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

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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 ezetemibe) 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 (Figure). Finally, we present novel web-based visualization tools for interacting with QSP models and visualizing simulations of clinical scenarios.

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 closer towards predictive science.

References:
**Figure: Methodology for Virtual Population creation and simulation**

**RCT transport sub-model**

**Parameters and ranges defining a phenotype**

**Rates**
- VC7SMC to HDL: $0.0017 \leq f_4 \leq 0.0857$
- CholP to HDL: $0.0017 \leq f_5 \leq 0.0857$
- CholMac to HDL: $0.0017 \leq f_6 \leq 0.0857$
- HDL to VLDL: $0.0158 \leq f_7 \leq 0.0238$
- HDL to LDL: $0.0017 \leq f_8 \leq 0.0026$
- VLDL to LDL: $0.0565 \leq f_9 \leq 0.0857$

**Identify virtual patients consistent with phenotype**

**Using novel methodology**

**Lognormal flux distributions**

- Red – $f_1$, $f_7$, $f_9$
- Blue – $f_8$

A randomly generated virtual population calibrated to a clinical phenotype is used to simulate population response to a therapy, or how changes in the levels of a given metabolite can impact lipid, carrier proteins, or PCSK9 (i.e., sensitivity analysis).