Conference Report

Speed and Safety in Drug Discovery: A Brief Conference Report

Safer Medicines Trust, a UK charity that focuses on the scientific evaluation of animal experiments by pressing for an evidence-based evaluation of their impact on human health, hosted a one-day meeting at the Royal Society, London, UK, on 26 November 2008.

The meeting was formally introduced by Dr Margaret Clotworthy of Safer Medicines Trust. This was followed by presentations given by 11 speakers from the UK, USA and Europe. A number of technologies were described that, if used together, may have the capacity to dramatically reduce our reliance on animal models that are often inadequate predictors of human drug effects and drug safety. At the same time, many of these technologies hold the potential to streamline drug development, improve clinical management, and positively inform the drug development process.

The first lecture of the day was given by Dr Robert Coleman, who has over 40 years of expertise in drug discovery and is now a consultant. This lecture served as a poignant reminder of the fact that drug discovery and development has become more challenging since the mid 1960s, because of increasing market competition and the more evident limitations of animal models. Dr Coleman made a call for pharmaceutical companies to drive the development of approaches that are human-focused. This, of course, requires safe and ethical clinical research, but also an improved supply of human tissues that can only be made possible by an infrastructure that affords researchers greater access to tissues to be used under the remit of the UK *Human Tissue Act 2004.*

Dr Katya Tsaioun (Apredica, Watertown, MA, USA) gave a general overview of how time-to-clinic can be, and is being, shortened by the timely and appropriate use of *in vitro* cell-based studies. Focusing on the fact that 40% of drugs fail because of problems with ADME that are not predicted by animal studies, a number of methods which could be used most effectively during the drug development process were outlined, including the use of Caco-2 cells to predict oral bioavailability, HERG expressing cells to examine potential problems with cardiotoxicity, and the GreenScreen™ for genotoxicity.

Dr Paul Newbold (AstraZeneca, UK) further developed this line of thinking by focusing on the interface between preclinical and clinical studies. Such a multi-disciplinary approach can assist with the translation of information from preclinical studies, to improve decision-making processes, such as whether a novel therapeutic candidate should be progressed to the clinic and how clinical trials should be designed and conducted. Dr Newbold's research is focused on respiratory diseases where specific phenotypes are displayed by patients. Hence, it is clear that representing all the possible phenotypes with animal models may create an overwhelming burden. Nevertheless, information about the efficacy and safety of a therapeutic candidate in different patient groups can help to ensure the recruitment of a representative patient population to clinical trials. Furthermore, by stratifying such studies according to patient phenotype, the statistical quality of clinical data could be vastly improved. Among the other areas touched upon in Dr Newbold's lecture were the use of human tissues to understand disease pathology, mathematical models to make predictions and fill knowledge gaps, chip-based systems to examine drug action, and human studies such as microdialysis, vacuum skin chamber studies and brain imaging. These core technologies were prominent during discussions throughout the day.

Professor Chris Hillier (Glasgow Caledonian University, Glasgow, UK), and co-founder of Biopta Ltd (Glasgow), focused on the first of these technologies — the use of human tissues — by reference to his work in the area of cardiovascular disease and vascular permeability to novel therapeutic modalities such as RNAi molecules. Blood vessels are possibly the most readily available tissue for research. Large blood vessels are subject to artherosclerosis and lose their vascular plasticity. However, it is the smaller blood vessels that are ubiquitously found through every tissue and are subject to the influences of nervous stimulation and small biogenic molecules such as nitrous oxide. Within each tissue, these vessels have different properties, such that isolating and studying the effect of drugs and disease on their function can be highly informative about whether a drug has specificity of action or can pass through the vessel wall into the target tissue. The fact that these very small vessels can be isolated with no lasting consequences to a donor, means that it is possible to look at vascular effects over long periods of time, before and after treatment, on vessels that accurately represent how a patient will respond to therapy. One example where this has been possible is in the assessment of vascular protection afforded by hormone replacement therapy.[1] Indeed, a minia-

turised well assay can help to screen for desirable and undesirable drug effects.

Gregory Baxter, founder of the Hurel Corporation (Beverley Hills, CA, USA),[2] examined how an assay platform composed of chambers that house human tissues or cells representative of different organs, can be used to create a simplified model of complex biological interactions within the body. Dr Baxter works closely with Michael Shuler — the man behind the animal-on-a-chip microfluidics devices. One vital aspect of the assay is ensuring that the chamber geometries closely mimic tissue size ratio in the body, in order that factors such as drug residence times, circulatory transit times, shear stresses and cell-to-blood volume most-closely resemble the *in vivo* situation. The benefits of such a system were illustrated by reference to Tegafur metabolism. Tegafur is used for the treatment of certain cancers such as bowel cancer. It is a prodrug that is converted to an active ingredient, 5-fluorouracil, in the liver. With a flow chamber method, however, it was found that there are possibly additional active metabolites that have not been detected by traditional cell-based assays. As illustrated for Tegafur, Sulindac and Tylenol, the Hurel assay also appears to be more sensitive than the traditional cell-based assay with regard to detecting possible adverse effects. Indeed, for Dantrolene, a drug used to alleviate muscle spasms, tightening and cramping in patients such as those suffering from multiple sclerosis, the Hurel assay was able to predict that the drug is hepatotoxic, even though this was not predicted in the traditional cell-based assay. Hence, it was suggested that the main use of such a system would be during the streamlining of candidates before *in vivo* studies.

Dr Baxter's Hurel system is capable of supporting primary liver hepatocytes and the HepG2-C3A liver cell line for a number of days. This is a vast improvement on how many of these cells can be maintained in cell culture flasks without a continuous renewal of cell culture medium. Professor Johannes Doehmer (consultant for Bioproof AG, Munich, Germany), looked at a battery of cell lines genetically-engineered to express human-specific variants of key cytochrome P450 enzymes. These cell lines in stand-alone assays allow the effects of xenobiotics on cell function and survival to be monitored alongside studies that examine the possible implications of people possessing certain variants of key metabolic enzymes. As such, these engineered cells could assist with the selection of representative volunteers for stratified clinical trials, as well as with the design of new treatments.[3] The Hurel system also represents a step-up from simple, single cell type *in vitro* systems towards a more-integrated, quasi-systems biology approach which is more capable of capturing information of relevance to the *in vivo* situation. One issue that must be addressed is how the data from such multi-parametric assay systems can be assembled and interpreted. Dr Quin Wills (SimuGen Ltd, Cambridge, UK) described how mathematical modelling, as opposed to bioinformatics, could help to streamline testing strategies, especially those reliant on data from toxicogenomics analysis. Another mathematical model described by Professor Zvia Agur (Institute of Medical Biomathematics, Optimata Ltd, Ramat Gan, Israel), is able to predict the effects of docetaxel, a cancer chemotherapeutic, on different patients suffering from mesenchymal chondrosarcoma. Based on predicting both efficacy and toxicity, this virtual system can help to tailor dosage regimes to the individual patient with a greater than 80% reliability, and has been shown to increase the clinical prognosis of specific patients.[4]

Animals are often poor models of the effects of vaccines and drugs on the immune system, because of inherent differences between the immune systems of humans and other species. Furthermore, human cell-based models often fail to capture both the complexity and variety of immune responses that may be seen in human individuals. Professor Russell Higbee (VaxDesign, Orlando, FL, USA) described a high-throughput assay, in which different components of the human immune system are sequentially incorporated with immune cells from different human donors, in order to capture innate and adaptive immune responses as well as inflammatory mediation. Because no mixing of cells from individual donors is necessary, responses representative of entire human populations can be captured. This model is capable of assisting with the selection of vaccine–adjuvant combinations, modelling immunoprotection afforded as a result of IgM to IgG class switching, and assessing the effects of biologicals. The system has also already been used to model diseases such as tuberculosis.[5]

The final two speakers focused on the most desirable model of human disease and physiology — humans. The first speaker, Professor Markus Mueller (Vienna Medical University, Vienna, Austria) described how microdialysis can be used to study drug distribution in humans. Microdialysis can also be used to develop dosage regimes in the clinic, based on pharmacokinetic data from patients exposed to microdoses — doses that are well below the pharmacologically active dose, which can be very different to those from healthy volunteers. However, whilst microdosing is a useful and minimally-invasive technique, it may have its limitations, including the fact that local effects may not be indicative of systemic, longer-range, or hormetic effects. A second

approach[6] — META ID™ — described by Dr Mark Seymour, (Xceleron Ltd, York, UK), may go some way toward resolving these problems, in that local sampling is not necessary to acquire biofluids. Instead, the method described by Dr Seymour requires that a very small amount of radioactive tracer-labelled drug is given, either by the intended route of delivery or intravenously, alongside a larger dose of the non-radioactive drug given orally. The levels of the radioactive tracer in biofluids and excreta, determined by using liquid chromatography and accelerator mass spectrometry, can then be used to estimate pharmacokinetic parameters.

Dr Ian Gibson MP, in his remarks on the meeting, made an important reference to the rising costs of healthcare in the UK. He envisaged that many of the technologies described at this meeting could have a positive impact in this respect, by making healthcare more affordable. Such approaches clearly hold the potential to improve the safety of medicines, enable individualised clinical management strategies, and reduce the demand for animal-based studies.

The conference proceedings for this meeting will be published as a supplement to the June issue of *ATLA*.

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References

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