conc / CSF Aβ level				
Monkey	12.07	90.1	2.04	0.0043
Human	22.3	63.0	4	0.0061

- IC50 values projected using inverse proportional scaling of the in vitro free fraction in plasma (fu):

$$IC_{50} \text{ human} = IC_{50} \text{ animal} * \frac{f_u \text{ (animal)}}{f_u \text{ (human)}}$$

## Free-Fraction in Plasma as a Predictor of Plasma IC50 for Aβ Levels in CNS



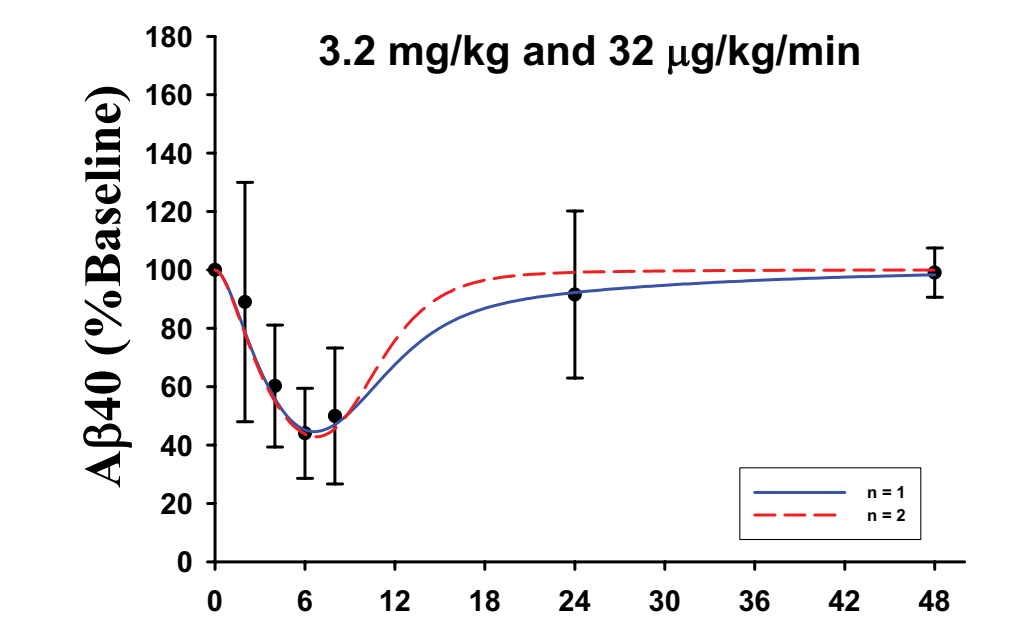
## Application to Early Decision Making

Establishment of this inter-species PK/PD scaling approach has allowed for its application in a variety of other Merck efforts that target Aβ production and CNS clearance. This method has subsequently informed Go / No-Go decisions on several compounds in early development.

## Example of Application to Early Development Compound Leading to No-Go Decision

- Compound in preclinical development
- For clinical studies, will need to remain 5- to 10-fold below Cmax value established in animal toxicity studies
- Question: Is there sufficient probability of a therapeutic window to justify continued development?
- Aβ model adapted by fitting to data from monkeys
  - Some uncertainty in Emax and n values due to limited data
- Human PK/PD predictions, base on protein binding scaled IC50
- No-Go decision based on low probability that compound would achieve sufficient Aβ response

## Example of Application to Early Development Compound Leading to No-Go Decision



Cmax Safety Margin	% CSF Aβ Reduction (at Peak) for Predicted IC50 (3-fold uncertainty range on IC50)	
	n = 1	n = 2
Assuming Human Emax = 70%		
5-fold - 1.3 μM	27 (12 - 46)	21 (3 - 55)
10-fold - 0.66 μM	17 (7 - 34)	7 (1 - 34)
Assuming Human Emax = 100%		
5-fold - 1.3 μM	39 (18 - 66)	29 (4 - 79)
10-fold - 0.66 μM	24 (10 - 49)	9 (1 - 48)

## Conclusions

- Semi-mechanistic PK/PD modeling allowed for characterization of the drug effect on CNS Aβ response across a variety of species including humans
- Because the same core equation describing response in brain tissue was used in all models, a cross-species scaling approach for the key IC50 parameter could be developed despite substantial differences in the time-course of response across the species
- Correction for plasma protein binding was required for successful inter-species scaling of IC50
- Establishment of this scaling approach has allowed for its application in programs targeting Aβ to aid Go/No-Go decisions with regards to candidates in very early development and discovery.

Reference

- L.B. Rosen, J.A. Stone, et al. The Gamma Secretase Inhibitor MK-0752 Acutely and Significantly Reduces CSF Aβ40 Concentrations in Humans. Oral presentation at 10th International Conference on Alzheimer's Disease and Related Disorders (July 16-20, 2006, Madrid, Spain).