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Integration of omic technologies and biokinetics for the development of improved human based test systems for nephrotoxicty

Paul Jennings
Innsbruck Medical University, Austria

Failure of compounds late in the clinical phase of drug testing due to the development of renal side effects is significant. It is believed that this is mostly due to the poor predictivity of current animal based models. Thus there is an urgent need to development of human *in vitro* systems that are better predictive for renal side effects. In the 7th framework project, Predict-IV, we have attempted to achieve this by the combination of a stable human proximal tubular line, with high content technologies and biokinetics. RPTEC/TERT1 cells were chosen as they are non-transformed, well differentiated and extremely stable and are cultured routinely in hormonally defined serum-free culture medium. Cells were exposed to 8 pharmaceutical nephrotoxins at 2 concentrations for 14 days in a repeat dose exposure regimen. Both functional and transcriptomic (TCX) analysis were conducted for all compounds. Proteomics (PTX), metabolomics (MTX) and *in vitro* kinetics were conducted for cisplatin, cyclosporine A (CsA) and adefovir dipivoxil. TCX proved to be an excellent tool for the identification of chemical induced stress response pathways e.g., unfolded stress response, metal stress response, HIF1 alpha mediated stress response and the Nrf2 oxidative stress response. MTX analysis was particularly useful in underpinning metabolic alterations of the Nrf2 induced oxidative stress and ATF4 pathway. PTX not only complimented TCX, but could provide additionally information such as drug protein binding, as shown for CsA-cyclophilin B interactions. Kinetic profiling of drug concentrations was crucial in the final interpretation of the data. This work demonstrates that integrated omic strategies are extremely useful in determining the biological effects of chemical stressors and will be of critical importance for the successful development of more predictive human *in vitro* models and biomarkers for drug safety assessment.

Biography

Paul Jennings was born and raised in Dublin Ireland and graduated with an honour in Bachelor of Science degree in 1996 from University College Dublin. His Ph.D. thesis was conducted at the Dept. of Pharmacology, Dublin, entitled "Novel approaches for *in vitro* nephrotoxicity testing". He completed his habilitation (Venia Docendi) in 2009 at the Physiology Dept. of the Innsbruck Medical University, entitled "Epithelial Cell Cultures as tools to study human disease and the adverse effects of pharmaceuticals and chemicals". He has 17 years experience in the field of *in vitro* methodologies and cell biology, and has over 40 publications in the field. He is an integral member of several key European Projects which aim to change current safety assessment regimes including, Predict-IV, SEURAT-1, and STEMBANCC.

paul.jennings@i-med.ac.at