Development of a semi-mechanistic pharmacokinetic/pharmacodynamic model of a small interfering RNA targeting liver proteins in mice and cynomolgus monkeys

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Introduction

- Small interfering ribonucleic acid (siRNA) is an emerging class of targeted therapies, whose role is to prevent RNA translation into protein. Pharmacokinetics (PK) of siRNAs typically exhibit transient plasma exposure in contrast to prolonged residence time in target tissues. Therefore, siRNAs have demonstrated durable pharmacodynamic (PD) effect, lasting from weeks to months.
- For liver targets, siRNAs are commonly conjugated to a tris N-acetylgalactosamine $(GalNAc)_3$ which specifically binds to the asialoglycoprotein receptor (ASGPR) that are highly expressed on the membrane of hepatocytes. GalNAc-siRNA is internalised via endocytosis and released as free siRNA into the cytoplasm. Then, free siRNA is loaded onto the RNA-induced silencing (RISC) complex, where it inhibits the RNA translation and leads to the protein knockdown [1].
- The interspecies translation of siRNA PK/PD models is challenging due to the temporal difference between PK moieties and PD biomarkers, in addition to the lack of mechanistic understanding. LY targets a specific liver protein, involved in the regulation of various lipids.

Objectives

1. Develop a semi-mechanistic PK/PD model in mice for LY
2. Translate and optimise the mouse PK/PD model to cynomolgus monkeys using allometric scaling

Methods

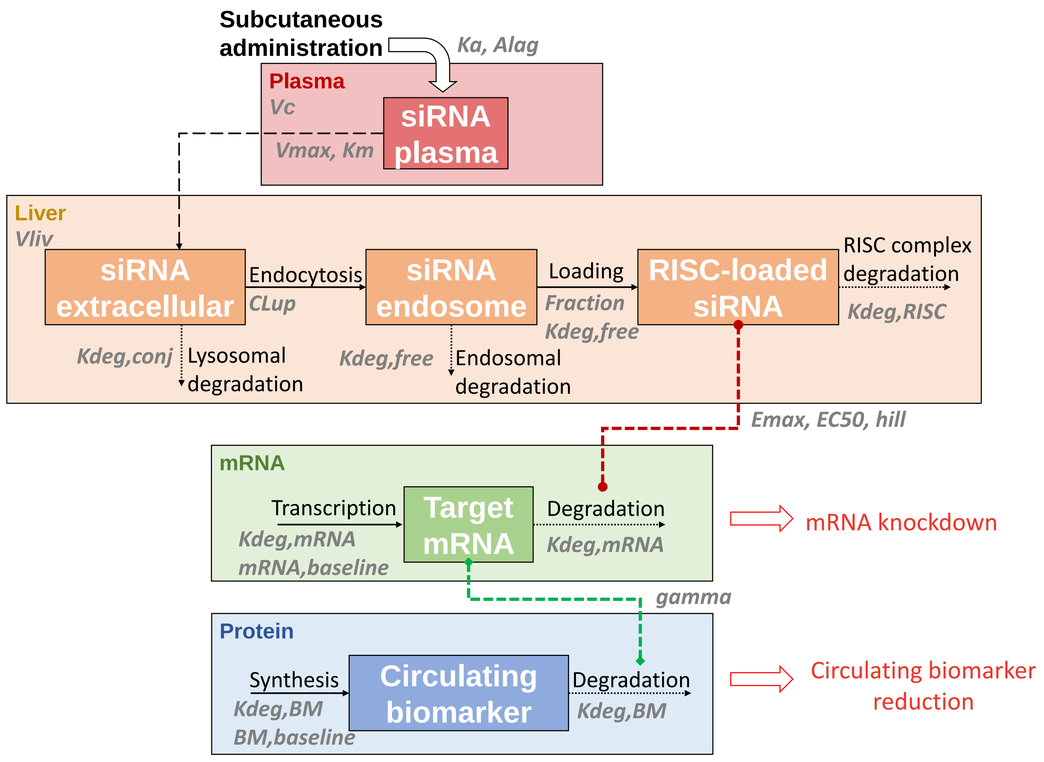

Figure 1. Schematic of LY semi-mechanistic PK/PD model

- A semi-mechanistic PK/PD model was developed in a stepwise approach using FOCE-I in NONMEM v7.4 (**Figure 1**) [1].
- Data from two dose-ranging mice studies (3-day PK/PD study (n=63) and 8-week PK/PD study (n=63) were used for model development. Mice received a single subcutaneous dose (placebo, 0.30, 1.75 or 10 mg/kg of LY) in both studies. LY siRNA concentrations were measured in plasma. Terminal liver biopsies were collected to quantify total siRNA (conjugated + free + RISC-loaded), RISC-loaded siRNA separately and target mRNA levels. A circulating biomarker was evaluated as a PD endpoint.
- The mice model was scaled to cynomolgus monkeys using data from a single-dose cynomolgus monkey study (n=12). Plasma siRNA, total liver, RISC-loaded siRNA concentrations and target mRNA were collected (up to 48 h and day 84 for plasma samples and incisional liver biopsies, respectively). Circulating biomarkers were not used due to large variability in measurements.
- First, allometric scaling based on body weight was considered on clearance and volume terms [2]. Physiological and response model parameters were also optimised to improve model descriptions of PK moieties and PD biomarkers.

Conclusions

- The semi-mechanistic PK/PD model developed in mice enabled to describe plasma and liver PK moieties and their influence on mRNA and lipids.
- Subsequently, the interspecies translation of the mice PK/PD model to cynomolgus monkeys was achieved with minimal parameter optimisation and allometric scaling.
- This PK/PD model provides a model-informed drug development (MIDD) framework for interspecies translation thus enabling dose selection for first-in-human study.

References:
[1] V.S. Ayyar, D. Song, S. Zheng, T. Carpenter, D.L. Heald, J Pharmacol Exp Ther 379 (2021) 134–146.
[2] Y. Huh, D.E. Smith, M.R. Feng, Xenobiotica 41 (2011) 972–987.

Results

- The semi-mechanistic PK/PD model adequately described the mice PK and PD data (**Figure 2** and **Table 1**).
- The mouse PK/PD model was scaled to cynomolgus monkeys by applying allometric scaling factors and parameter optimisation was required for absorption and response model parameters (**Figure 3** and **Table 1**).

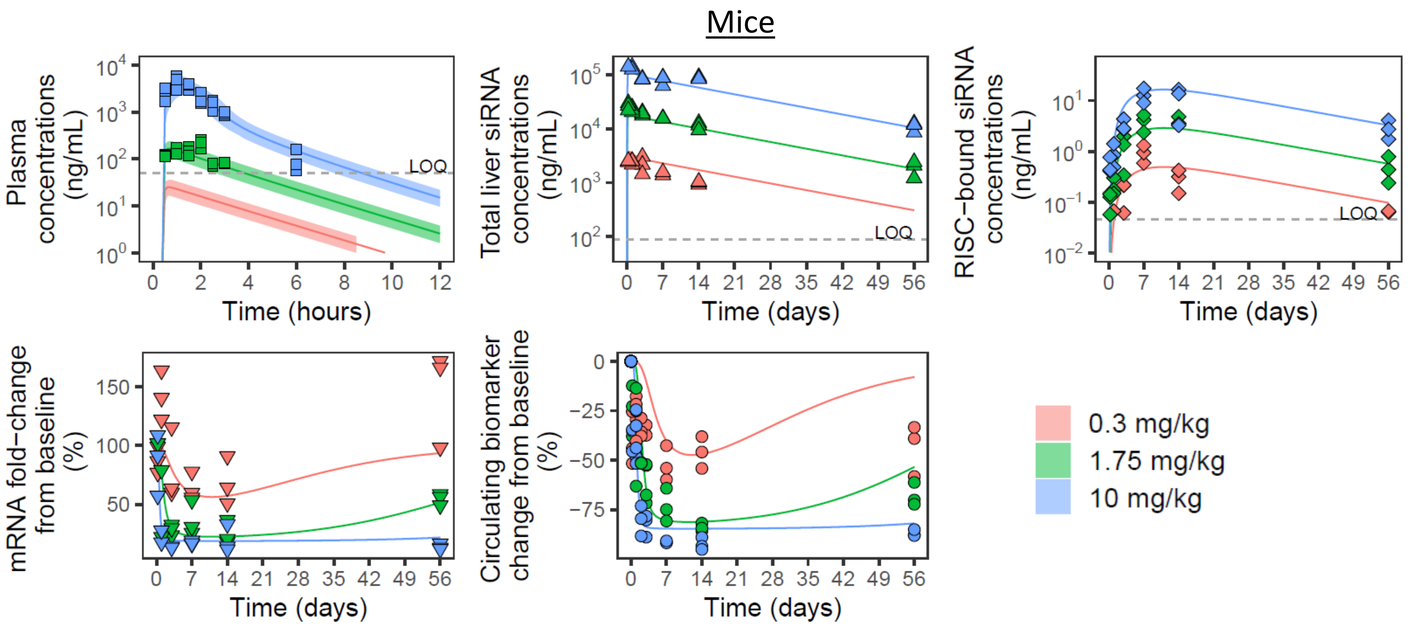

Figure 2. Predicted PK and PD-time profiles for mice. Symbols represent observed LY PK and PD data. Lines represent mean predictions and shaded areas are the 90% prediction intervals

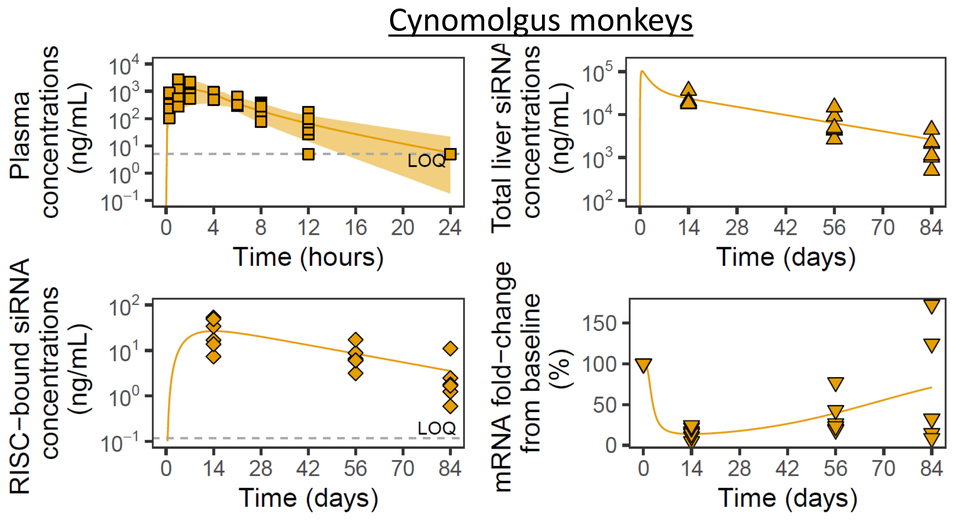

Figure 3. Predicted PK and PD-time profiles for cynomolgus monkeys. Symbols represent observed LY PK and PD data. Lines represent mean predictions and shaded areas are the 90% prediction intervals

Table 1. Parameter estimates of the LY siRNA semi-mechanistic PK/PD model

			Mice		Cynomolgus monkeys	
	Parameter	Unit	Estimate (RSE%[1])	BSV[2] (RSE%[1])	Estimate (RSE%[1])	BSV[2] (RSE%[1])
Plasma	Ka	1/h	0.356 (12%)		0.231 (15%)	0.0706 (62%)
	Vc	mL	4.2 (32%)	0.332 (38%)	AS[7]=1.18 (6%)	0.606 (41%)
	Alag	h	0.421 (7%)		NA[8]	
	Vmax	ng/h	78400 (9%)		AS[7]=0.692 (1%)	
	Km	ng/mL	754 (10%)	0.0619 (74%)		0.0357 (78%)
Total liver	CLup[3]	mL/h	0.0514 (35%)		AS[7]=0.402 (14%)	
	Kdeg,conj[4]	1/h	0.0131 (26%)			
	Kdeg,free	1/h	0.0017 (6%)			
RISC-loaded	Fraction		0.0013 (20%)		0.0077 (11%)	
	Kdeg,RISC	1/h	0.0087 (30%)			
Target mRNA	mRNA,baseline		1 FIX			
	Emax		4.4 (33%)		14.7 (5%)	
	EC50	ng/mL	1.28 (73%)		32.4 (7.8%)	
	hill		1.61 (42%)			
	Kdeg,mRNA	1/h	2.64 FIX[5]			
Circulating biomarker	BM,baseline[6]	mg/dL	2280 (3%)	0.0224 (39%)	NA[8]	NA[8]
	gamma		-1.12 (6%)		NA[8]	
	Kdeg,BM	1/h	0.0239 (39%)		NA[8]	

[1]RSE%: relative standard error (%); [2]BSV: between-subject variability; [3]Clup: liver uptake clearance; [4]Kdeg,conj: degradation rate of conjugated siRNA; [5]Kdeg,mRNA was fixed to literature data; [6]BM: biomarker; [7]AS: allometric scaling factor $(BW_{cyno}/BW_{mouse})^{AS}$; [8]not included in the cynomolgus monkey model