Beyond the Liver; An *in silico* Screening Tool for Tissue-Specific Oligonucleotide Delivery Receptors

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Conclusion

A first of a kind whole-body PBPK model for oligonucleotides has been developed. Trained initially on a single-compound single-species data, this model has demonstrated cross-species and cross-modality extrapolation capabilities. Such groundbreaking versatility positions it as a pivotal instrument in the advancement of novel targeted oligonucleotide therapeutics

Background & Objective

- Oligonucleotides intracellular delivery can be challenging due to their size and polarity.
- Several approved agents successfully targeted the liver by leveraging through conjugation with GalNAc leveraging the hepatic ASGPR receptors.
- Applying the same concept to other tissue requires identifying and evaluating optimal receptors for the target tissue.
- Traditional *in vivo* experimental evaluation of tissue targeting efficiency can be prohibitively expensive and time intensive.
- We propose to significantly enhance the process by introducing a PBPK-based *in silico* screening approach.

Methods

Modelling Platform

- The PBPK model was developed based on a biologics PBPK platform implemented in **QSP Designer** (V2.0.0.53; Certara, Sheffield, UK) [1].
- The platform allows a generic structure of a bodily tissue to be specified (Figure 1), then, the whole-body PBPK model is automatically built (Figure 2).
- The automation allows large PBPK models with several hundreds of ODEs, and thousands of reactions, parameters, and rules to be effortlessly and accurately generated.

Generic Organ Structure

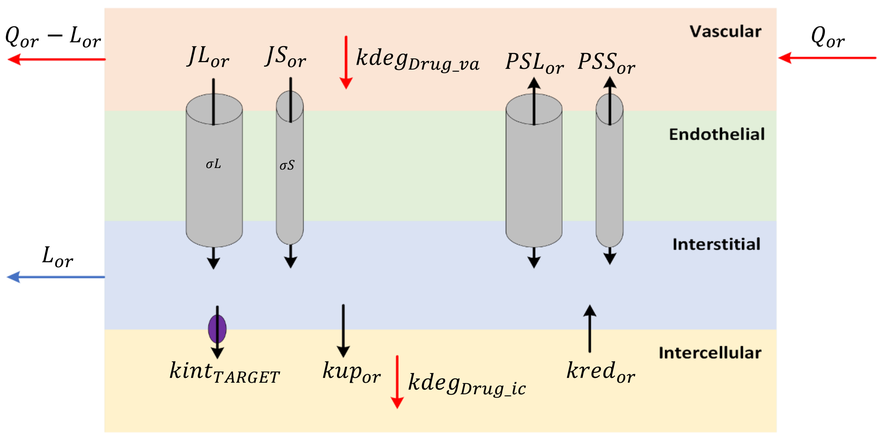

Figure 1 Schematic presentation of the key pharmacokinetic processes and parameters of the generic organ model.

Data Collection and Modelling Approach

- Non-conjugated ASO data following IV administration in rats was used to estimate the linear uptake (kup_{or}) and redistribution ($kred_{or}$) rate constants for each of the observed tissues.
- The fitted model was then validated against other ASO data from mice and rats following both IV and SC administration.
- Receptor Mediated endocytosis was then added to the model and parameterised for ASGPR-GN3 receptor ligand pair using literature values.
- The model was validated against IV and SC administered GN3-conjugated siRNA plasma and liver PK data.

Table 1: Summary of published data used to develop and validate the PBPK model. Green row: data used in training; Yellow rows: data used in validation.

Oligonucleotide Type	Dose (route)	Species	Measurement	Reference
Non-conjugated ASO	30 mg/kg (IV)	Rats	Plasma, kidney, liver, heart, bone, spleen, lung, pancreas, and gut.	[2]
Non-conjugated ASO	3.6 mg/kg (IV)	Rats	Liver, kidney, lung, and bone.	[3]
Non-conjugated ASO	10 mg/kg (IV)	Rats	Plasma, liver, kidney, and gut.	[4]
Non-conjugated ASO	0.6 mg/kg (IV)	Rats	Plasma, liver, kidney, spleen, bone, and lung.	[5]
Non-Conjugated ASO	30 mg/kg (IV)	Mice	Plasma, liver, kidney, heart, gut, lung, and spleen	[6]
Non-conjugated ASO	1 µg (IV)	Mice	Plasma, liver, kidney, heart, gut, lung, and spleen	[7]
Non-Conjugated ASO	6 mg/kg (IV)	Mice	Plasma, liver, kidney, heart, lung, and spleen	[8]
Non-Conjugated ASO	1 mg/kg (SC)	Mice	Liver	[9]
GN3-Conjugated ASO	140 mg/kg (SC)*	Mice	Plasma, liver, kidney	[10]
GN3-Conjugated siRNA	10 mg/kg SC	Mice	Plasma, liver, kidney	[11]

* Multiple doses

Full-PBPK structure

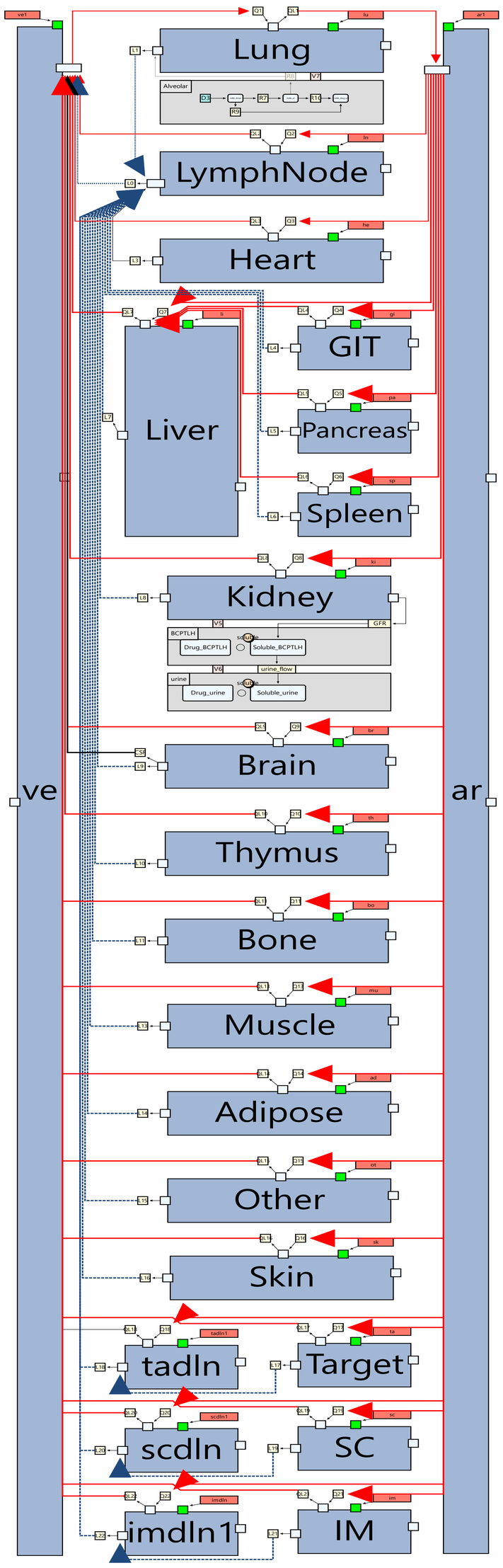

Figure 2: Full-PBPK model structure as designed in QSP Designer. Each greyish-blue colour represents an instance (copy) of the generic organ structure.

Results

Non-Conjugated ASO – Rats – IV

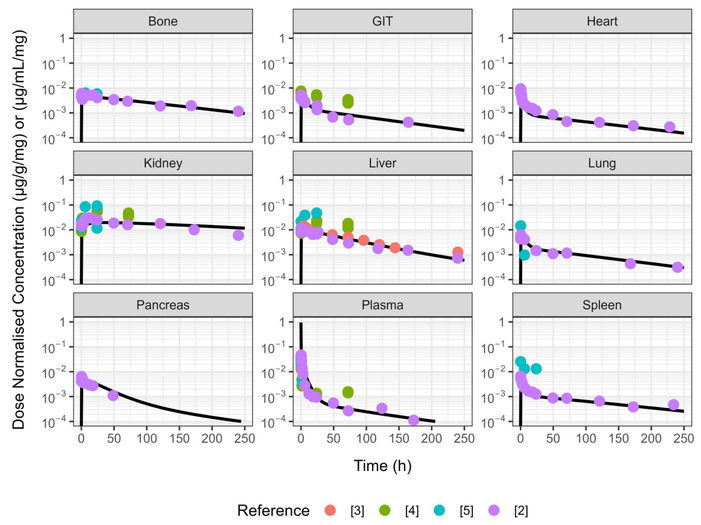

Figure 3: Model predicted tissue concentration-time profiles (solid black line) versus dose-normalised tissue concentration from different rats studies of non-conjugated ASO. Data from [2] was used for training whereas the rest of the data were for validation only.

Non-Conjugated ASO – Mice – IV

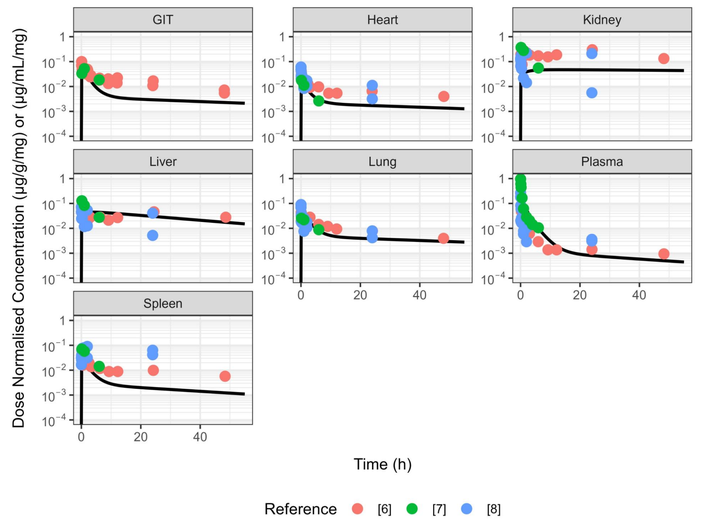

Figure 4: Model predicted tissue concentration-time profiles (solid black line) versus dose-normalised tissue concentration from different mice studies of non-conjugated ASO. None of the data were used to train the model.

GN3-Conjugated Oligos – Mice – SC

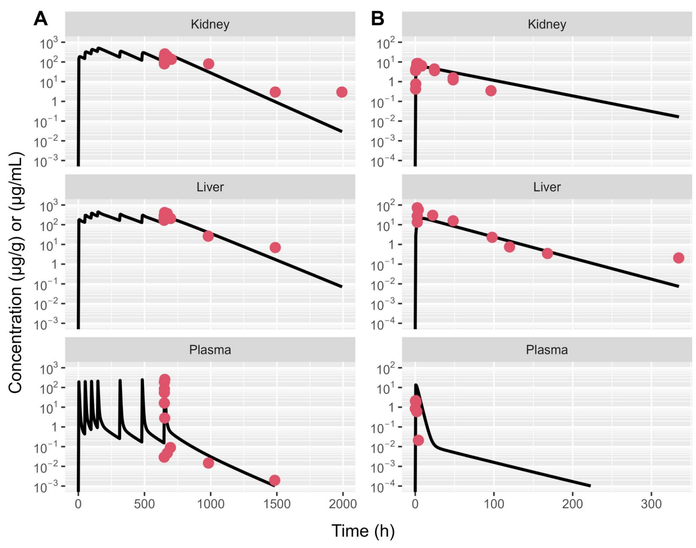

Figure 5: Model predicted tissue concentration-time profiles (solid black line) versus dose-normalised tissue concentration of GN3-conjugated ASO (**A**)[10] and GN3-conjugated siRNA (**B**)[11]. None of the data were used to train the model's system parameters.

References

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