Better science for safer medicines: the human imperative

Kathy Archibald[1], Katya Tsaioun[2], J. Gerry Kenna[1] and Pandora Pound[1]

[1]Safer Medicines Trust, Kingsbridge TQ7 9AX, UK
[2]Evidence-Based Toxicology Collaboration, John Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA
Corresponding author: Pandora Pound. Email: pandora@safermedicines.org

Introduction

Early in 2018, the UK's BioIndustry Association and the Medicines Discovery Catapult[1] published a remarkable report calling for the process of drug discovery to be 'humanised' in order to ease the productivity crisis in pharmaceutical research. The mission of the Medicines Discovery Catapult is to help UK biotech companies transform so that the UK can maintain its position as one of the prime locations for developing new medicines. The UK industry leaders interviewed for the report stated that the key problem with the current system was the poor ability of existing pre-clinical models to reliably predict safety and efficacy in humans. Human drug-induced toxicities that are poorly predicted by animal safety studies (i.e. animal/human concordance < 60%) include toxicities of the liver,[2–4] the heart,[5,6] the immune system,[2,3] the skin,[2,3] the endocrine system[2,3] and the central nervous system.[7] Poor human predictivity results in only a small proportion of drug candidates translating into treatments for humans despite having first appeared safe and effective in animal studies, with recent approval rates ranging from 13.8%[8] to 9.6%.[9] To remedy this situation, the BioIndustry Association and Medicines Discovery Catapult report identified an urgent need to 'retool' drug discovery with the many human-relevant technologies that have been developed, in order to make the early stages of research more predictive of how drugs work in humans and consequently to have better drug candidates entering human trials, leading to lower rates of attrition.

The UK government's innovation agency has also recognised the potential of human-relevant approaches for improving drug safety and efficacy.[10] Like the Medicines Discovery Catapult, it identifies pre-clinical animal studies as the problem, observes that companies and regulators are increasingly recognising the limitations of such studies and suggests that new technologies could ultimately replace animals for testing drug efficacy and safety. The agency envisions a thriving 'non-animal technology' sector in the UK, with huge market potential and opportunity for driving UK economic growth. However, while noting that the UK has world-leading research in this area as well as companies able to take advantage of new commercial opportunities, it highlights that significant investment in non-animal technologies is taking place in the US and Europe. Indeed the Netherlands, in a bold move, has declared its aim to lead the world in phasing out the use of animals in the regulatory safety testing of medicines and chemicals by a target date of 2025, regarding new technologies as having huge potential to increase research relevance and to deliver more reliable risk assessments, while maintaining existing safety levels.[11,12]

Human-relevant approaches

The new approaches creating such optimism do not consist of one-by-one replacements of specific animal tests[13] but represent a completely new, human-focused and systems-biology[14] based approach to drug discovery, incorporating a range of in vitro, in silico and human in vivo methodologies. They are driven by the need to reduce costs and increase the speed and accuracy of drug discovery, as well as by an enormous appetite for change.[15] The generation of human-induced pluripotent stem cells (iPSC) has been a significant development; as they possess the genetic background of the individual they can be used to create disease- or patient-specific models, such as 'organoids'. These are simplified in vitro versions of organs, capable of modelling some specific function of that organ.[16] In the field of cystic fibrosis for example, patient-derived intestinal organoids have been used to select an effective therapy, which was then used to successfully treat the patient.[17] Human-induced pluripotent stem cells are anticipated to transform biological research and healthcare,[18] with stem cell banks being established worldwide and the global market for human-induced pluripotent stem cells technology estimated to reach $2.9 billion in 2018.[10]

The creation of micro-physiological systems, known as 'organs-on-chips', is another revolutionary development. Organs-on-chips are bio-engineered devices that mimic key aspects of the physiology and function of human organs, replicating some of the complexity of the human body environment on a microscopic scale. They are able to mimic blood, air and nutrient flow, as well as mechanical forces such as peristalsis and can be continuously monitored to obtain a profile over time. Organs-on-chips enable the study of basic biological processes, the modelling of diseases and investigation of the effects of drugs. They can potentially identify safety and efficacy issues earlier and more reliably in the drug development process, enabling the design and selection of drug candidates that are more likely to succeed in human clinical trials. The US is making significant investments in organ-on-chip technologies.[19]

The US government is also investing in other new technologies for drug safety screening. For its 'Tox21' initiative 10,000 chemicals are being tested using a panel of automated high-throughput human cell-based screening assays. Incorporating data from these assays into computational models can result in models that greatly outperform the predictive ability of models built with animal toxicity data.[20] The global market for cell-based assays in drug discovery, safety and toxicology is expected to reach US$21 billion in 2018.[10] Toxicology is also adopting a new conceptual framework for risk assessment known as Adverse Outcome Pathways. These describe in detail the complex chain of biological processes that occur from the moment a chemical enters the body and enable a more comprehensive understanding of how toxicity is expressed. This new systems biology approach harnesses the power of mathematical modelling to make predictions, for example physiologically based pharmacokinetic mathematical models are used to predict the absorption, distribution, metabolism and excretion of substances. Additionally, human-focused models (such as the cystic fibrosis organoids mentioned above) allow 'surrogate' trials to be conducted before advancing to actual clinical trials, providing a vital, physiologically relevant bridge between pre-clinical investigations and clinical outcomes and bringing the possibility of personalised medicine closer.

Emerging evidence of effectiveness

Many of the new technologies, such as human-induced pluripotent stem cells and cell-based assays, are gaining increasingly large scale investment because of the potential they have shown to date; nevertheless they need to be effective, reliable and evidence-based.[13] The intergovernmental Organisation for Economic Cooperation and Development is currently developing guidance on improving the reliability of human in vitro methods.[21] Evidence is only just beginning to emerge but initial comparisons with animal data suggest they may be better at predicting adverse drug reactions. A micro-liver comprising human liver cells, for example, is able to predict liver damage from Fialuridine, the drug that killed five patients in a 1993 clinical trial[22] and many other liver-toxic drugs whose adverse effects had not been predicted by animal tests.[23] A blood vessel chip is able to accurately model and predict thrombosis induced by monoclonal antibody drugs that caused thrombosis in clinical trials, an adverse reaction that had not been predicted in pre-clinical testing.[24] Meanwhile, an innovative in silico 'drug trial' tested 62 drugs and reference compounds in more than 1000 simulations of human cardiac cells. The computer model predicted the risk of human drug-induced heart arrhythmias with 89% accuracy, compared with animal studies that showed up to 75% accuracy.[25] Cardiac toxicity can also be predicted in vitro: an assay using primary human heart cells to assess the potential of drugs to disrupt heart rhythm or contractility (two serious liabilities responsible for many drug failures) demonstrated excellent prediction of real clinical outcomes, with 96% sensitivity and 100% specificity in the reference drugs tested. Furthermore, a comparison between human and dog heart cells for two of the test drugs highlighted the inability of canine models (default models for drug cardiac safety assessment) or canine tissues to accurately predict the risk of these adverse effects on the human heart.[26] Table 1 provides further examples of human-relevant methods that can predict human drug toxicities that are poorly predicted by animal studies.

Emerging evidence also suggests that the new technologies may be more capable of elucidating mechanisms of toxicity than animal studies. For example Bavli et al.[35] used liver-on-chip technology to investigate why Rezulin (a type-2 diabetes drug) had caused unexplained liver damage in clinical trials. Using the chip they found that even low concentrations of Rezulin caused liver stress before any damage was visible. The same team was able to identify a mechanism of toxicity of Paracetamol using similar technology.[36] Van Esbroeck et al.[37] used human cells to investigate the off-target effects of BIA 10-2474, a drug that killed a healthy volunteer and hospitalised four others in France. They found that BIA 10-2474 deactivated multiple proteins and that this caused disruption to the metabolism of human nerve cells, effects that had not been predicted by safety testing in animals.

The evidence so far is very encouraging; however, systematic comparisons of animal versus human-relevant methods would provide more definitive evidence. As a step in this direction, the Evidence Based Toxicology Collaboration (www.ebtox.org) is using systematic review methodology to compare animal and human in vitro data in terms of how well each predicts human adverse effects (on the liver), taking two anti-diabetic drugs (Troglitazone and Rosiglitazone) as case studies.[38] Further evidence will accumulate once there is wider uptake of these technologies. Systematic reviews will be vital in synthesising this evidence to provide high quality comparisons; indeed they are already being used to explore the evidence base for human-relevant technologies in toxicology as the focus shifts from animal to human biology.[39]

Ensuring safety during the transition to human-relevant methods

Human safety is the paramount consideration when adopting innovative approaches. A wealth of legacy data on drug safety and test performance is currently being systematically reviewed[40] and as a safeguard during the transition to human-relevant methodologies, this evidence can be used alongside techniques such as 'read-across' (using information from a data-rich substance for a data-poor substance that is considered sufficiently similar) and computer modelling[41] to provide a 'weight of evidence' approach. This integrated approach to testing and assessment[42] has been developed and accepted as the best method by regulatory agencies in the areas of skin and eye irritation, driven by the ban on animal testing for cosmetics. It has recently been demonstrated that machine-learning software combined with big data can now be used to create sophisticated read-across-based tools that greatly outperform animal studies in predicting chemical safety, with an accuracy of 80%–95%, compared to 50%–70% for the respective animal tests.[43]

As a further safeguard, low-risk approaches such as microdosing (whereby drugs are administered in doses small enough to be safe, but large enough for the cellular response to be studied) can be used to aid prediction of drug kinetics and hence drug dose when advancing to first testing in humans.[44]

Microdosing is used in a number of ways, including in 'Phase 0' trials, in identifying drug-drug interactions and – increasingly – to assess absolute bioavailability (i.e. to determine what fraction of the therapeutic dose actually reaches systemic circulation), helping to establish a safe dosing level. It can also be used to determine the pharmacodynamic activity of a drug, and allows the measurement of drug concentrations in single cells.[45]

Clinical trials also need to be longer, larger and more diverse in order to pick up rare adverse drug reactions (which animal studies cannot predict[46]), and adverse drug reactions and deaths need to be properly reported.[47,48] Human-relevant technologies can address some of these issues through the use of human-derived biomarkers to select trial participants.[49,50]

Validation

New technologies need to be fit-for-purpose.[15] In other words, if they are intended to be used to test drug safety they need to be acceptable to regulators. Unfortunately, however, regulators currently only accept safety data derived from new technologies if the latter have been validated against historical

Table 1. Human-relevant methods that can predict human drug toxicities that are poorly predicted by animal studies.

Organ system affected	Human relevant model[a]	Reference
Hepatic	In vitro hazard matrix (cell cytotoxicity + bile salt efflux pump inhibition + mitochondrial toxicity + covalent binding to hepatocyte proteins)	27,28
	Micropatterned hepatocyte co-cultures	29
	Human liver spheroids	30
	Hepatocyte high content cell imaging	31
	Quantitative systems toxicology modelling	32
Cardiac	CiPA panel assays	6,33
CNS	Human-induced pluripotent stem cell-derived neuronal cell cultures	34

[a]The performance of these assays was assessed by testing drugs whose toxicity/lack of toxicity in humans was known.

animal data. This makes little sense as the tests must predict how the drugs will behave in humans, not animals, and means that the new tests cannot succeed if the drug in question affects animals differently from humans, which is often the case.[13,51,52] An expert group convened by the UK's National Centre for the Replacement, Refinement and Reduction of Animals in Research recommends that regulatory authorities develop 'Performance-Based Standards' aimed directly at human safety rather than at reproducing the results of animal studies. The group also advocates using 'safe-haven' trials, where traditional and new methodology data are submitted in parallel to develop experience and regulatory confidence in new methods.[53] Two roadmaps issued by the United States government suggest that validation needs to be more flexible if promising new technologies are to be integrated into the system.[54,55] One suggests that some new technologies might be 'qualified' for specific and clearly defined contexts of use, exempting them from formal validation procedures.[54] Indeed the US Food and Drug Administration has recently committed to a leading role in qualifying Emulate's 'organs-on-chips' technology for use in regulatory toxicology testing.[19] It has also been suggested that innovators need to start by finding out what regulators need and want, rather than developing a technology and then hoping that regulators can find a use for it.[56] Both US roadmaps emphasise a need for innovators and regulators to communicate to a much greater extent about each other's needs.[54,55]

Conclusion

There is clearly great optimism about human-relevant approaches to drug discovery, particularly regarding their potentially greater ability to predict human adverse drug reactions (when compared with animal studies) and their potential to weed out failures earlier on in the drug discovery process. Nevertheless, there are obstacles to reducing our existing reliance on animals. The current research paradigm perpetuates animal-based approaches through 'lock-in' mechanisms such as investments in infrastructure, or funding mechanisms.[57] These create 'path dependence' and can make change difficult.[58] Similarly regulations can stifle innovation and perpetuate animal-based approaches. Funding incentives could disrupt the current institutional lock-in to animal research by prioritising funding for human-based biomedical research over funding for 'improved' animal models.[19] After all, even 'improved' animal models introduce uncertainty into the system due to species differences.[59] The funding of systematic reviews in

this area would allow high quality evidence to be generated and explored. Regulations could be amended to allow innovation to flourish, as happened in Japan with the development of human-induced pluripotent stem cells technology.[60] Right now there is a tremendous opportunity for the UK to seize the initiative on humanising drug discovery and to revolutionise medicine through more intelligent, human-relevant research. Human-relevant approaches have potential to offer insight into the functioning of the integrated human system, to speed up drug discovery, save money and improve the safety and efficacy of medicines. A shift in focus by funding and regulatory bodies would allow their potential to be fully explored.

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