Development of a PBPK model for anti-transferrin (TfR) antibodies to predict brain and systemic pharmacokinetics

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Objectives: To develop a catenary physiologically based pharmacokinetic (PBPK) model that facilitates consideration of receptor mediated transport (RMT) of anti-TfR monoclonal antibodies (mAb) into the mouse brain, by incorporation of receptor characteristics (expression, internalization, trafficking) and mAb-TfR association (kon) and dissociation (koff) kinetics.

Methods: Physiological parameters and TfR receptor characteristics were obtained from literature. The brain vascular reflection coefficient ($\sigma_{br,v}$) and coefficients representing inter-antibody differences in pinocytosis (F1) and vascular RC (F2) were estimated from the plasma and brain pharmacokinetic (PK) data of an untargeted mAb 7E3 [1]. The model was evaluated by predicting the systemic and brain exposure of 5 anti-TfR affinity variants (A-E), with $K_d$ values of 1.7, 6.9, 65, 111 and 5000 nM [2]. Model simulations were carried out for a range of kin, kon, and koff values to determine optimal mAb and receptor characteristics.

Results: The model (Figure 1) was able to characterize the digitized 7E3 PK. Mean values (CV%) for $\sigma_{br,v}$, F1, and F2 were estimated to be 0.294 (27.2%), 1.82 (12.3%) and 0.995 (0.0487%). Simulations were able to reasonably describe the digitized PK of the 5 affinity variants. The observed and predicted brain to plasma (B/P) area under the curve (AUC) ratio for the high affinity mAb TfRA was 0.0089 and 0.0088 respectively, and calculated % predictive error (PE) was 1.31%. While for the low affinity mAb TfRD, the observed and predicted B/P AUC was 0.011 and 0.0089 with %PE 20.1. Simulations suggested that high affinity mAb was minimally sensitive to kint, while for a low affinity mAbs (110-5000 nM), optimal range of kint was predicted to be 0.0183-1.83 min^{-1}.

Conclusions: Simulations suggest low to moderate affinity mAbs had higher brain:plasma ratios compared to high affinity mAb, due to favorable binding in the vascular space, and rapid dissociation relative to internalization within the interstitial space. This PBPK model may be easily extended to other RMT targets.

References: