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Biosketch

Scott Q Siler, Ph.D. is the President of DILIsym Services, Inc. Dr. Siler graduated with a Ph.D. in Nutrition from the University of California, Berkeley and worked for more than 12 years integrating physiology and mathematics with the company Entelos. As a Principal Scientist at Entelos, Dr. Siler oversaw the early development efforts of what would become the current DILIsym® model, as Entelos and the Hamner Institutes collaborated on the effort. Entelos and the Hamner Institutes subsequently agreed to dissolve their collaboration involving DILI modeling. Dr. Siler began working with the Hamner Institutes as a consultant and Co-Project Lead in 2011 and continues to serve as both co-project Lead and a technical contributor. Dr. Siler also oversaw and contributed to the development of the Metabolism PhysioLab during his time at Entelos. Moreover, he led multiple projects evaluating potential treatments for type 2 diabetes.

Abstract: Modelling drug-induced lipotoxicity

An unintended consequence of some medications is interference with the management of lipids in the liver, resulting in steatosis. In particular, de novo lipogenesis, hepatic fatty acid uptake, VLDL-triglyceride release, and hepatic fatty acid oxidation can all be affected by drugs and contribute to steatosis. The accumulation of lipids can elicit lipotoxicity, oxidative stress, and resultant hepatocyte loss. Several drugs have been reported to cause steatosis and generate liver signals during clinical trials, although it has been unclear if lipotoxicity was a driving force in the observed liver injury. DILIsym® is a predictive, mechanistic, mathematical model of drug-induced liver injury (DILI) that is being developed and maintained through the DILI-sim Initiative, a public-private partnership involving scientists in academia, industry, and the FDA. The DILIsym® model consists of various sub-models that are mathematically integrated to simulate patient response, and lipotoxicity mechanisms have been recently added. The current work utilized several components of DILIsym®, including a physiologically-based pharmacokinetic (PBPK) sub-model representing drug distribution, sub-models of mitochondrial dysfunction and lipotoxicity, hepatocyte life cycle, and liver injury biomarkers. Simulated patient populations (SimPops™) have also been created by varying key parameters consistent with experimental data. We used DILIsym® to predict steatosis and serum ALT levels observed in clinical trials for three drugs: The potent fatty acid oxidation inhibitor, Etomoxir, the microsomal transfer protein inhibitor, Juxtapid, and the apoB100 antisense oligonucleotide, Kynamro. The frequency and severity of the signals observed in the clinical trials was consistent with DILIsym® predictions. Moreover, the simulation results established a plausible mechanistic role for lipotoxicity in serum ALT elevations observed in the clinical trials of each drug. These simulation results highlight the value in utilizing simulations to predict DILI injury due to lipotoxicity for drugs in development and then identifying accompanying clinical trial protocols and patient recruitment strategies that can minimize steatosis and liver injury.