Enhancing the Utility of Systems Pharmacology Modeling in Pharmaceutical R&D: Lessons from the Development of a PCSK9 Inhibitor Model

Karim Azer[1], Jeffrey E. Ming[1], Tu Nguyen[1], Alex Koszycki[1], Meera Varshneya[1], Ruth Abrams[1], Britta Goebel[2], Nassim Djebli[3], Poulabi Banerjee[4], Derek W. Bartlett[5], Mike Reed[5], Benedetto Piccoli[6], Sean McQuade[6], Edouard Ribes[7], Jeffrey Barrett[1]

[1]Sanofi, Bridgewater, NJ, USA; [2]Sanofi, Frankfurt am Main, Germany; [3]Sanofi, Montpellier, France; [4]Regeneron, Tarrytown, NY; [5]Rosa & Co., San Carlos, CA; [6]Rutgers University, Newark, NJ, USA; [7]Sanofi, Paris, France.

Abstract

Objectives: We describe a methodology for using a quantitative systems pharmacology (QSP) model to describe variability in response to treatment. An interactive visualization environment that facilitates QSP simulations is presented. The methodologies are illustrated using a QSP platform, designed to support development of alirocumab, an anti-PCSK9 antibody.

Methods: We highlight the biology incorporated in a QSP platform to address mechanistic scenarios of interest to PCSK9 inhibitors. A methodology has been developed for using this QSP model to perform virtual population simulations and represent variability in treatment response. This is based on flux balance analysis and control theory approaches, and was developed for translating pre-defined patient phenotypes into virtual populations. An overall framework for simulation and visualization of QSP results is presented.

Results: A QSP platform integrating peripheral and liver cholesterol metabolism, PCSK9 function, and currently available lipid-lowering therapies (statins, fibrates, and ezetimibe) is utilized to simulate effects of PCSK9 inhibition and combination therapies on lipids. A randomly generated virtual population (e.g. statin responder/non-responder) is used to simulate population response to a therapy, or how changes in a metabolite impact lipid levels, carrier proteins (e.g. ApoB), or PCSK9 levels. Finally, we present novel web-based visualization tools for interacting with QSP models and visualizing simulations of clinical scenarios.

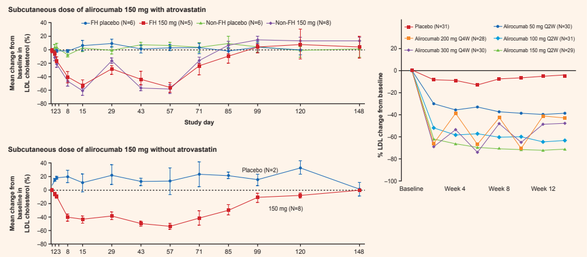
Lipid Metabolism and Plaque Dynamics

- A whole-body systems pharmacology model of lipid metabolism and atherosclerotic plaque dynamics is being developed.
  - Current quantitative lipid models do not encompass a comprehensive mechanistic examination of PCSK9 inhibition.
- Goals of systems model:
  - To gain insights into the mechanistic basis for effects of alirocumab on lipids.
  - Study effect of patient pathophysiological variability on response to a PCSK9 inhibitor.
  - Assess potential effects of PCSK9 inhibition on plaque size and composition.
  - Develop an easily usable tool for illustrating changes in lipid/plaque parameters with different scenarios (concomitant medications, regimens, patient populations).

Lipid Module Major Elements

- The systems model must capture several key elements of alirocumab activity (Figure 1):
  - Alirocumab PK.
  - Magnitude of decrease in LDL after single and multiple doses.
  - Effect of concomitant medication use (statins).
  - Dynamics of LDL change (saw-tooth).
  - Up-titration effects.
  - Magnitude of changes in other lipids.

Figure 1. Key elements of alirocumab activity

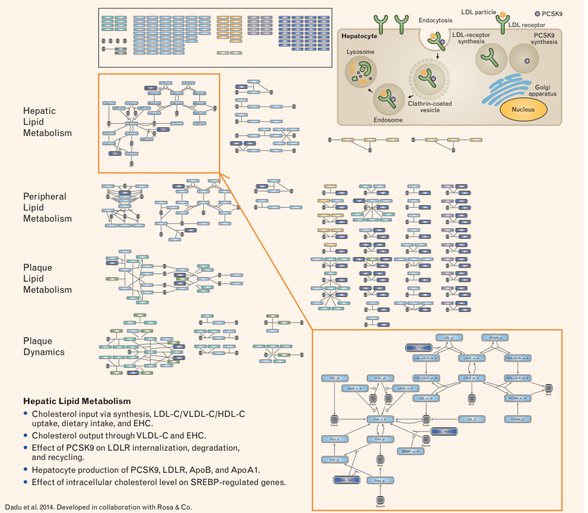


Stein et al. 2012 (left-hand panels); Mckenney et al. 2012 (right-hand panel).

PCSK9/Cholesterol Model (Figure 2)

- Hepatic Lipid Metabolism (see Figure 2 inset)
- Peripheral Lipid Metabolism:
  - VLDL-C, LDL-C, and HDL-C in circulation.
  - Peripheral cholesterol uptake through LDLR.
  - Peripheral cholesterol production.
  - Reverse cholesterol transport (RCT).
  - Effect of intracellular cholesterol level on LDLR through SREBP.

Figure 2. PCSK9/cholesterol model



Hepatic Lipid Metabolism

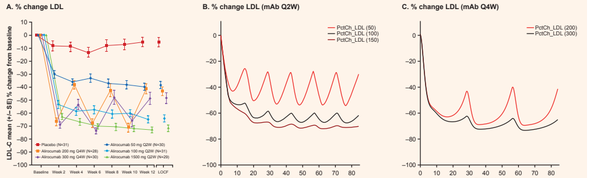
- Cholesterol input via synthesis, LDL-C/VLDL-C/HDL-C uptake, dietary intake, and EHC.
- Cholesterol output through VLDL-C and EHC.
- Effect of PCSK9 on LDLR internalization, degradation, and recycling.
- Hepatocyte production of PCSK9, LDLR, ApoB, and ApoA1.
- Effect of intracellular cholesterol level on SREBP-regulated genes.

Dadu et al. 2014. Developed in collaboration with Rosa & Co.

Alirocumab Effect on LDL-C Over Time (Figure 3)

- Phase 2 multiple-dose study in FH patients on stable statin dose (Figure 3A) (McKenney et al. 2012).
  - 50, 100, or 150 mg Q2W; or 200 or 300 mg q4W.
  - Decrease in LDL-C in a dose-dependent fashion.
  - Less fluctuation in LDL-C with Q2W dosing.
  - Good agreement between simulated and observed change in LDL (Figure 3B-C).

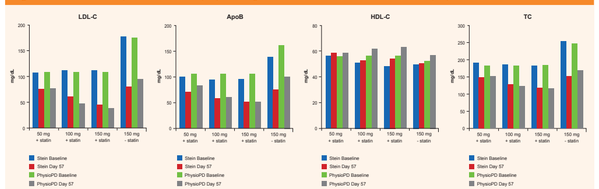
Figure 3. Alirocumab effect on LDL-C over time (calibrated to clinical study results). (A) clinical study data (McKenney et al. 2012). (B) and (C), simulated data



Alirocumab Multiple-Dose Effect on Lipid Profile (Figure 4)

- Alirocumab multiple-dose study (Stein et al. 2012):
  - Phase 1 multiple dose study in patients with hypercholesterolemia.
  - 50, 100 150 mg alirocumab (or placebo) Q4W x 3; with statin (150 mg also without statin).
  - Decrease in LDL-C in a dose-dependent fashion (150 mg ~65% decrease).
  - Patients not on statin had similar decrease in LDL-C (-57%).
- Good agreement between simulated and observed lipid parameters at Day 57 (Figure 4).

Figure 4. Alirocumab multiple-dose effect on lipid profile. Agreement between observed and simulated lipid parameters



Steps to Virtual Patient Creation and Simulation

- For a given clinical phenotype of interest (e.g. statin responders), identify biological rationale driving phenotype.
- Given the biological rationale, specific pathways and model parameters are identified that drive the phenotype of interest.
- The list of parameters and respective ranges define a space that needs to be sufficiently sampled to create a virtual population of interest.
- Upon creation of this virtual population of interest, one can simulate the effect of combination therapy in the phenotype represented by the virtual population.

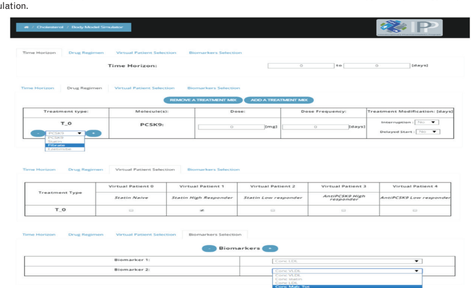


Table 1. Parameters used for virtual patient definitions

	Parameter	Description
Hepatic cholesterol homeostasis	bileacid_chol_secretion_rate_k (1/h)	Rate of bile salt entering GI
LDL receptor turnover	LDLR_en_H_degradation_rate_k (1/h)	Hepatic unbound LDLR degradation rate
	LDLR_en_P_degradation_rate_k (1/h)	Peripheral unbound LDLR degradation rate
SREBP-regulated gene targets	Chol_ic_H_production_rate_k (nmol/h)	Hepatic cholesterol synthesis
	LDLR_ic_H_production_rate_k (nmol/h)	LDLR synthesis rate, hepatocytes
	LDLR_ic_P_production_rate_k (nmol/h)	LDLR synthesis rate, peripheral
	PCSK9_ic_H_production_rate_k (nmol/h)	PCSK9 synthesis
	SREBP_PCSK9_nh	Hill coefficient for SREBP-regulated PCSK9 synthesis
	SREBP_LDLR_nh	Hill coefficient for SREBP-regulated LDLR synthesis
PCSK9 binding and clearance	PCSK9_LDLR_en_Kd (nM)	Affinity of PCSK9 for LDLR at acidic pH (endosome)
	PCSK9_LDLR_pl_Kd (nM)	Affinity of PCSK9 for LDLR at neutral pH (plasma)
	PCSK9_pl_clearance_rate_k (1/h)	PCSK9 clearance
Cholesterol exchange between HDL and VLDL/LDL	HDL_to_VLDL_exchange_rate_k (1/h)	Transfer of cholesterol from HDL to VLDL
	HDL_to_LDL_exchange_rate_k (1/h)	Transfer of cholesterol from HDL to LDL

Figure 5. Methodology for creation of virtual population

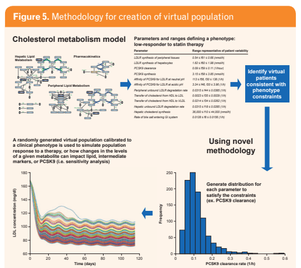


Figure 6. Simulation using virtual population

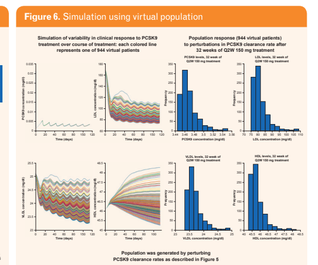
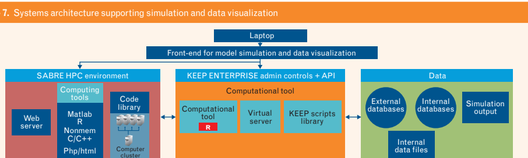


Figure 7. Systems architecture supporting simulation and data visualization



Conclusions

- A QSP framework developed to explain variability in treatment response, and to facilitate QSP simulation capabilities was applied to a PCSK9 inhibitor. This framework can be adapted across disease areas, strengthening utility of QSP modeling for linking mechanisms to endpoints, addressing mechanistic questions pertinent to drug development, and bringing this field (McAuley et al. 2012) closer towards predictive science.

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Disclosures

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