CG has more than twenty years of experience of molecular bioanalysis, working with cell culture and in vivo models. He leads the molecular and cellular toxicology group within the MRC Centre for Drug Safety Science (CDSS), a leading UK centre based at the University of Liverpool, with a critical mass of scientists studying mechanisms of adverse reactions to drugs, and which is the coordinator of the Mechanism-based Improved Prediction of Drug-Induced Liver Injury (MIP-DILI) IMI programme. He is plays a leading role in the new IMI project TransQST, which will develop quantitative systems toxicology models to improve our understanding of adverse drug reactions. He is also leading the liver project in the UK Regenerative Medicine Safety platform, developing innovative methods for the assessment of the safety of stem cells and regenerative therapies, including cell labelling using nanoparticles and cell tracking. He is programme director of the Pharmacology degree programme at Liverpool, and runs Masters teaching programmes on Innovative methods of in vitro safety assessment and Safety of regenerative medicine therapies in the European Safescimet training programme.

Abstract:
Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury

It is clear that current preclinical testing paradigms, based on in vitro models, are poorly predictive of the potential of a new drug candidate to cause DILI. Furthermore, it is estimated that between 38% and 51% of compounds showing liver injury in man do not show similar effects in animal studies. There is therefore a clear need for improved model systems that more faithfully reflect human hazard. In particular, new in vitro test systems
based on human cells or tissues are required, which reflect the *in vivo* situation with respect to drug metabolism, cellular adaptation and toxicological response. Currently available human systems, such as primary cells and immortalised cell lines, suffer from a variety of limitations with respect to the prediction of the multiple forms of DILI that occur in the clinic. Primary cells, particularly fresh ones, are difficult to source and show a variable and unstable phenotype. Cell lines, whilst providing a stable and reproducible platform, are generally poorly reflective of the *in vivo* phenotype, particularly with respect to drug metabolism. Single cell models, whether primary or immortalised, lack the intricacies of a multicellular environment. Thus, it is essential to define what purpose a particular test system is fit for. In the MIP-DILI consortium we have therefore determined the physiological and pharmacological phenotype of single cell systems prior to evaluation of the toxicological phenotype using a series of training compounds. The same approach is being used to inform the development of more complex 3-D models in an attempt to recapitulate multi-step and multi-cellular forms of human DILI. What is now required is a concerted multidisciplinary research effort, embracing academic, industry and regulatory partners, to deliver a portfolio of robust and well characterised predictive platforms that are fit for purpose according to well-defined criteria. A roadmap is being developed based on the integration of established and emerging test systems, whereby the complexity of the model increases from single cell 2D to multi cell 3D systems that are used in a logical fashion to assess DILI liabilities of new drugs before they are given to man.

345 words