Development of a mathematical model for neonatal Fc receptor recycling to design human serum albumin mutants with extended half-lives

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Background

- The half-life of therapeutics can be improved by linking these molecules to albumin.
- The half-life of albumin is prolonged because of its binding to the FcRn receptor which recycles albumin back to the plasma instead of being catabolised.
- It is hypothesized that albumin constructs (mutants) with an increased affinity for the FcRn receptor can have a prolonged in vivo half-life compared to albumin itself.

Objective

- Predict the effect on terminal half-life for human serum albumin (HSA) mutants with improved FcRn affinity compared to HSA WT in Mouse, Cynomolgus monkey, and Human.
- Evaluate the utility of animal models as quantitative screening models for HSA mutants.

Methods

- Literature search for:
  - PK models on FcRn recycling of albumin and IgG, which has a similar FcRn mediated mechanism as albumin.
  - Model parameters.
- Model validation: Comparison of model predictions with literature and study data.
- Simulations: Quantification of the relationship between FcRn affinity and *in vivo* half-life.

Model

- The detailed PK model proposed by Kim et al. 2007 was used (figure 1A).
  - Kim et al. 2007 applied a simplified version of the model.
- The detailed model was extended to include competition between endogenous and exogenous albumin (figure 1):
  - Endogenous and exogenous albumin compete for binding to free FcRn receptor, R:

$$R = Rtot - B_E - B$$

  - Change in FcRn affinity to exogenous albumin was characterized by a change in the dissociation rate, K_{off}.

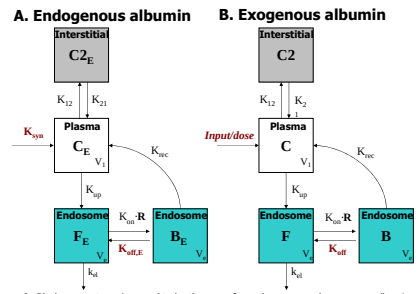

Figure 1, Mechanism-based PK model describing the distribution, degradation and recycling of endogenous (E) and exogenous albumin. C: Plasma concentration, C2: Interstitial concentration, F: Free concentration, B: Bound concentration, R: Free FcRn receptor.

Parameters

- For mouse and human all but three parameters could be found in literature
  - Chaudhury 2003, Chaudhury 2006, Ferl 2005, Garg 2007, Kim 2007, Smithers 1961.
- We could identify the unknown parameters (Ksyn, Ve, Rtot), starting with a set of ODEs for the model in figure 1A, and applying the following steady-state principles:

albumin synthesized = albumin eliminated

$$\frac{dC_{E,SS,KO}}{dt} = 0 \quad \Rightarrow Ksyn$$

$$\frac{dC_{E,SS}}{dt} = 0 \quad \frac{dB_{E,SS}}{dt} = 0 \quad \Rightarrow Ve$$

$$Rb_{SS} = \frac{B_{E,SS}}{Rtot} \quad \Rightarrow Rtot$$

where $C_{E,SS}$ and $C_{E,SS,KO}$ are the plasma concentration of endogenous albumin at steady state in the presence or absence of FcRn recycling, respectively, and Rb_{SS} is the receptor occupancy at steady state.

- Monkey parameters were scaled from human.

Data

huFcRn transgenic mice study:

- 15 mg/kg HSA and three HSA mutants dosed iv.
- huFcRn transgenic mice (n=10 per treatment).
- Plasma concentrations collected at 0, 16, 48 and 96 h (grp A, n=5) or 0, 24, 72 and 120 h (grp B, n=5).

Results

- **The model predictions of the PK of albumin were in good agreement with literature-reported data (figure 2).**
- **The model could predict the PK profiles (figure 3) and half-life (table 1) for the α and β mutants tested in the huFcRn transgenic mice. The half-life of mutant γ were lower than predicted due to instability of the mutant.**
- **Larger increases in half-life of HSA mutant are predicted in human and monkey compared to the huFcRn transgenic mice models (figure 4).**
  - **Due to the high affinity of endogenous murine serum albumin (MSA) for the huFcRn receptor and thus high receptor occupancy, large changes in affinity only cause small increases in half-life in the huFcRn transgenic mouse.**
- **A study with 3 huFcRn transgenic mice may not be sufficient to capture a difference in half-life due to the high variability of the data, especially at high affinities (figure 5).**

Model validation (literature)

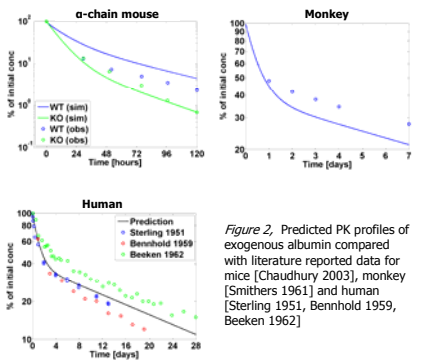

Figure 2, Predicted PK profiles of exogenous albumin compared with literature reported data for mice [Chaudhury 2003], monkey [Smithers 1961] and human [Sterling 1951, Bennhold 1959, Beeken 1962]

huFcRn transgenic mice study

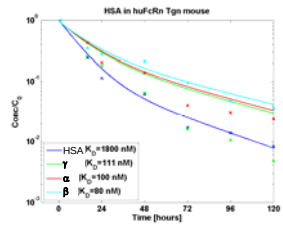

Figure 3, Model was used to simulate the huFcRn transgenic mice data on HSA WT and 3 mutants (γ, α and β) with different FcRn affinities.

	Half-life (h)		Fold change	
	obs	pred	obs	pred
HSA	24.7	23.6	1	1
γ	17.7	30.5	0.72	1.29
α	28.7	31.4	1.16	1.33
β	30.2	33.6	1.22	1.43

Table 1, Observed and predicted half-life determined from the log-transformed concentrations in the interval 24-120h.

Prediction of half-life increase

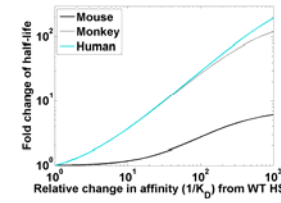

Figure 4, Predicted relative change in half-life of HSA for huFcRn transgenic mouse, monkey and human.

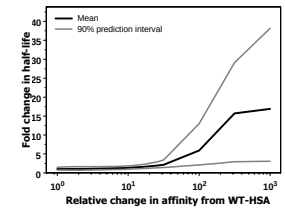

Figure 5, Expected uncertainty in half-life prediction for huFcRn transgenic mice study with 3 mice per HSA mutant (based on 500 simulations).

Conclusions & Perspectives

- A mechanism-based PK model for albumin was developed and verified against literature and study data.
- We demonstrate that a mathematical model can be used to quantify the relationship between FcRn affinity and *in vivo* half-life in different animal models and humans.
- The PK model is useful to: (1) identify optimum affinity to obtain desired half-life extension (2) design animal experiments to confirm half-life extension, (3) function as an early screening method for compounds
- Half-life increases are smaller for the transgenic mouse than for monkey and human.

Find the poster here

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