75. Food, health and animal research: on the need for ethical reflections on uncertainty in animal research

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Abstract

Both food and biomedical research on animals are meant to further our knowledge about improving health. However, due to a generally low translational value, the use of animals for research has become a contentious issue, hence calls for more efficient replacements. However, data obtained through the current alternatives to animal testing, such as *in vitro*, are also deemed insufficient without an *in vivo* component. Because, whatever their translational potential might be, most research models' physiological and genetic traits closely mimic those of humans. This raises the question to what extent factors other than inter-species differences contribute to inefficiency of animal studies and whether improving them can make up for these differences. Moreover, the need to further health-related research on animals should be weighed against the moral mandate to avoid unnecessary harm. However, the problem of uncertainty in determining the translational value of animal studies for clinical trials complicates answers to such questions. In this paper, we argue that a more integrated approach by all the relevant stakeholders to actively improving translatability of animal models within the research chain would help inform responsible research strategies, thereby improving the ethical acceptability of animal research.

Keywords: translational strategies, integration, responsible research

Problems of translation as an ethical problem

Scientific evidence supporting potential health benefits of probiotics have contributed to their dietary and clinical use becoming commonplace all around the world. However considerable uncertainty still remains as to the exact mechanism behind the health effects of these bacteria. Low methodological quality, poor experiment design, and regulatory hurdles have all been blamed for this uncertainty. Moreover, problems associated with applying data from animal studies to clinical trials add to the complexity. This is because proceeding to clinical trials without ensuring reliability of animal data could result in unwanted consequences. For example, in 2008, a Dutch trial of probiotics for acute pancreatitis led to 24 unexpected deaths despite the researchers having followed through preceding studies on both humans and animals (Sheldon, 2008). A two-year investigation by the Dutch authorities found that the flaws with the study's design, approval, and conduct were all contributing factors to its failure in clinical trials. The fact that the product developed for this trial had only been tested on animal models raised the question whether the ethics committees that approved this study had weighed the usefulness of animal data critically enough (Sheldon, 2010). It is important to note that similar probiotic experiments on both humans (Weale *et al*., 2003) and animal models (Elzaquirre *et al*., 2002) had yielded promising results prior to this study, but nevertheless fell short of ensuring a reliable basis for an extensive clinical trial.

The shortcoming associated with animal-to-human translation is not limited to the probiotic studies. Recent systematic reviews of experiments on animals have consistently shown that there are different arrays of obstacles to translating data from animal research into the ones that would tangibly contribute to human health. Some argue that such obstacles render animal studies ethically unjustifiable, casting doubt over the use of animals in general. But an assumption underlying the argument for continued use of animals is that the evidence for a minute proportion of animal studies finding their way into clinical trials should suffice to confront the sceptics alone. Such assumption usually focuses on the physiological

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and genetic similarities the human organism shares with those of animals such as mice and rats. However, taking ethics seriously in the face of these obstacles to translation remains an important issue for current innovative projects that aim to replace the inefficient ways with solutions that would improve the translational value of animal models. The idea is that attempting a drastic change in methodologies to determine the translatability of a particular line of research could offer genuine chances for practical debate on ethics. Such a debate would focus on the use of animals in research and the use of animal data in clinical trials.

The background of current problems

There seem to be a clear ethical imperative to strive for optimised methods and models in animal research. Nonetheless, two sets of problems appear to be associated with the process of choosing the right animal models for a better overall efficiency:

The first set arises from the inevitability of uncertainty when it comes to bench-to-bedside translation. This uncertainty arises from biological differences between humans and animals. If we establish that the negative contribution of these differences to the inefficiency of animal research cannot be considerably diminished by changes in methodology, the ethical acceptability of the current laboratory practices would be difficult to defend solely on account of the current level of translational success. On the other hand, it is not certain how dismantling the existing system, which requires a vast quantity of animals, could be justified from prevalent ethical perspectives across the research chain. Thus, the conflict worth exploring in this paper will be between the moral imperative to continue health-related research and the imperative to justify the exploitation of animals' lives in exchange for small chances of clinically relevant input.

The second set of problems is based on a hypothesis that clearly defined measures to regulate the use of animals in laboratories can potentially pose hurdles to scientific innovations that would ultimately improve the situation for animals. That is, being bound by rules on numbers and the choice of animal models, researchers could be dissuaded by what they would see as a flaw in the distribution of responsibility within the research chain. Thus, in light of the first set of problems mentioned above, a second conflict emerges: Is it morally permissible to hinder innovations by controlling quantitative and qualitative aspects of selecting animal models?

As far as the current literature on the efficiency of food and biomedical research on animals is concerned, these problems are shared universally, only in different measures. Nonetheless, practical engagement with a holistic approach to the research chain with a clear aim of increasing translatability and ethical acceptability seems to be scarce. Thus, besides an overview of the existing literature, the multidisciplinary project attached to this paper will also rely on data found by an ongoing systematic review of animal studies for Cystic Fibrosis (Leenars, 2016) and Rheumatoid Arthritis (Leenars, 2015). The protocols of these reviews are designed to connect the dots between shortcomings in animal studies and those in clinical trials. The goal is to identify the break in the research chain and find translational strategies for its amendment. The ideal strategies would entail a fair distribution of responsibility across the research chain and should be applicable to all health-related research. In what follows, we discuss the normative challenges of putting forward a strategy as a morally responsible one.

The problem of uncertainty

Despite the fact that the clinical relevance of animal research has rarely been questioned by the stakeholders within the research chain, evidence suggests that researchers do regularly act upon the assumption that it rarely informs clinical trials with sufficient certainty. For example, systematic reviews of a series of studies on treatment of stroke, wound healing and fluid resuscitation for bleeding trauma patients have shown that the clinical trials were conducted without taking into account the findings from preliminary animal experiments partly because they were judged as being unreliable (Pound *et al*., 2004). However, as Bakhle (2004) argues, such a finding does not automatically pave the way for questioning animal use in general as it only accounts for a very small proportion of research. This means that selective investigations cannot give a fair idea of the extent to which animal research actually contributes to improving human health. Thus, given the complexity and scope involved in conducting a general overview of this contribution, a coherent discussion on animal use is bound to take place on a case by case basis. However, this also implies that a low animal-to-human translatability within a particular study cannot be weighed against the overall benefits of animal research.

Focusing on the translational success of particular studies can potentially assist researchers in determining the right animal model for their similar projects. For example, BALB/c mouse, one of the most widely used strains in experimentation, was used in a study to measure the influence of a probiotic on its gastrointestinal tract (GIT). The clinical trial that followed this experiment showed a similar functionality of this probiotic on human GIT with comparable success, contributing to this strain becoming a staple probiotic model (Dunne *et al*., 1999). However, a purely statistical analysis, more often than not, fails to consider the normative aspect of dealing with the problem of uncertainty. This problem stipulates responses to two interrelated questions:

1. Can we morally justify at least some animal experiments when the translational outcome is always uncertain?
2. If yes, which measurable criteria should be taken into account to define a 'responsible' amount of uncertainty?

To answer these questions, we can start by the uncontroversial premise that uncertainty is the very aspect of scientific research that has been driving the search for new knowledge through applying hypotheses to practice. If we accept that the route to medical progress will always have uncertainty as an inevitable component, then at first glance, not much can be said about how we should deal with it from a normative standpoint. Depending on the position we take on the moral spectrum regarding the treatment of non-human animals, we would either have to oppose all kinds of animal experimentation on absolutist moral grounds and jeopardise medical progress, or define an acceptable level of uncertainty for ethical research. If, as Festing and Wilkinson (2007) argue, we grant that stopping all animal testing now would be detrimental to human health, the abolitionist position will be less tenable than those that would allow animal testing conditionally.

One way to tackle unsatisfactory or non-pragmatic aspects of responses from classic ethical positions is to shift the normative spotlight on the intention of the researcher and the goals set out by different players within the research chain. The practical realisation of such move could be as follows. First, we could use empirical data from particular studies to show that robust translational strategies could contribute to efficiency and therefore ethical acceptability of a line of research. A prerequisite for applying such strategies to the function of the research chain is to improve communication between the stakeholders. Because an effective communication between the stakeholders creates room for ethical dialogue on uncertainty across the chain, the chances for a more responsible evaluation of translatability increases. Moreover, a multidisciplinary approach which would integrate clinical and preclinical stages means that the stakeholders will deal with a clearer representation of uncertainty at stake. The idea is that, making

decisions on the use of animals based on the level of uncertainty requires a coherent and consistent identification of this problem by both animal researchers and the users of translatable data.

Thus, in addition to the regulative principles such as the 3R, an integrated response to uncertainty based on translatability will help make research more responsible. However, attending to the problem of uncertainty also highlights another moral dilemma we would face in our search for strong translational strategies. Institutional hurdles that could frustrate scientific innovations and effective changes within the research chain could be explored from a normative point of view.

The need of a more integrated approach

Ensuring an acceptable rate of translational success as a component of efficiency in health-related research necessitates innovation and change in the status quo. Since genuine innovation requires sufficient space for researchers to think out of the box, we might have to rethink some of the limitations we impose on the research chain. Most regulatory restrictions on animal use do fulfil their objective of ensuring a better animal welfare in laboratories. However, plain rules to control and assess numbers, models and replacement of animals may not do justice to the translational complexity that is inherent in animal studies. A 2011 survey of Canadian researchers' views on the 3R as the staple welfare component of research regulations demonstrates that the replacement tenant is largely considered unrealistic by the chain insiders (Fenwick *et al*., 2011). Moreover, it reflects a sceptic view of reduction and refinement. This is because, reducing numbers, reusing models and some refining measures applied to an experiment could potentially create obstacles in achieving clinically relevant results. The first obvious response to this survey is to propose institutional and regulative changes that would capture the complexity of particular research chains and allow for some flexibility for scientific innovation (Tamayo, 2008). Then, the changes which would affect the quantity and the manner of animal use have to be ethically justified. However, these justifications should be offered while taking into account a dichotomy of duties that are usually conferred upon the researchers: To further knowledge that is demonstrably useful for human health, and to avoid unnecessary harm to animals. The following proposal for a revision of the current system could help reconcile the two duties.

As a first step, we could assess whether research regulations focused on directly influencing animal use (e.g. the need for the approval of an ethical committee) can improve animal welfare better than those that are focused on overall efficiency. The advantage of welfare-based rules such as the 3R is that they help incorporate a binding normative component to the decision-making process for research applications. This automatically encourages extra attention to efficiency. Because cost-effectiveness analyses imbedded in welfare regulations seek to justify experiment on animals based on its predicted use and necessity for humans. However, as discussed above, basing justifiability on the translational value of animals can be quite objectionable. This is because normative evaluations are usually expected to rely on at least some invariable factors. One consequence of relying on translatability is that having to make predictions without verifiable certainty becomes inevitable for most health-related research.

A patient-cantered evaluation of efficiency in research chain, however, seems to fill the normative gap left by uncertainty. If we direct the energy and the resources put into ensuring a particular level of welfare for animals into securing consistent clinical outcomes in a research chain, a more holistic approach can be possible. This approach will juxtapose the needs of patients with the interests of animals in a more effective way than the welfare approach does. Because choosing efficiency as the overriding principle would open up the flow of ethically relevant data between the two ends of the chain. Patients and clinicians will be able to achieve a better understanding of the pre-clinical complexities in translation, thereby making a more informed use of the data available. Likewise, animal researchers are more likely to act on the necessity to contribute directly to finding health solutions.

The normative questions applicable to this approach would be asked on a case by case basis, taking into account our ethical duties to both humans and animals. In practice, the need to replace, reduce, or refine will remain as a guiding principle as they can be conducive to efficiency regardless of its ethical relevance. However, the responsibility to fulfil this need should be shared by all the relevant stakeholders. That is, the researchers who directly engage with animals should not have to carry the moral burden to justify their experiment plans isolated from other stakeholders. This view can be defended as follows:

All welfare-based positions on animal experimentation are bound to define in quantitative and qualitative terms what constitutes responsible research. These positions might differ on the use of certain species or models within one specie. However, when an experiment plan fulfils the necessity criterion for human health, what is remained of the ethical evaluation will take the form of an empirical investigation that can confine the researcher to limited choices on methodology and numbers. What is problematic in this system is that applying the necessity check and welfare evaluation will not always mean that a research proposal will have a higher chance of producing clinically relevant data. Whereas, an active push for decision-making based on translational value across the chain will mean all stakeholders will have a shared understanding of what could improve the result. For example, clinicians and patients involved in treating a disease could weigh in the necessity discussion as well as that of the suitable methodology. Similarly, animal researchers could conduct systematic reviews of their line of research to ensure the clinical goals match those found in basic research.

Thus, for all the abovementioned reasons, ethical justification of continuing research on animals in the face of uncertainty have to be backed by concrete strategies to maintain an efficient level of translation between animal studies and clinical trials. Moreover, where an empirical investigation forms the basis of solutions to ethical challenges, the integrated approach discussed above can help increase animal welfare by ensuring a more holistic approach to conflicting moral views across the chain. Because extending a patient-cantered focus to the whole of the research chain will encourage a more robust and consistent understanding of problems of translation and uncertainty in animal studies.

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