

A mechanism-based model is able to simultaneously explain the effect of rhLCAT and HDL mimetics on biomarkers of reverse cholesterol transport



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Introduction

Reverse cholesterol transport (RCT) is the process by which cholesterol is transported from the peripheral tissue to the liver for excretion from the body. RCT is mediated by high density apolipoprotein A1 (ApoA-I) containing lipoproteins (HDL). Increasing RCT has been proposed as a mechanism for the treatment of atherosclerotic plaques.

Lecithin-cholesterol acyltransferase (LCAT) is a liver derived enzyme essential for RCT. It promotes maturation of HDL particles by converting free cholesterol (FC) to cholesterol ester (CE), hereby facilitating liver uptake of CE either directly or, via transfer to low density lipoproteins (LDL) by cholesteryl ester transfer protein (CETP).

Stimulation of RCT has been demonstrated in humans following administration of ApoA-I preparations and ACP-501 (recombinant human LCAT) [1, 3, 4].

A mathematical model was developed to describe both the effects of IV administration of recombinant human Lecithin-cholesterol acyltransferase (rhLCAT) and HDL mimetics (HDLm) on biomarkers of reverse cholesterol transport (RCT) in humans.

Objective

Develop a mathematical model that describes the effect of rhLCAT and HDL mimetics on biomarkers in humans.

Methods

- For the ACP-501, HDL-C, CE and ApoA-I data was available.
- It was assumed that total HDL-C = HDL-FC + HDL-CE and total CE = HDL-CE + apoB-CE (Fig.1)



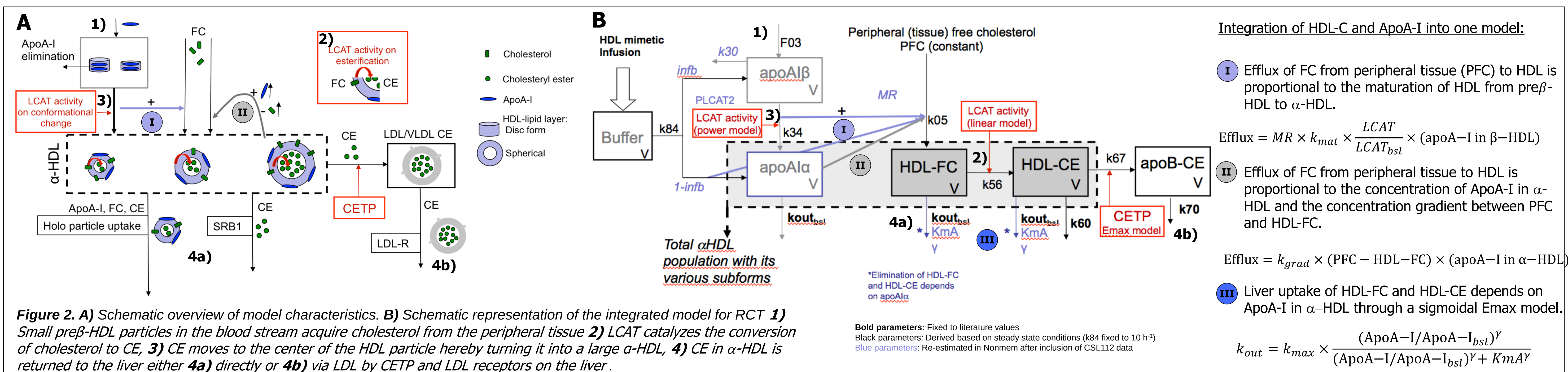
Figure 1: Relationship between the observed cholesterol endpoints.

- PK models were developed for ACP-501 and HDLm, and the estimated PK parameters fixed in the combined model.
- A literature study was performed to identify the important pathways and reactions describing RCT and obtain system specific parameter values.
- A PD model was first developed for ACP-501, and hereafter the model was updated to describe the effect of ApoA-I on RCT. Finally, the model was fitted simultaneously to the PD data after infusion of ACP-501 and ApoA-I.
- The model was evaluated using and was externally qualified using two independent clinical studies of HDL mimetics [5, 6].

Model assumptions

- The input of ApoA-I (in preBeta form) reflects its synthesis and is assumed constant. Recycling of ApoA-I lead by remodelling of HDL particles after elimination was not considered. In the model input of ApoA-I is the rate limiting step in the RCT process during high doses of rhLCAT infusion.
- Free cholesterol in tissue is assumed to be in abundance as compared to free cholesterol in plasma and therefore the free cholesterol concentration in tissue is fixed to a constant value.
- It is assumed that the efflux of free cholesterol can be described by two processes (Fig. 2).
- One process dependent on the maturation of HDL
- One process dependent on the concentration of ApoA-I in α -HDL and the concentration of HDL-FC as compared to the (constant) concentration of free cholesterol in tissue.
- The rates of elimination for HDL-CE, HDL-FC and apoB-CE are fixed to literature values [7].
- The elimination of HDL-C (HDL-CE and HDL-FC) is assumed to increase with an increase from baseline in total ApoA-I.
- It is assumed that the transport of CE from HDL to apoB (LDL/VLDL) is dependent of the HDL-CE concentration and can be described by an Emax model.
- LDL/VLDL were not considered separately, but considered as apoB.

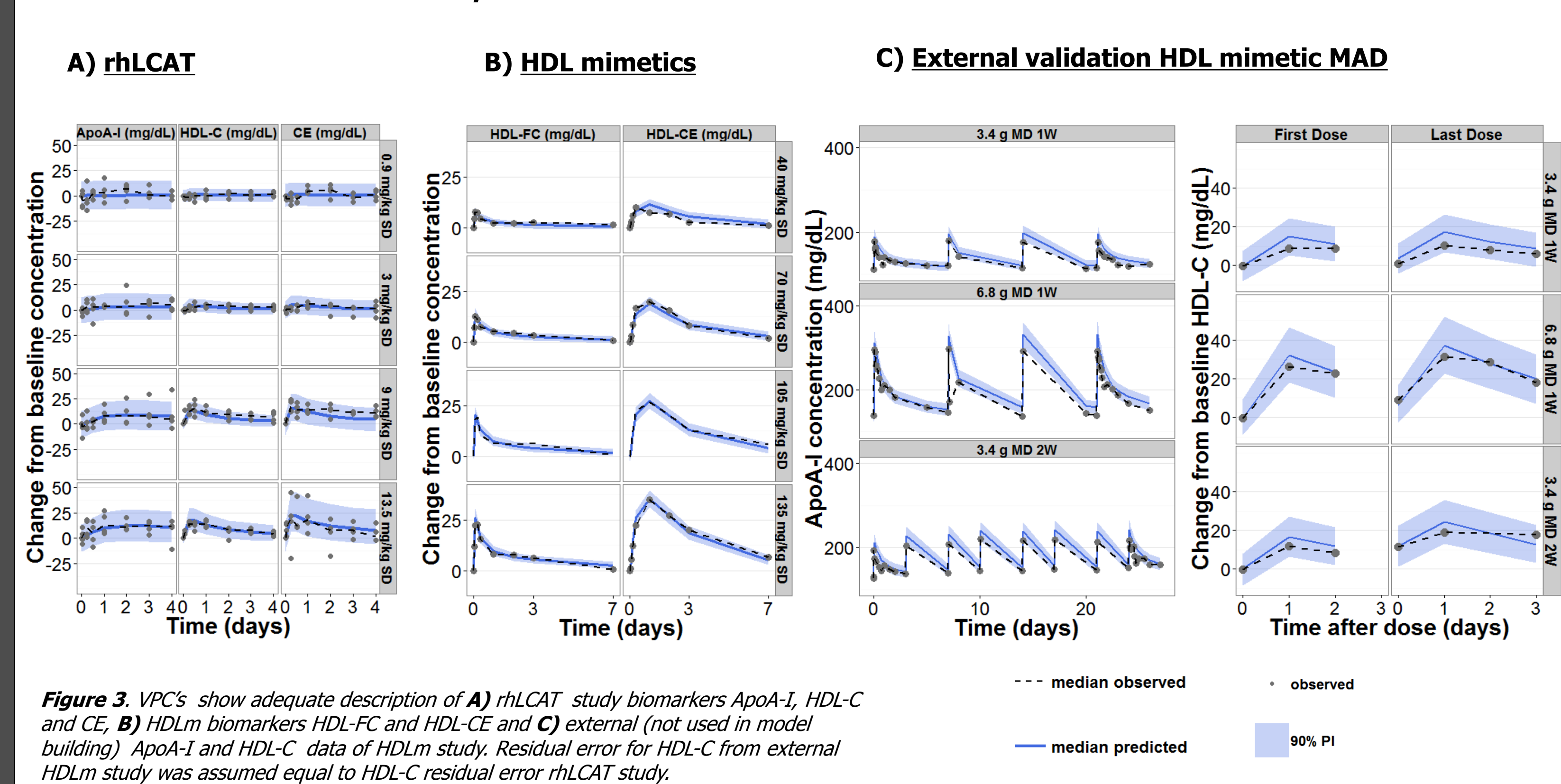
Model



Results

- Although stimulation of RCT by HDL mimetics and rhLCAT are related to different mechanisms of action, the developed eight compartment mechanistic model was able to adequately describe both the observed plasma rhLCAT concentrations and the time-course of relevant biomarkers, including the fraction of esterified and unesterified cholesterol within HDL particles.
- Both internal and external model validation using VPC showed adequate model fit and good predictive performance. HDL-C AUC showed high correlation with the amount of cholesterol movement from the peripheral tissue and can be used to compare the effects of HDL mimetics with rhLCAT on RCT.

Visual predictive checks: internal and external model validation



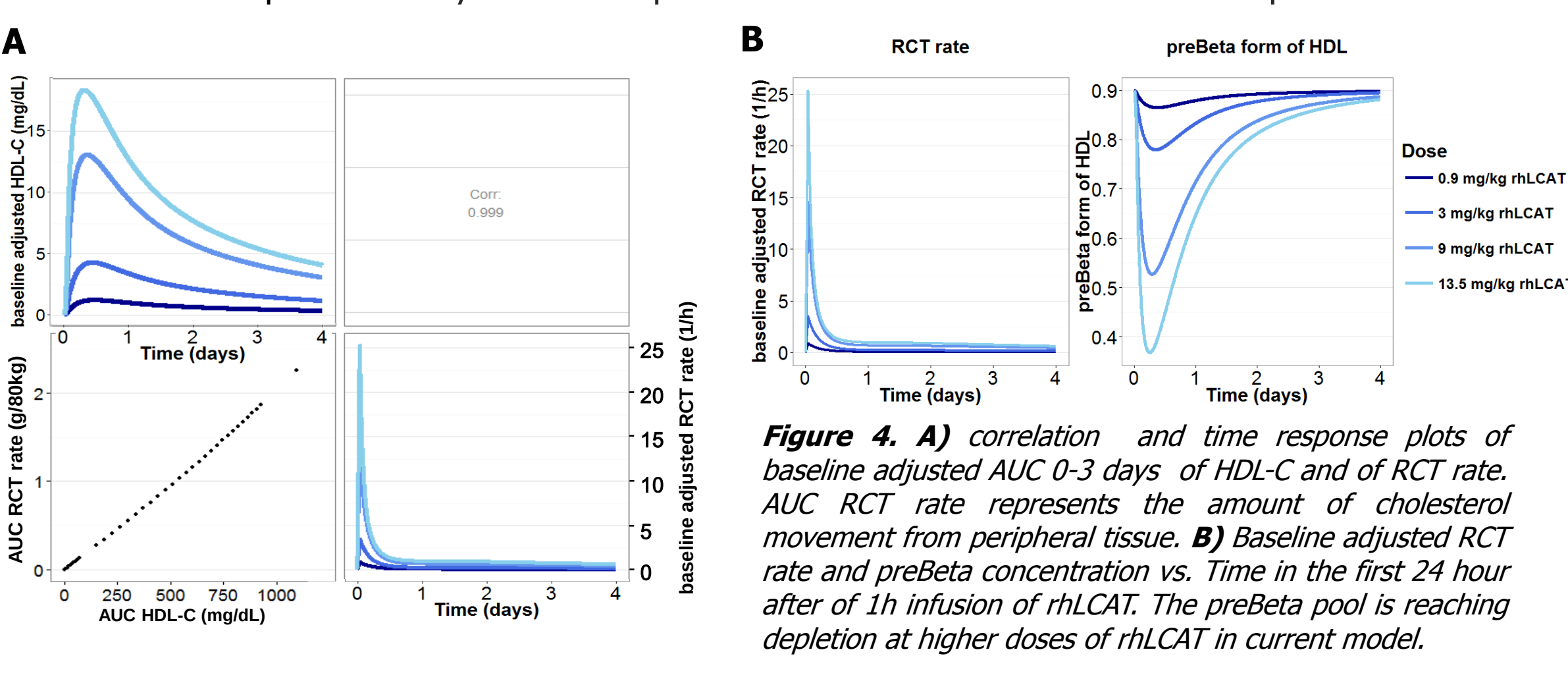
Effects of rhLCAT and HDLm on RCT

Effect of rhLCAT on RCT:

- A power model describes the effect of LCAT on esterification of FC to CE in HDL
- Esterification = $k_{est} \times LCAT - HDL-FC$
- LCAT catalyzes the maturation of HDL from pre β -HDL to α -HDL through a linear model
- Maturation = $k_{mat} \times LCAT^p \times (apoA-I \text{ in } \beta-HDL)$

Effect of apoA-I on RCT:

- Infusion of apoA-I directly results in apoA-I x MR FC to be attached to a HDL particle.



Conclusions & Perspectives

- We have generated a model that describes the time-dependent dynamics of lipid biomarkers within HDL particles by integrating literature and study data from two compounds with different mechanisms of action. This is the first to integrate the effects of HDL mimetics and rhLCAT preparations on RCT and describes both the conformational change of the HDL particle from pre- β -HDL to α -HDL as well as the effect of this conformational change on the efflux of cholesterol.
- The developed model was used for rhLCAT Phase IIa dose selection.

References

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