

A High Content Screening Platform for the Accurate Prediction of Nephrotoxicity

Authors : Sijing Xiong, Ran Su, Lit-Hsin Loo, Daniele Zink

Abstract : The kidney is a major target for toxic effects of drugs, industrial and environmental chemicals and other compounds. Typically, nephrotoxicity is detected late during drug development, and regulatory animal models could not solve this problem. Validated or accepted in silico or in vitro methods for the prediction of nephrotoxicity are not available. We have established the first and currently only pre-validated in vitro models for the accurate prediction of nephrotoxicity in humans and the first predictive platforms based on renal cells derived from human pluripotent stem cells. In order to further improve the efficiency of our predictive models, we recently developed a high content screening (HCS) platform. This platform employed automated imaging in combination with automated quantitative phenotypic profiling and machine learning methods. 129 image-based phenotypic features were analyzed with respect to their predictive performance in combination with 44 compounds with different chemical structures that included drugs, environmental and industrial chemicals and herbal and fungal compounds. The nephrotoxicity of these compounds in humans is well characterized. A combination of chromatin and cytoskeletal features resulted in high predictivity with respect to nephrotoxicity in humans. Test balanced accuracies of 82% or 89% were obtained with human primary or immortalized renal proximal tubular cells, respectively. Furthermore, our results revealed that a DNA damage response is commonly induced by different PTC-toxicants with diverse chemical structures and injury mechanisms. Together, the results show that the automated HCS platform allows efficient and accurate nephrotoxicity prediction for compounds with diverse chemical structures.

Keywords : high content screening, in vitro models, nephrotoxicity, toxicity prediction

Conference Title : ICT 2016 : International Conference on Toxicology

Conference Location : London, United Kingdom

Conference Dates : February 25-26, 2016