



## **DILI-SIM: A SYSTEMS MODEL OF THE LIVER ALLOWING PERTURBATIONS BY XENOBIOTICS IN MULTIPLE SPECIES**

Richard Ho

*Entelos, Inc., USA*

Drug-induced liver injury (DILI) is the leading cause of liver failure and can result in regulatory action in the United States; to assist with the identification of compounds with risk of DILI, Entelos and The Hamner Institutes are building DILI-sim, a mathematical model of liver homeostasis and perturbation, in collaboration with the FDA. DILI-sim allows examination of the mechanisms of liver impairment such as those arising from acetaminophen, isoniazid, valproic acid, and other xenobiotics. While preclinical screening usually identifies overtly hepatotoxic compounds before clinical trials, some dose-related 'intrinsic DILI' is still discovered only in humans, and some compounds elicit 'idiosyncratic DILI' – currently unpredictable hepatotoxicity often at low drug doses that can occur after weeks or months. DILI-sim represents physiology specific to human, rat, and mouse in order to explore the differences between species, address translational issues, and help focus experimental research into poorly understood mechanisms of intrinsic and idiosyncratic DILI. Changes in the physiological homeostasis of hepatocytes are represented in the DILI-sim model by interaction with xenobiotic metabolism and clearance, with hepatotoxicity predicted to arise from alterations in repair/regeneration, reactive metabolite effects, mitochondrial damage, and pro- and anti-inflammatory mediator secretion from Kupffer cells and other non-parenchymal or innate immune cells. In subsequent versions, DILI-sim will expand to include the adaptive immune system and mechanisms of cholestatic liver injury. Our goal is for the simulation capabilities provided by DILI-sim to combine with preclinical and clinical research to reduce the risk of DILI in patients worldwide.