A Physiologically-Based Pharmacokinetic and Pharmacodynamic Model of Liraglutide

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BACKGROUND

Liraglutide, known commercially as Victoza(R), is a Glucagon-Like Peptide 1 (GLP-1) agonist used in the treatment of type 2 diabetes and obesity. The objective of this study is to develop a physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model of liraglutide. Through this study, the aim is to develop a better understanding of liraglutide pharmacology and improve personalized medicine approaches.

METHODS

Over 200 articles on liraglutide pharmacology were reviewed for manual data curation into the PK-DB–of them, of which 38 are being used to build the model. The data is now being used to run PBPK model simulations that will provide information on liraglutide behaviour in the various body compartments.

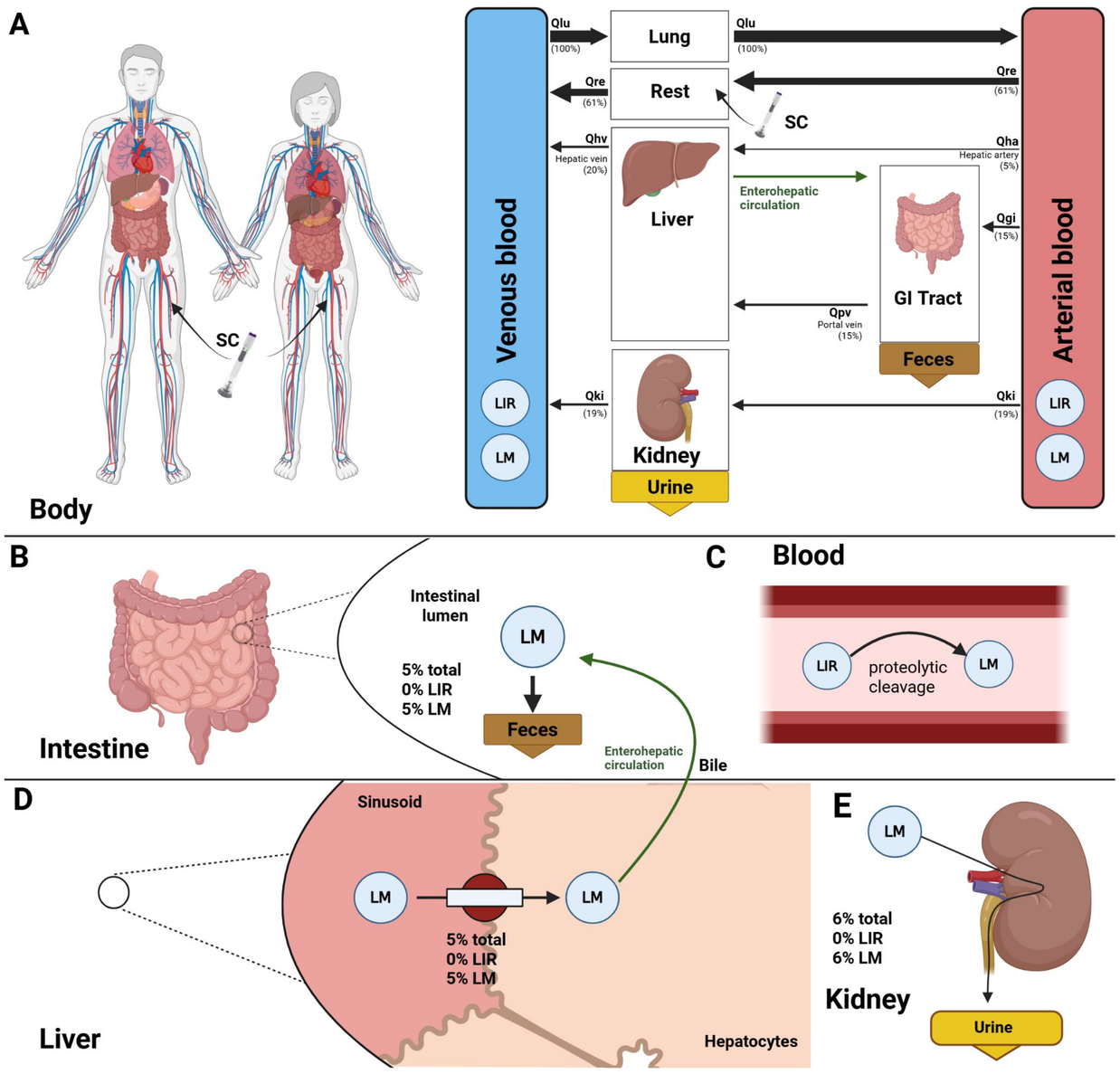

Figure 1. Physiologically-based pharmacokinetic (PBPK) model of liraglutide. (A) The whole body model. It incorporates subcutaneous administration of liraglutide, and its distribution into the circulatory system and various organs. **(B)** The intestine model, where dissolution and absorption of liraglutide occurs. **(C)** The blood model, where liraglutide is metabolized from the parent drug into two minor metabolites via proteolytic cleavage. **(D)** The liver model, where 5% of liraglutide metabolites are processed to the feces. **(E)** The kidney model, where 6% of liraglutide metabolites are excreted via the urine. The parent drug is not excreted.

Identifier	Data		Data Curation					Health					Pharmacokinetics				Pharmacodynamics							
study	pk	pd	docs	repo	upload	simulation	fitting	healthy	diabetes	overweight	renal	hepatic	plasma/serum liraglutide	urine	feces	bile liraglutide	bodyweight	HbA1c	glucose	insulin	glucagon	c-peptide	blood pressure/CV issues	gastric emptying
Agerso2002	☑	☑	☑	☑	☑	☑	☐	☑	-	-	-	-	☑	-	-	-	-	-	☑	☑	-	-	-	-
Buse2009	☐	☑	☑	☐	☐	☐	☐	-	☑	-	-	-	☑	-	-	-	☑	☑	☑	☑	-	-	☑	-
Damholt2006	☑	☑	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Feng2023	☑	☐	☑	☐	☑	☐	☐	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Flint2010	☑	☑	☑	☑	☑	☑	☑	☑	-	-	-	☑	☑	-	-	-	-	-	-	-	-	-	-	-
Idorn2016	☑	☐	☑	☑	☑	☑	☐	-	☐	-	☑	-	☑	-	-	-	-	-	-	-	-	-	-	-
Jacobsen2009	☑	☐	☑	☑	☑	☑	☑	-	-	-	☑	-	☑	-	-	-	-	-	-	-	-	-	-	-
Jiang2011	☑	☑	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Kapitza2011a	☑	☑	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Liu2023	☑	☐	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Mader2016	☑	☐	☑	☑	☑	☑	☑	-	☑	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Mai2020	☑	☐	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Xu2023	☑	☑	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-
Zhou2022	☑	☐	☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-

Figure 2. Overview of liraglutide studies currently in the PK-DB. Data was collected from studies on PubMed and PKPDAI and manually curated. Data of interest included drug administration route and formulation, subject parameters (e.g. sex, weight, BMI, health state), pharmacokinetic outcomes (e.g. concentration-time data), and pharmacodynamic outcomes (e.g. weight loss, glycated hemoglobin, and gastric emptying). Model building, parameter estimation, and validation are primarily based on concentration time course data.

RESULTS

Data simulations include studies on hepatically and renally impaired populations, groups that received multiple doses, and groups that were given market liraglutide and test formulations. With some preliminary parameter optimization, the PBPK model was able to predict results congruent with the original study data.

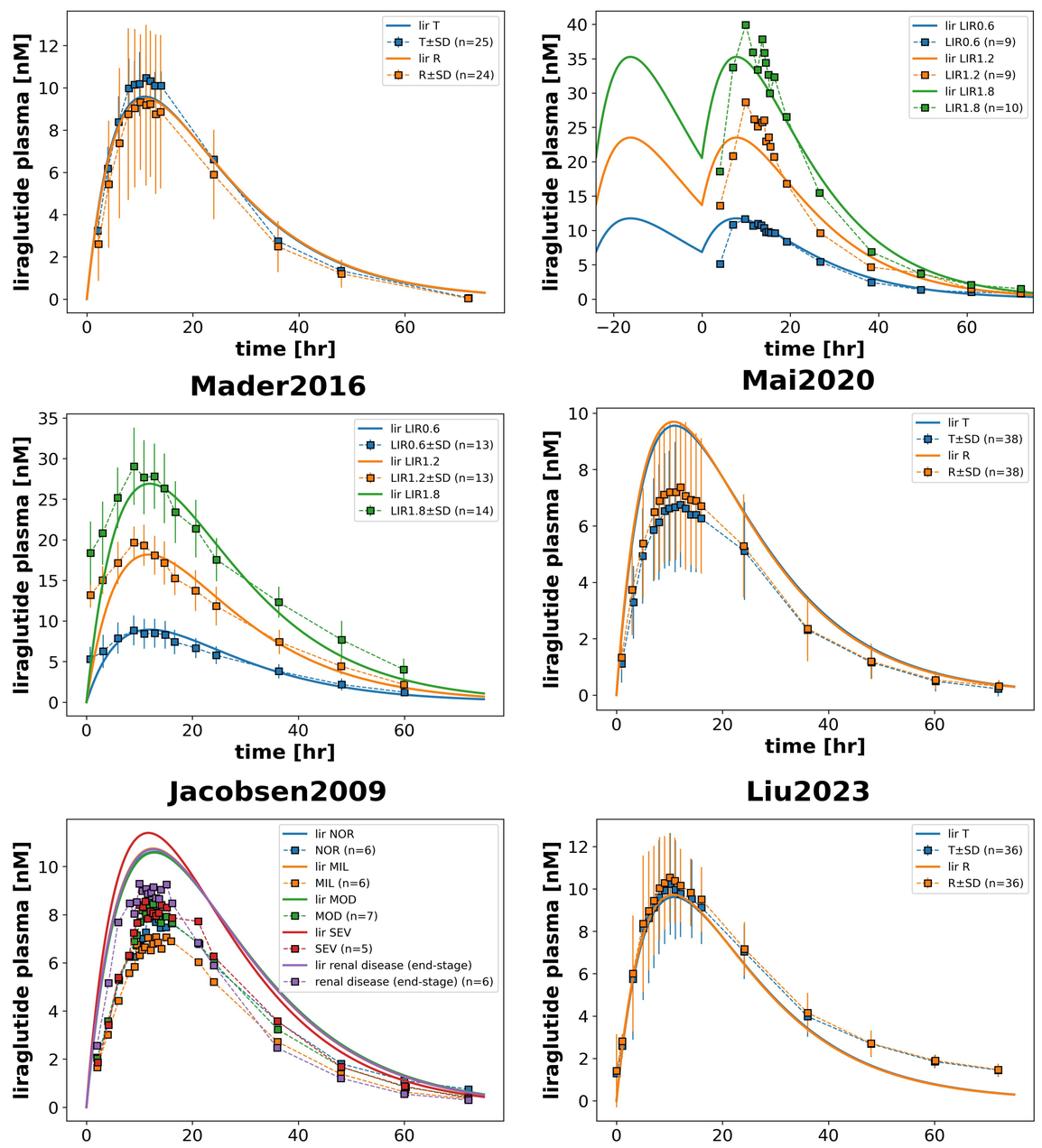

Figure 3. Model predictions. Example studies that include data from the original paper (dotted lines) and predictions by the PBPK model (solid lines) after preliminary parameter optimization.

FUTURE DIRECTIONS

Currently, we are developing a pharmacodynamic model of liraglutide. In particular, as one of six approved pharmacotherapies for obesity, developing a model of the weight loss effects of liraglutide is the next goal. This stage will include using ordinary differential equations to model liraglutide weight loss mechanisms, and implementing them into the overall PBPK/PD model.

HUMBOLDT INTERNSHIP PROGRAM (HIP) EXPERIENCE

My time so far with the Humboldt Internship Program has been incredibly educational and fulfilling, learning about computational pharmacology and being able to integrate several skills and fields in one project. I would like to thank Dr. König for his leadership and patience, as well as the teams at Humboldt University and University of Toronto for their support. I would also like to thank my family and friends for their confidence and support, and my fellow program participants for making the experience unforgettable.

FUNDING

IT was supported by the Humboldt Internship Program 2025, as well as the Dept. of Pharmacology and Biomedical Toxicology and Centre for International Experience at the University of Toronto. MK was supported by the BMBF within ATLAS by grant number 031L0304B and by the DFG within QuaLiPerF by grant number 436883643 and by grant number 465194077 (SPP2311, SimLivA). This work was supported by the BMBF-funded de.NBI Cloud within the German Network for Bioinformatics Infrastructure (de.NBI) (031A537B, 031A533A, 031A538A, 031A533B, 031A535A, 031A537C, 031A534A, 031A532B).