Comment on the Talking Points in *EMBO reports*, June 2007

Frank Gannon's introduction to the Talking Points about the use of animals in scientific research (Gannon, 2007) underestimated the burgeoning field of animal replacement techniques. Although it is clearly important to be aware of the philosophical arguments against animal research, it is also vital to discuss the scientific issues that surround the debate.

Non-animal research methods have enormous potential to replace animal experiments both now and in the future; furthermore, these cutting-edge techniques often outperform the animal experiments that they replace. The British government now recognizes non-animal techniques as 'advanced methods' that broaden the scope of animal models and overcome some of their limitations.

The article mentions that the implementation of the European Union's REACH (Registration, Evaluation and Authorisation of Chemicals) directive will lead to the use of up to 45 million animals in toxicity tests. This was the original figure suggested by the European Commission; however, recent expert analysis has reduced this figure to an estimated 8–9 million animals (EC, 2006). Approximately half of this massive reduction is due to the application of alternative non-animal techniques; indeed, both UK and European laws require the use of non-animal replacements whenever they are available (UK Government, 1986; EEC, 1986). This huge contribution is made possible by the development of groundbreaking techniques such as Q(SAR)s—quantitative structure–activity relationships—as well as various *in vitro* methods, which have saved the lives of millions of animals and improved safety for humans.

The acceptance of replacement tests by regulatory agencies is slow, but it is occurring. The European Centre for the Validation of Alternative Methods (ECVAM; Ispra, Italy) has validated more than 18 full or partial replacement methods, 8 of which have gained regulatory acceptance. In May 2007, four new tests to replace animals—mainly rabbits—in skin and eye irritancy tests were validated at the European level. The skin tests, which use reconstructed human skin, will completely replace whole-animal tests in all skin irritation studies and save an estimated 20,000 rabbits in Europe alone (ECVAM Scientific Advisory Committee, 2007).

Non-animal replacement methods in toxicology are not just cell-based tests. A whole range of non-animal tests are now available to regulators, and these can be combined or used in isolation to make test results more far-reaching and relevant to humans than the animal studies that they replace.

Computer modelling techniques can predict the likely effects of a drug on a range of cells and organs, before specific human cells are selected for *in vitro* studies. These tests represent progress towards improving safety for humans. The largest survey of drug testing data so far showed that the results of only 43% of toxicity studies of pharmaceuticals using rodents were concordant with human clinical trial results (Olson *et al*, 2000). Overall, 92% of the drugs that pass animal toxicology studies go on to fail in clinical trials (FDA, 2004). Clearly, we need more effective methods and non-animal replacements are providing the solution.

Of course, cell-based tests and modelling techniques do not "represent a whole-body system", as pointed out by Simon Festing and Robin Wilkinson (Festing & Wilkinson, 2007), but they have the advantage of representing human cells and tissues, and not those of a different species. In addition, whenever it is safe and ethical to use them, studies of healthy volunteers and patients provide gold-standard data on the whole human organism.

Animal experiments are also being replaced by human-based methods in medical research. During the 1990s, the Dr Hadwen Trust (Hitchin, UK) funded groundbreaking research at Aston University (Birmingham, UK) in human brain imaging. This work showed that a new type of non-invasive brain scanner—magnetoencephalography (MEG)—could be used to study human brains both safely and reliably. MEG detects electrical activity in the human brain with a spatial discrimination of approximately 2 mm and a temporal resolution of 1 ms (Hall *et al*, 2005), and is increasingly being used to replace invasive experiments on non-human primates and cats. This is just one example of the huge potential of non-animal replacement techniques in medical research.

There is only one solution that ensures the safety of humans while maintaining our ethical obligation to animals, and that is to develop and apply more non-animal replacement techniques. This requires an increased commitment and investment at the highest level, but we are already seeing the benefits of these applications.

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Comment on 'The ethics of animal research' by Festing & Wilkinson

Simon Festing and Robin Wilkinson's scientific defence of animal research rests on their claim that the development of new medicines and treatments is "all made possible by animal research" (Festing & Wilkinson, 2007). Yet the Advertising Standards Authority (ASA; London, UK) has ruled that such claims are misleading (ASA, 2005).

Europeans for Medical Progress (EMP; London, UK) is an independent organization dedicated to the safety of patients. Our concern is that patients are endangered by an unwarranted reliance on results from animal models that have not been validated and are frequently misleading. We seek unprecedented scientific scrutiny of animal tests to predict drug safety—the track record of which is abysmal. Our aim is to ensure that biomedical research practices are rigorously evidence-based.

However, the results of evidence-based medicine often conflict with the agenda of special interest groups (Dickersin *et al*, 2007). We wonder why the Research Defence Society (RDS; London, UK) opposes an independent comparison of animal tests with the latest human-based tests for drug safety, and why they have even lobbied members of the British Parliament (MPs) not to support EMP's initiative. Surely, all sides should agree that an evaluation of the scientific strengths of animal-based testing of drugs is a positive exercise? However, no independent comparison of the relative efficacy of animal-compared with human-based methods has ever been attempted. All four enquiries mentioned by Festing & Wilkinson in their Talking Point (Festing & Wilkinson, 2007) concluded that reviews of the reliability and relevance of animal research are necessary. The House of Lords Select Committee report concluded this was "a matter of urgency" (UK, 2002). The report further acknowledged that, "all sides of the debate on animal procedures say that animals are highly imperfect models. It will be for the benefit of science, and ultimately of human health, if better methods of research and testing could be developed."

Festing & Wilkinson also did not acknowledge the failings of animal research, such as the fact that 92% of new drugs fail in clinical trials, even following success in animal tests (FDA, 2004), as dramatically illustrated by the recent TGN1412 trial. Approximately 150 stroke treatments that were successful in animals have failed in clinical trials (www.camarades.info), sometimes injuring or killing patients, for example Aptiganel (Birmingham, 2002). Vioxx® (Merck, Whitehouse Station, NJ, USA) caused hundreds of thousands of heart attacks and strokes despite animal testing indicating that it was cardioprotective (Topol, 2004). How much more evidence of failure is needed before we consider directly assessing the worth of animal tests relative to the latest tests that are now available?

In January 2007, a systematic study in the *British Medical Journal* based on six reviews found that animal tests accurately predict human response less than 50% of the time (Perel *et al*, 2007). A study of the translation of animal research into human treatments cautioned those who conduct clinical research to expect "poor replication of even high-quality animal studies" (Hackam & Redelmeier, 2006).

Festing & Wilkinson highlighted the difficulty of mimicking a whole living system; however, the answer is unlikely to be found in studying the wrong system: "[A] relative lack of severe toxicity in animal models should never be construed as a guarantee of safety in man, as the story of thalidomide taught us" (Goodyear, 2006). This is where technologies such as microfluidics and, in particular, microdosing, come into their own. Festing & Wilkinson's criticisms of microdosing are unsupportable. By 2010, 90% of pharmaceutical companies plan to use microdosing (Wilkinson, 2007), and the European Medicines Agency (EMEA; London, UK) and the US Food and Drug Administration (FDA; Rockville, MD, USA) support its use to reduce the time, cost and risks associated with developing new drugs (EMEA, 2004; FDA, 2006).

In the light of so much evidence of the hazards posed by misleading animal data, unsubstantiated claims that Festing & Wilkinson make in their Talking Point, such as, "[t]he benefits of animal research have been enormous", are an inadequate form of justification. In addition, stating that, "it would have severe consequences for public health and medical research if it were abandoned" does not withstand scrutiny in the face of promising advances such as microdosing, microfluidics, virtual organs and virtual clinical trials. UK Biobank (Stockport, Cheshire, UK) promises to build substantially on an exciting breakthrough just announced by The Wellcome Trust (London, UK). The identification of many new genes implicated in serious, common diseases was only made possible by the analysis of DNA from thousands of patients and volunteers (Todd *et al*, 2007).

Medical progress depends on a continued focus on humans and their varying susceptibility to diseases and drugs. Now that we have the technology to design and test drugs specifically for humans, what is the value of animal tests? Cancer Research UK (London, UK) acknowledges that "We do trials in people because animal models do not predict what will happen in humans" (Burtles, 2006).

It seems that the public remains to be convinced about the merits of animal testing. In a 2006 Sky News poll—which dwarfed the surveys quoted by Festing & Wilkinson—52% of almost one million people said they were not in favour of testing on animals (news.sky.com/skynews/polls/displayresults/1,,91153-1003444-2,00.html). Our own survey of GPs revealed that only 21% would have more confidence in animal tests for new drugs than in a battery of human-based safety tests, and that 83% would support an independent scientific evaluation of the clinical relevance of animal experimentation; figures which the polling company has never disputed (www.curedisease.net). Furthermore, a majority of MPs also support an independent scientific evaluation of the use of animals as surrogate humans in drug safety testing and medical research (Hancock, 2006). It seems that provivisectionists are alone in opposing scientific scrutiny of the controversial practice they defend.

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Response by Festing & Wilkinson

The commitment of the scientific community to developing alternatives to refine, replace and reduce the use of animals in scientific research and regulatory toxicology has been shown many times. New methods have revolutionized high-throughput screening for the pharmaceutical industry, and thus reduced the need for tens of thousands of animals. From simple advances like pregnancy tests, to complex brain imaging techniques, scientists—not anti-vivisectionists—are continually developing new methods to replace the use of animals.

In some cases these new tests can outperform animal studies and their use should be applauded, but to make the generalization that non-animal methods are therefore 'superior' in all areas of biomedical research, or to make a broad judgement as to 'relative efficacy', is scientifically meaningless. Scientific methods can only be assessed on a case-by-case basis. For example, computer modelling is good at predicting protein folding, but isolated human cells will never be able to tell us the full story about the regulation of blood pressure.

The Dr Hadwen Trust might make a small contribution to the field of replacement techniques; nonetheless, Gill Langley is a well-known anti-vivisectionist who uses the debate about alternative methods to undermine the use of all animals in research wherever possible. It is true that non-animal methods can sometimes overcome the limitations of animal studies, nevertheless, in many cases, animal studies are needed to overcome the limitations of alternative methods—as with the blood pressure example just given. *In vitro* studies can actually have a much higher failure rate than animal studies in predicting what will happen in humans. The Ames test to assess the mutagenic potential of a chemical, for example, is riddled with false positives. There are also strict ethical limitations about what can be studied in humans. This is why, as responsible scientists, we must use all available research methods, as long as they are humane and well-considered. The strong ethical reasons to minimize studies in animals are incorporated in the 3Rs approach, which we discussed at length in our original article (Festing & Wilkinson, 2007). We agree with the Dr Hadwen Trust that the development and application of more non-animal replacement techniques is important; however, until these are available, some animal research will still be necessary.

As in any field of scientific controversy, there are pressure groups, some of which will deliberately and systematically distort scientific arguments to their own ends. The organization Europeans for Medical Progress (EMP; London, UK), is an animal rights group that purports to speak on behalf of patients. In fact, nothing could be further from the truth. The reality is that patient organizations in the UK overwhelmingly support the use of animals in biomedical research; more than 100 medical research charities supported an ethical statement on the use of animals in research (AMRC, 2006).

It is worth looking in some detail at the verdicts made by the Advertising Standards Authority (ASA; London, UK) about several complaints made about animal research-related advertising. In 2005, the ASA upheld five complaints (ASA, 2005a) against a leaflet by EMP for claims that were unsubstantiated and untrue. The ASA also commented that, "citing specific cases where animal tests had proved misleading or unhelpful did not, in itself, show that the general approach was misconceived, as implied by the claim" (ASA, 2005a).

In a separate adjudication (ASA, 2005b), to which EMP refer in their correspondence (Archibald & Clotworthy, 2007), the ASA rejected two complaints made by the EMP against a scientific leaflet by the Association of Medical Research Charities (AMRC; London, UK). The ASA agreed that "at some stages of research there is no alternative to using animals" and that many medical advances were "made possible with animal research". The ASA did uphold one complaint: they requested that the claim of the leaflet should be amended to state that "some of the major advances in the last century relied on animal research", rather than the original—"would have been impossible without"—because the burden of proof required by the word 'impossible' was too great. This complaint was upheld on semantics, not as an indictment of the scientific validity of animal research.

Contrary to the claims of EMP, the Research Defence Society (RDS) has long argued for independent verification of the validity of animal studies. Our website contains an article (Macleod & Sandercock, 2005) explaining why systematic reviews are important and useful, and calling for more. We have liaised with the teams involved in the recently published systematic reviews to which the EMP refer in their Correspondence. The views of these teams are that improvements are needed both in the design and conduct of clinical trials, as well as in animal studies. These groups do not agree with the interpretation by EMP that all animal studies are scientifically invalid.

To suggest that the use of animals to test medicines means that animal tests are responsible for any side-effects is nonsense. It is primarily human clinical trials that are intended to identify adverse side-effects in new drugs. In the case of the drug Vioxx®, for example, it was extensively studied during clinical trials using many thousands of patients before being approved by more than 70 regulatory agencies around the world. Many took Vioxx® in these studies for more than a year and severe toxicity was not reported—a testament to the success of animal and other pre-clinical tests at protecting those early volunteers.

EMP quote Michael Goodyear (Dalhousie University, Halifax, Canada) to remind us that a lack of severe toxicity in animal models should never be construed as a guarantee of safety in man (Archibald & Clotworthy, 2007). Our response is that of course scientists accept the limitations of animal studies—but they do provide real, useful, life-saving data. Just because seat belts do not guarantee car safety does not mean that you should not use them. In any case, Goodyear in fact argues for the

