Extension of Simcyp Brain Model for Proteins to Investigate Transferrin Receptor Transport.

Harvey Leung[1,2], Indranil R. Rao[1], Katherine L. Gill[1], Arshad Majid[2], Iain Gardner[1]

[1] SimCYP (a Certara company), Sheffield, UK; [2] The University of Sheffield, Sheffield, UK

Harvey.Leung@certara.com, Indranil.Rao@certara.com

Background

Drug delivery to the brain is one of the greatest challenges in treating CNS disorders. A single-cell layer of endothelial cells form a tightly regulated interface between the vascular system and central nervous system (CNS) known as the blood-brain barrier (BBB) (1). Penetration of monoclonal antibodies across this barrier into the brain interstitial space is low.

The transferrin pathway allows the transport of iron molecules across the BBB via the binding of iron-bound transferrin to transferrin receptor and transcytosis across the brain endothelial cell (BEC). Manipulation of this pathway by binding to its components has allowed the transport of large molecules such as antibodies across the BBB experimentally.

Bi-specific antibodies which utilize anti-TFR as brain targeting arm and anti-BACE1 (an enzyme cleaving amyloid precursor protein) as therapeutic arm have been reported in the literature.

Recently, Kanodia *et al.* published a cynomolgus monkey model for anti-BACE1 antibodies where they showed that very potent antibodies to the transferrin receptor had lower pharmacodynamic effects in the brain compared to antibodies with weaker affinity due to TFR-mediated elimination in blood (2).

Methods

The 5-compartment brain model in Simcyp was modified by the addition of an endothelial cell compartment (Figure 1).

The following processes were modelled:

1) Binding of IgG to the transferrin receptor in the brain vascular compartment

2) Internalisation of the IgG-TFR complex in the endothelial cells

3) Release of IgG from the complex

4) Recycling or transcytosis of IgG by transferrin receptor

5) TMDD models were included in the systemic blood compartment and in the brain

Figure 1 depicts the modified 6-compartment brain model.

Amyloid-β turnover was modelled with an indirect response model and the effect of the antibody was modelled as inhibition of production of Amyloid-β. Peak effect is the maximum reduction of Amyloid-β. The average effect is calculated by the below equation

$$Average\ Inhibition = 100 * \frac{A\beta_{Baseline,AUC} - A\beta_{AUC}}{A\beta_{Baseline,AUC}}$$

Aims

Our aim was to see if the full PBPK model with the 6-compartment creates the same trend as observed in the publication by Kanodia *et al.*

References

(1) Pardridge W (2007) Blood-brain barrier delivery. Drug Discov Today 12:54-51.
(2) Kanodia J, et al. (2016) Prospective Design of Anti-Transferrin Receptor Bispecific Antibodies for Optimal Delivery into the Human Brain. CPT Pharmacometrics Syst Pharmacol 283-291.
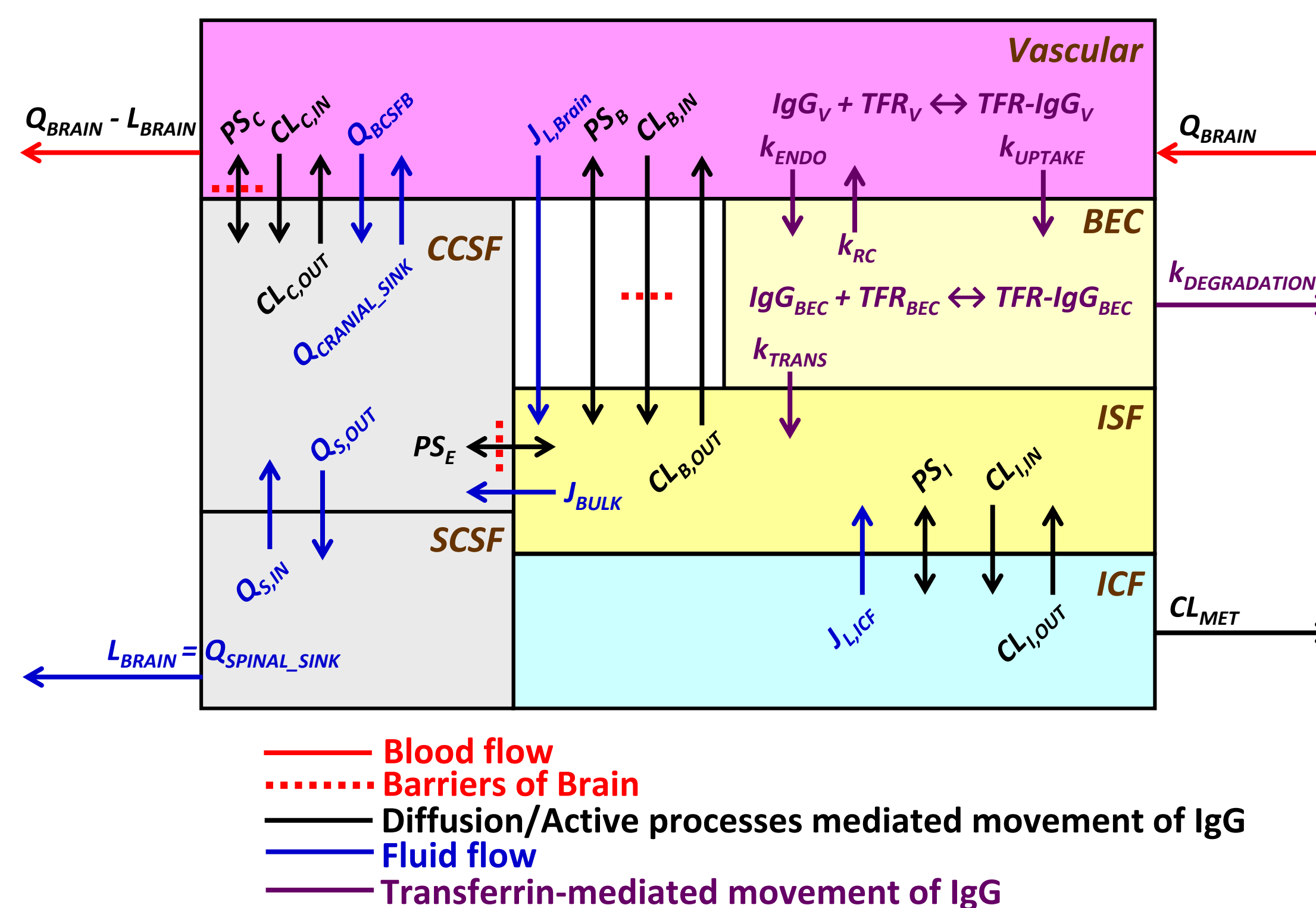
Figure 1. 6-Compartment brain model

Results

Spinal CSF to plasma ratio data was extensively collected from the literature for healthy volunteers for IgG, Albumin and various other small and large proteins. The hydrodynamic radius was calculated with the default Simcyp equation. Figure 2 shows the observed vs. the predicted Spinal CSF to plasma data. The predicted Spinal CSF:Plasma ratio correctly predicted the observed values
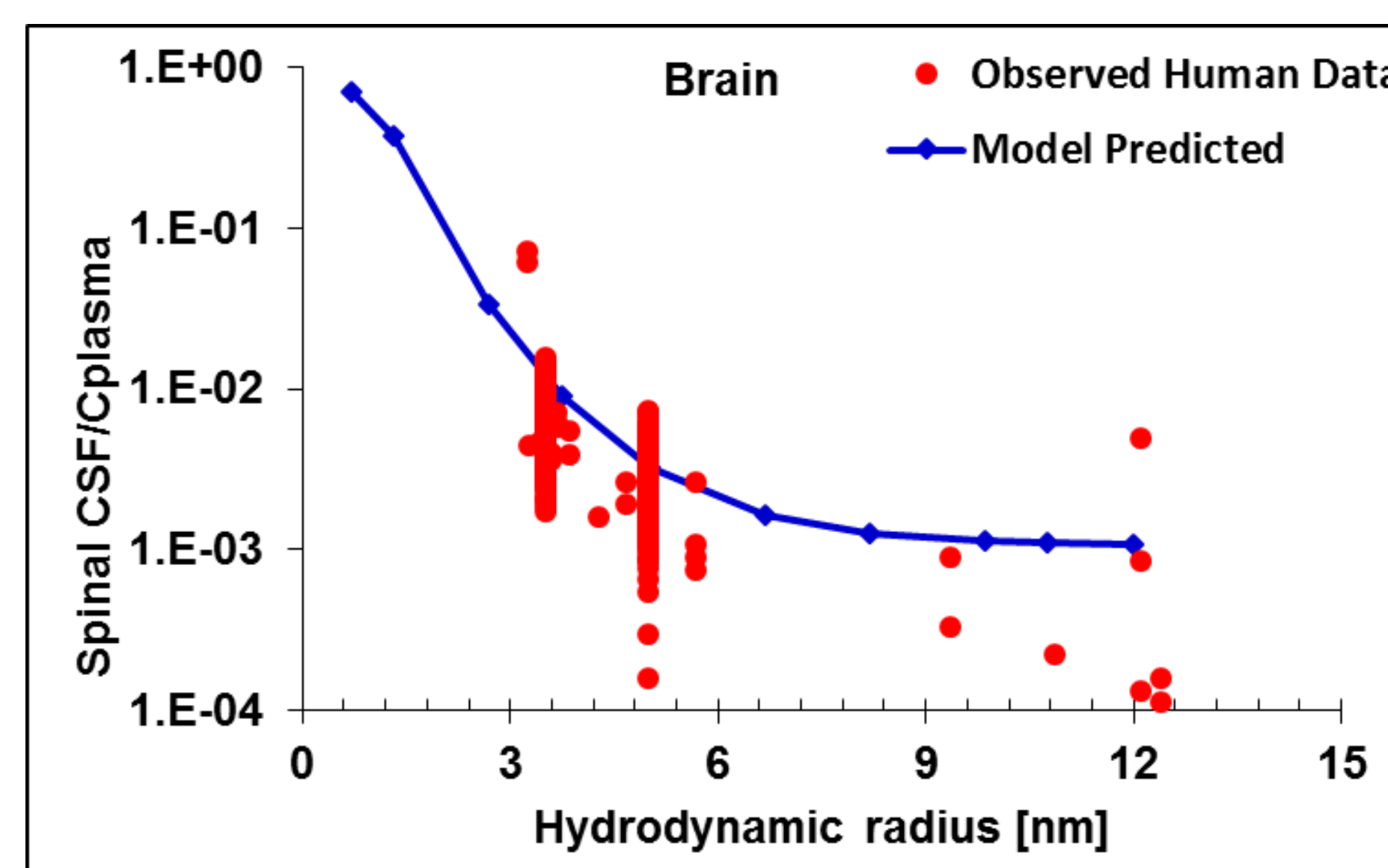

Figure 2. Spinal CSF to Plasma Ratio in Humans

Figure 3 shows the antibody concentration in plasma and brain interstitial space when IgG-Transferrin receptor binding has a k_D of 3nM (Figure 3A) and 30,000nM (Figure 3C). At 3nM, transferrin receptor-mediated clearance in blood clears the BACE1 antibody within 7 days (Figure 3A). Correspondingly, the drug is also cleared from the brain ISF compartment. Since brain ISF concentration drives the reduction of Amyloid-β, the PD effect returns below 50% around 7 days and reaches its baseline value after 14 days (Figure 3B). For a k_D of 30,000nM, the antibody does not bind to transferrin receptor in the blood and hence antibody remains in the brain for longer (Figure 3C). Correspondingly, the higher antibody concentration in the brain ISF even after 14 days, keeps Amyloid-β levels below 50% of baseline (Figure 3D).

Figure 4 shows the relationship between IgG-TFR binding k_D and PD effect. The average and peak inhibition is lower at lower TFR K_D values. For very high k_D values a lower PD effect is seen as the antibody has lower brain uptake via the TFR. For antibodies with intermediate k_D (5 μM to 30 μM for average inhibition; 100nM to 3000 nM for peak inhibition), there is a good balance between receptor-mediated clearance and brain uptake such that the PD effect is maximal.
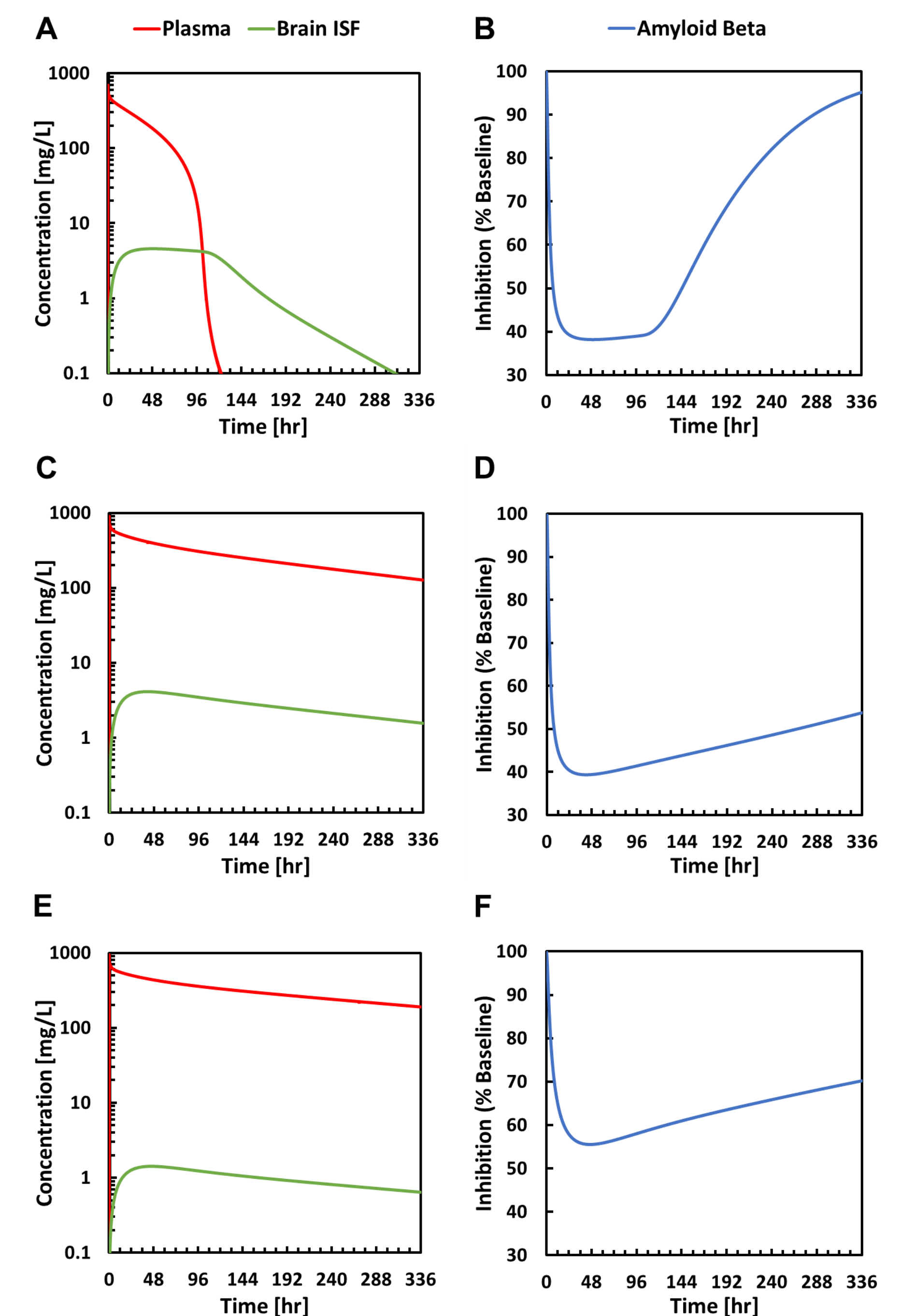

Figure 3. A, Plasma and brain ISF concentration when antibody-transferrin receptor k_D of 3nM. B, amyloid-β inhibition at 3nM k_D. C, Plasma and brain ISF concentration at k_D of 30,000nM. D, amyloid-β inhibition at 30,000nM k_D. E, Plasma and brain ISF concentration without TfR binding. F, amyloid-β inhibition without TfR binding.
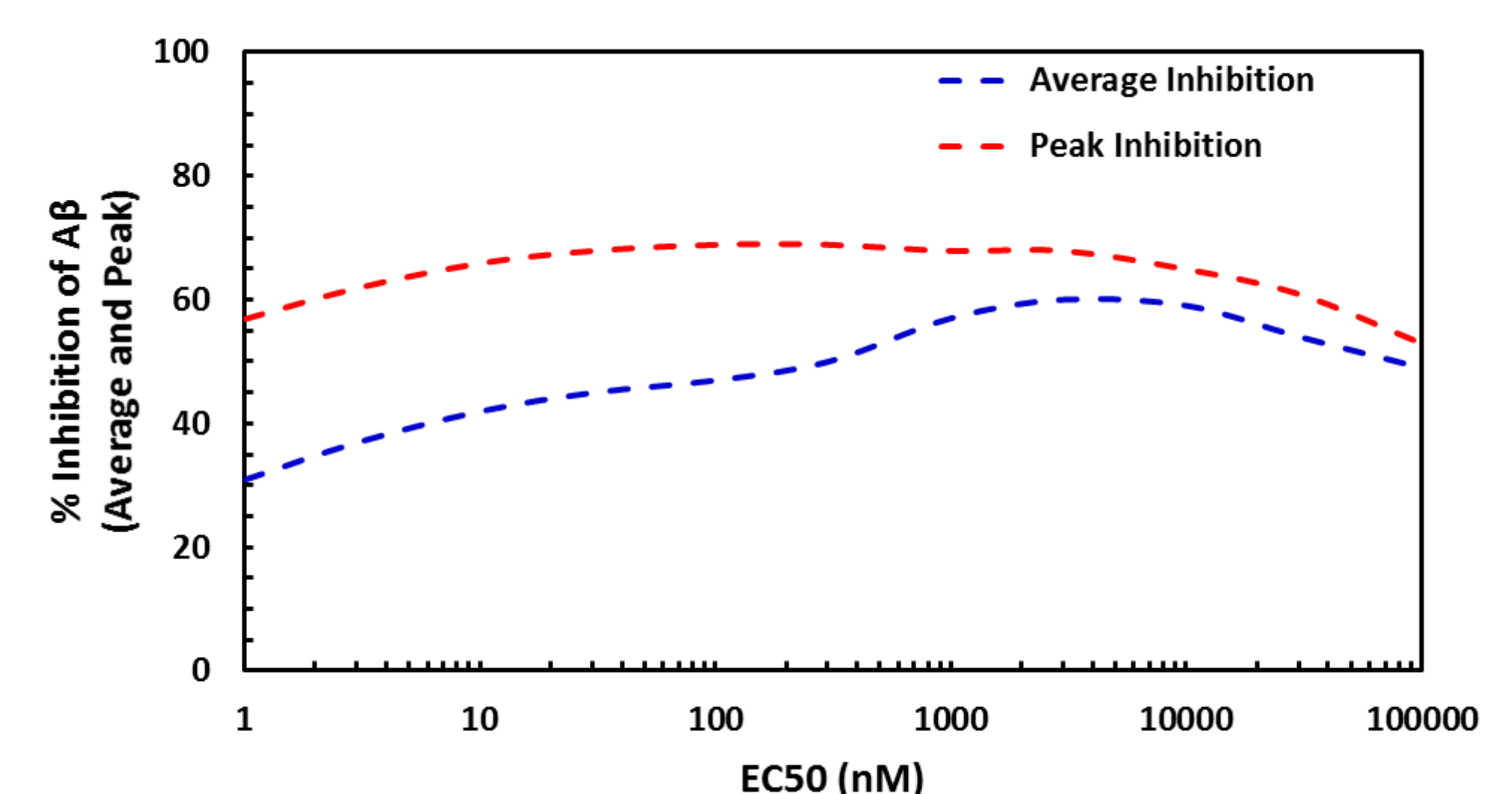

Figure 4. Average (Blue) and Peak (Red) inhibition of amyloid-β at 30 mg/kg dose of anti-TFR antibody with the same BACE1 arm but with varying affinity to transferrin receptor

Discussion

◆ Using a full PBPK model and accounting for TFR transport the experimental relationship between TFR potency and PD effect was simulated.

◆ This type of modeling can be performed for other bi-specific antibodies

◆ Different relationships between maximal and average PD effect and TFR binding potency were observed.

Acknowledgments