ID 03.4

In silico modelling of crosstalk between DNA damage and oxidative stress for prediction of cellular adversity

E.J. Burgers[1]*, C.J.S. Eugenio[1], M.M. Heldring[1], R.P. Sharma[1], L.S. Wijaya[1], B. van de Water[1], J.B. Beltman[1]

[1] Division of Drug Discovery and Safety, Leiden Academic Centre for Drug Research - Leiden University, Leiden, The Netherlands
** e.j.burgers@lacdr.leidenuniv.nl*

Drug Induced Liver Injury (DILI) is a major problem for the drug development industry. Therefore, we urgently need methods that predict drug adversity with high fidelity and early in the drug development process. Computational approaches are thought to contribute to this challenge because they can make predictions and increase mechanistic understanding in a time and cost efficient way. Exposure of cells to toxic compounds activates various stress pathways and activity within these pathways is known to contribute to DILI. Therefore, computational descriptions of stress pathway activity based on experimental measurements could be a crucial step in the improvement of adversity predictions.

Genotoxic chemicals mainly cause activation of the DNA damage response (DDR), whereas other xenobiotics give rise to the oxidative stress response (OSR). Activation of these pathways can also occur via pathway crosstalk. Currently available computational models describe these individual stress pathways well with ordinary differential equation models, yet do not include crosstalk. Therefore, we here investigate the effect of connecting OSR and DDR models via multiple previously reported modes of crosstalk. Specifically, with our models we investigate the stimulating effect of NRF2 on MDM2 and NQO1 on P53, and the inhibitory effect of phosphorylated P53 on SRXN1 and of SRXN1 on BTG2. We compare the behaviour of the coupled model with previously published data of HepG2 GFP-reporter cells exposed for 60 hours to various concentrations of Diethyl Maleate and Etoposide, respectively OSR and DDR inducers. Model simulations show that the mentioned interactions can indeed qualitatively explain the characteristic dynamics of OSR and DDR proteins, and we are investigating which interactions are required to explain the dynamics also quantitatively. In the future, we aim to couple the model further to models describing the pharmacokinetics and cellular adversity, thereby rendering a novel approach for DILI prediction.

Keywords:
DNA damage response; Oxidative Stress response; computational modelling; Drug Induced Liver Injury;