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COMMENTARY

Less is more: reducing the reliance on animal models for nausea and vomiting research

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Animals have been used as experimental models for centuries and their use has enabled researchers to make significant advances in many areas of human health and disease. However, this is not always the case and there are limitations in using animal models as surrogates for humans, which have hampered the development of efficacious therapeutics for some pathologies. Scientific limitations, together with ethical concerns, legislative changes and the current economic climate are driving researchers to look for and develop alternative non-animal research tools. Technological advances in tissue engineering, 'omics' approaches and *in silico* modelling for example, are enabling scientists to conduct their research without using animals in a broad range of disciplines, including complex multi-system reflexes such as nausea and vomiting.
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Abbreviations: 3Rs, replacement, reduction, refinement; NC3Rs, National Centre for the Replacement, Refinement and Reduction of Animals in Research

Imagining research and testing in the biosciences without the use of animals is difficult. A recent survey in the UK showed that the majority of researchers working under the provisions of the Animals (Scientific Procedures) Act 1986 did not think that the use of animals could ever be replaced (National Centre for the Replacement, Refinement and Reduction of Animals in Research; NC3Rs, 2009). Does this show a lack of innovation, inertia or simply the reality of the biosciences in the 21st century?

Experiments on animals have been carried out for nearly 2000 years. Today, animals are used across a wide range of disciplines, including pharmacology, to address a multitude of questions in basic and applied research. It is hard to dispute that research using animals has contributed to improvements in human health and medicine, or indeed that this research will continue to be important. Although of course that is a debate that continues to rage, and has been further fanned by the recent publication of the revised European Directive regulating the use of animals.

It is also hard to dispute that the scientific community has not made significant strides in applying the principles of the 3Rs – replacement, reduction and refinement – as they were first articulated by scholars Russell and Burch in their publication *The Principles of Humane Experimental Technique* 50 years ago. Perhaps most notable are the enormous changes that have been made in the way animals are housed and cared for, where even during the last decade, standards have changed beyond all recognition. But what about replacement – has there been as much progress in finding scientifically robust and relevant alternatives to the use of animals?

This question is difficult to answer, other than to say yes and no. That is not sitting on the fence. There has been some progress and, for example, three-dimensional *in vitro* models of human skin (Kidd *et al.*, 2007; Lelievre *et al.*, 2007) have recently been validated and accepted as alternatives to the use of animals for testing of skin irritation potential in the European Union (European Centre for the Validation of Alternative Methods; ECVAM, 2008). This landmark importantly coincides with the European ban on animal testing of cosmetic products. But what is the incentive for developing alternatives other than ethical considerations (or legal requirements as is the case with the cosmetics ban), and are we making the most of the scientific and technological advances in the biosciences to replace the use of animals?

Ethics is an important driver and it is clear that society continues to be concerned about the use of animals in research. Indeed, polls of public opinion repeatedly show that the majority of the public are conditionally accepting of such use, provided it is for medical purposes and that the 3Rs are

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implemented. However, if there is to be real progress in alternatives to the use of animals then this has to be driven by, and led by, scientists. There are real gains to be made here, not least to support the UK science base, improve competitiveness and accelerate the development of new medicines.

Animals are often used as surrogates for man. They are in many cases good models of humans but they also have limitations. These limitations have been acknowledged as a major bottleneck in the development and assessment of the efficacy and safety of medicines. Various initiatives aimed at improving pharmaceutical development, including the US Food and Drug Administration's (2004) paper on 'Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products' and the European Commission and Pharmaceutical Industry (2007) partnership, the 'Innovative Medicines Initiative', have incorporated the need for alternatives to *in vivo* studies.

In terms of environmental protection a similar picture emerges. The US National Research Council (NRC) Committee on Toxicity and Assessment of Environmental Agents (2007) recently published a vision and strategy for toxicity testing in the 21st century, which recognized that the current approaches, relying primarily on *in vivo* mammalian studies, are unable to fully meet today's complex demands for toxicity testing, and advocated a new testing paradigm primarily based on non-animal tests.

The big question is, therefore, are scientists switched on to the opportunities and challenges of finding alternatives to the use of animals? Traditionally, work directed at the 3Rs has been seen as a satellite activity of limited value and variable quality. But there is a real change starting to emerge in the UK, where 3Rs research is becoming an integral part of the mainstream and aligned with the best that science and technology have to offer. It would be naïve to underestimate the difficulty in finding replacements to the use of animals but it would be equally remiss not to explore and exploit the opportunities that are presented by tissue engineering, 'omics', bioinformatics and so on to benefit both scientific endeavour and animals.

But how ambitious should we be? In this issue Holmes *et al*. (2009) describe the challenges and opportunities for replacing the use of vertebrates in the study of a multi-system reflex, using nausea and vomiting as a test case. Examples of complex biological responses like this are often used to illustrate the impossibility of finding alternative approaches to using animals. However, there is an urgent need to embrace this challenge as Holmes *et al*. articulate, because the animal models that are currently used are not without their problems. One of the major reasons for drug failure late in development is nausea and emesis as side effects in humans (for examples see Hoffmann *et al*., 2003; Pi-Sunyer *et al*., 2006; Spina, 2008). Holmes *et al*. (2009) proposed a new testing strategy for assessing emetic liability that should not only reduce the use of animals but also improve the efficiency of drug development. This will not happen overnight but having identified the opportunities there is now a need for exploration and validation.

Not all areas of replacement have to be as difficult as this test case. Translation of the principles is the key to progress and it is here that lessons should be learnt. There are many advantages of scientists taking the lead to advance science through the 3Rs and the UK's national 3Rs Centre (the NC3Rs) was established to support and facilitate this. If replacements are to be a reality then there is a need to consider the robustness of existing animal models and to think openly and innovatively about the possibility of alternatives, working across scientific disciplines to enhance the use and translation of knowledge and expertise. The NC3Rs provides a platform for doing this and funding for research. The UK is at the forefront of the life sciences globally, has some of the brightest minds and significant investment in new technologies. Now is the time to be maximizing the impact that this has on science and animal welfare. Holmes *et al*. have demonstrated this can be a win–win situation.

References

ECVAM (2008). *Validated models-Two in vitro skin irritation tests: EpiDerm SIT and SkinEthic RHE assay*. Available at: http://ecvam.jrc.it/ (accessed 10 February 2009).

European Commission and Pharmaceutical Industry (2007). *Innovative Medicines Initiative*. Available at: http://imi.europa.eu/index_en.html (accessed 10 February 2009).

Hoffmann IS, Roa M, Torrico F, Cubeddu LX (2003). Ondansetron and metformin-induced gastrointestinal side effects. *Am J Ther* **10**: 447–451.

Holmes AM, Rudd JA, Tattersall FD, Aziz Q, Andrews PLR (2009). Opportunities for the replacement of animals in the study of rausea and vomiting. *Br J Pharmacol* **157**: 865–880.

Kidd DA, Johnson M, Clements J (2007). Development of an in vitro corrosion/irritation prediction assay using the EpiDerm skin model. *Toxicol In Vitro* **21**: 1292–1297.

Lelievre D, Justine P, Christiaens F, Bonaventure N, Coutet J, Marrot L *et al*. (2007). The EpiSkin phototoxicity assay (EPA): development of an in vitro tiered strategy using 17 reference chemicals to predict phototoxic potency. *Toxicol In Vitro* **21**: 977–995.

NC3Rs (2009). *Survey of UK licence holders*. Available at: http://www.nc3rs.org.uk/opinionsurvey (accessed 10 February 2009).

Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J (2006). Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* **295**: 761–775.

Spina D (2008). PDE4 inhibitors: current status. *Br J Pharmacol* **155**: 308–315.

US Food and Drug Administration (2004). *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. Available at: http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf (accessed 10 February 2009).

US National Research Council (NRC) Committee on Toxicity and Assessment of Environmental Agents (2007). *Toxicity testing in the 21st century: a vision and a strategy*. Available at: http://dels.nas.edu/dels/rpt_briefs/Toxicity_Testing_final.pdf (accessed 10 February 2009).

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