Human relevant science benefits humanity

by Kathy Archibald, Chair, Safer Medicines Trust

Coronavirus: we've never had a better opportunity to harness the power of human relevant approaches

Unprecedented research efforts are underway across the world to combat the covid-19 pandemic. Much of this work involves testing potential treatments or vaccines in various animal species, both for safety and effectiveness. What is the likelihood that these animal studies will help us to find a vaccine or treatment within the ambitious timescale of 12 to 18 months? According to Dr Francois Busquet (2020) and expert colleagues from the European Center for Alternatives to Animal Testing (CAAT-Europe), “Animal-based testing would be too lengthy, and it largely fails, when a pathogen is species-specific or if the desired drug is based on specific features of human biology... As viral infections are the prototypic species-specific diseases, they make animal testing challenging even without such time pressures. Their duration and costs... do not support such ambitious goals.”

Fortunately, as Busquet and colleagues note, several animal-free technologies do lend themselves to antiviral drug development. A variety of human relevant approaches, such as 3D human organoids, organ on chip devices and computational approaches are now available, which not only save precious time but also provide insights into human diseases that animal studies simply cannot. Some of these enabling technologies, including miniature human lung constructs and artificial lymph nodes, are already being used in covid-19 research and could play a crucial role in accelerating vaccines and treatments. These disruptive technologies create major opportunities to advance our understanding of diseases in ways that have never been possible before. Busquet and colleagues state that some are able to “provide much more robust and exacting data than any animal experiment could deliver”. While these technologies are not as long established as animal research, their track record is already very positive. They represent a tremendous investment for future medical progress and promise to pay dividends both in the current crisis and beyond.

Harm to humanity from animal research

Although animal research and testing has played a central role in the life sciences for decades, its contribution has not always been positive. Society has suffered from its frequent failure to identify potentially dangerous chemicals of all kinds, including medicines, which kill hundreds of thousands of people every year and harm many millions more, through adverse reactions to properly prescribed prescription medicines. The scale of this problem was the motivation for founding Safer Medicines Trust, which exists to promote more effective, human relevant means to protect patients and the public. It is impossible to know how many people have been denied medical treatments because animal research has misled or delayed research into so many diseases, or how many people have been harmed by chemicals whose toxicity was undetected or underestimated by
animal-based safety testing. These serious human harms deserve serious attention. Efforts and initiatives to use human relevant technologies to assess the safety of medicines and chemicals and to study human models of human diseases will reduce these burdens on humanity. Indeed this was the subject of an article I wrote in the *Journal of Animal Ethics* (Archibald, 2018) entitled: “Animal research is an ethical issue for humans as well as for animals”.

In the current issue of the *Journal of Animal Ethics* Nina Kranke (2020) critiques this article and highlights another facet of human harm from the use of animals in science, which I had not mentioned. She suggests that conducting animal research can harm the mental health of personnel tasked with administering substances, procedures or euthanasia to the animal research subjects. She asserts – and I agree – that the distress caused to those whose responsibility it is to care for and (almost invariably) kill the animals is an important issue. As Terry Whiting and Colleen Marion (2011) propose, there is a risk of “perpetration-induced traumatic stress” for veterinarians involved in the destruction of healthy animals, which has also been identified in staff who euthanize animals in surgeries, animal shelters, and laboratories (Rohlf & Bennett, 2005). Similarly, some farmers were reported to suffer post-traumatic stress disorder following the foot and mouth disease crises in the UK and the Netherlands in 2001 (Mort et al, 2005, Olff et al 2005). The delivery of euthanasia and its negative effect on the mental health of practitioners has been a concern for many years. Systematic reviews have revealed that in the UK, the rate of suicide in the veterinary profession is at least three times the general population rate (Platt et al, 2010), with some studies suggesting that young female veterinarians are at the greatest risk of negative mental health outcomes such as suicidal ideation, other mental health difficulties, and job dissatisfaction (Platt et al, 2012). “Test Subjects”, a short film by BAFTA-winning director Alex Lockwood (2019) powerfully reveals the pressure exerted on a trio of former doctoral students to use animals in their studies and the life-changing emotional toll it takes on them.

Clearly, there are negative consequences from society’s exploitation of animals: primarily for those directly involved in the exploitation – but also for society as a whole, through the collective outsourcing of our “dirty work” to others. It is discomfiting to know that others perform tasks on our behalf that we would not wish to perform ourselves. For many, it is profoundly distressing to know that animals are used in ways they believe to be unacceptable but are unable to stop. They can suffer feelings of “bystander guilt” (Bar-On, 2001) and grief. “Not in my name” is a frequent refrain.

In addition to the direct psychological impact on people whose employment involves causing harm to animals (even when they believe that harm is justified and every effort is made to minimise it) I believe there may be another serious cost to society and to science from our widespread and normalised use of animals in science. Who knows how many potentially great doctors, vets or medical researchers chose a different career because their opposition to using animals prevented them from pursuing such a course? Ironically, those who are motivated by compassion to become doctors, scientists or vets are encouraged
not to be emotional or sentimental, yet what other professions have greater need of compassionate practitioners?

While I agree with Kranke that such issues certainly merit serious consideration, I would argue that the number of individuals affected directly by their participation in animal experimentation is minuscule compared with the number of patients, consumers and citizens who are affected by unsafe medicines, or unsafe household, agricultural or industrial chemicals, or by constrained medical progress – all of which result from an over-reliance on research that uses non-human animals at the expense of methods that target the species in question: humans. These are the harms that Safer Medicines Trust addresses, since their impact on science, medicine and society is so negative and so extensive.

A question of evidence

Kranke suggests there are two problems with my argument. First, she writes that my point is limited to biomedical research and that, “particularly in basic research in the life sciences, many animal experiments are not conducted to gain knowledge of human health and disease.” However, a precondition of any animal experiment being approved is that the benefits to humans (or the environment) must outweigh the suffering of the animals involved. Therefore it would seem that even basic research needs to have relevance to human health otherwise it should not pass the harm/benefit assessment.

Second, Kranke dismisses my central argument that significant scientific advances have now made it possible to study human biology to an extent that obviates most uses of animals, while powerful evidence shows that animals are a poor model for humans and cannot reliably predict the safety or effectiveness of medicines or other chemicals. She writes: “it is not true that animal experiments are generally unreliable” but gives no evidence to substantiate this conclusion.

Yet it is actually true that animal experiments are generally unreliable and there is an abundance of high quality evidence, much of it from systematic reviews (universally accepted as one of the highest forms of evidence) unequivocally demonstrating this (see, for example, Bebarta et al, 2003; Crossley et al, 2008; Henderson et al, 2013 and 2015; Hirst et al, 2014; Holman et al, 2016; Kilkenney et al, 2009; Korevaar et al, 2011; Lindner, 2007; Macleod et al, 2015; Mobley et al, 2013; Mueller et al, 2014; Sena et al, 2010; Tsilidis et al, 2013; Zeiss et al, 2017; van der Worp et al, 2010), as well as the inability of animal experiments to predict human response (see, for example, Begley & Ellis, 2012; Contopoulous-Ioannidis et al, 2003; Cummings et al, 2014; Geerts, 2009; Ioannidis, 2012; Kola & Landis, 2004; Leenaars et al, 2019; Leist & Hartung, 2013; Malfait & Little, 2015; Perel et al, 2007; Pound et al, 2004; Scott et al, 2008; Seok et al, 2013; Vatner, 2016; Vesterinen et al, 2010). Indeed the poor quality and poor translation of animal studies is a widely acknowledged fact among those conducting animal experiments and is the subject of much discussion within fields of translational research (see, for example Lalu et al, 2019, and in the field of translational stroke research, deGraba & Pettigrew, 2000; del Zoppo, 1995; Dirnagl, 2016; Lyden & Lapchak, 2012; Marbacher, 2017; Sharp & Jickling, 2014;
Turner et al., 2011; Wiebers et al., 1990; Xu & Pan, 2013; Pound and Ram, 2020). In contrast, Kranke would be hard pressed to find good evidence that animal models are a reliable and valid means of predicting either the safety or effectiveness of medicines or other chemicals for humans (Bailey & Balls, 2019).

**Moving towards human relevance**

Fortunately, scientific advances have now made it possible to study human biology to an extent that makes most animal experiments redundant. Organ on chip devices (e.g., Jang et al., 2019), induced pluripotent stem cells (e.g., Blinova et al., 2018), predictive computer models (e.g., European Medicines Agency, 2018) and many other tools offer a variety of human relevant means to identify effects on human biological pathways that animal tests are simply unable to detect. The scientific and economic opportunity is immense, as outlined in a recent White Paper by the Alliance for Human Relevant Science (2020).

This is clearly the reason behind the ever-increasing demand for micro-physiological systems and the concomitant declining demand for mouse models. Indeed, the impending closure of the two leading animal breeding and research centers in the UK has recently been announced; the animal facility at the Wellcome Sanger Institute in Cambridge (Else, 2019) and the Harwell Institute’s Mammalian Genetics Unit (Brown, 2019) in Oxford. Both planned closures are reported to be a consequence of a move towards using technologies such as cell lines and organoids in genetics research, instead of animals. As the *State of the Discovery Nation 2019* report notes: “The use of complex cell models is being driven by a combination of decreased trust in the translational value of animal models and increased availability of data to support the validity of complex human cell models” (Medicines Discovery Catapult & UK BioIndustry Association, 2019).

I see this as a vindication of the transformational utility of the human relevant models and tools that scientists have now been working on for a generation or more. It is also a watershed moment in our quest to uncover the mechanisms of the many diseases and toxins that blight us and to find new ways to prevent, treat or cure them. Studying animals is an excellent way to learn more about animal biology. But most life science research is aimed at learning more about human biology, and for that there is no substitute to studying humans.

**References**


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