The Academy of Medical Sciences response to POST Consultation on Technology alternatives to animals in life sciences research: Deadline 28 September 2025

Q8. Please briefly explain how your research expertise is relevant to the POSTnote topic. E.g. if you teach a course, or if you've published a paper linked to the topic.

The Academy of Medical Sciences is one of the UK's four National Academies, and is the independent, expert voice of biomedical and health research.

This response draws on the experience of our Fellowship of leading researchers, former grant awardees and programme alumni.

Their expertise includes: neuroscience, neurogenetics, hearing loss, computational models, oncology, cardiovascular medicine, toxicology and drug development. They have long-standing interests in animals in research and have used a variety of in vivo models and species.

Q9.What are the key issues relevant to the POSTnote that you would like to make us aware of? E.g. a link to a relevant policy document, or statistics that relate to the topic. If possible, please provide links to sources for any statements you make.

Introduction:

As an inaugural signatory of the Concordat on Openness on Animal Research in the UK, the Academy welcomes efforts to replace, reduce and refine the use of animals used in research. The UK has stringent monitoring and control of animal research by the Home Office in accordance with the 3Rs principle, which ensures ethical practice. This is widely welcomed and accepted by the scientific community.

We welcome the need for an ongoing, balanced assessment of progress on and limitations of alternatives to the use of animals in research. Doing so will prevent a premature movement away from the use of animals in research and limit potential damage to ongoing, innovative health research involving animals and the UK's world leading position in this space.

Our response provides examples of Fellows' research, to outline where there are limitations to using technology alternatives as replacements for animal models. It also outlines some of the unintended consequences of moving to alternatives before the technology is ready, as well as barriers to adoption. It does, however, provide examples of where technology alternatives are complementary to animal models.

Complexity of animal physiology

Fellows expressed the immense difficulty of replicating the complexity of whole animal physiology within replacement models, including AI. Examples are listed below:

- Organ development and structure which requires input from multiple cell lineages (vascular, neurological, immunological and tissue specific cells such as hepatocytes) as well as from local and systemic signals (such as neurological, endocrine, cytokine, and microbiota).
- Tissue–tissue or cell–cell interactions (e.g. spinal cord motor neurons synapsing onto skeletal muscle in the adult environment, with key interactions with microglia and other cells that modulate disease).
- Complex diseases, such as motor neurone disease (MND), that are also driven by multiple cell types and have numerous possible targets for therapeutic targeting (although alternative models may provide insight into specific mechanisms).
- Drug and chemical toxicity can be complex and involve multiple organs, cell types and physiological states. Current in vitro technologies to predict toxicity cannot replicate this complexity and will not be able to in the foreseeable future.
- Safety, tolerability and complex mechanistic actions.
- Variability (genetics, lifestyle, comorbidities and sex differences), but there is the opportunity for patient-specific models to be developed.

Complementary technology alternatives

There are some instances where technology alternatives currently complement, but cannot replace, animal models. Examples below relate to brain research:

- Non-invasive technologies, like functional magnetic resonance imaging (fMRI) and electroencephalography (EEF) enable mapping of various brain functions in humans, but currently lack the resolution to indicate cellular mechanisms involved. Animal research remains essential for single-cell and network-level insights, providing insights that current technologies cannot replicate. These approaches are critical for developing more precise and well tolerated therapies for neurological and psychiatric disorders.
- In the last decade, two new technologies have allowed researchers to record simultaneously thousands of single cells in awake, behaving animals. While promising, they still rely on animal models, as current alternatives cannot replicate the complexity of whole-brain network activity, which is essential for studying neurodegenerative diseases such as Alzheimer's Dementia.
- Animal research is also still essential for brain-machine interfaces and therapies like deep brain stimulation, as these depend on intact neural circuits and long-term safety testing.
- Effective drug action within cell and tissue models cannot perfectly predict the effect of the same drug at the multicellular level. Therefore, currently, we cannot use solely in vitro models to learn about behavioural outcomes in health and disease. This is particularly important when considering long-term effects, such as that of early life stress on later mental health. In vitro models don't give us the long-range complexity of the whole animal, such as giving us access to the effects of the microbiome on neurodegeneration or the complex interactions of ageing.

- Continuing to work with animals would help to ensure we maintain the current scope and pace of basic research which offers the likelihood of understanding and addressing critical neurological issues.
- There are unprecedented opportunities to create more sophisticated animal models such as humanised models, which are more predictive of human biology and human drug responses. The application of such models can, at the same time, markedly reduce animal use and reduce attrition in drug development.

Limitations of alternative models

Fellows have highlighted that there are some major limitations to alternative models. For example, within hearing research, in vitro models and organoids remain too limited to replace animal models:

- Hearing requires an intact blood supply, immune system, and feedback from the brain to function, and all cell types need to be fully functional (not just sensory hair cells) for normal hearing to occur. There has been interest and some research effort into producing organoids that include hair cells, but the development of cells that look like they might be hair cells in these organoids appears to stall at an immature stage, and an organoid cannot hear.
- Imaging techniques of the human inner ear are currently insufficient to give a clear understanding of the pathology of deafness at a cellular level and our measurement techniques for human deafness are limited in giving insight into the biological basis of the hearing loss. One Fellow was not aware of any feasible substitute for using the mouse to establish the necessary details of the pathology of hearing loss to support development of treatments.
- Public databases can provide valuable background for research, such as insights into the function of specific proteins gained from in vitro experiments. However, it is challenging for in vitro experiments to provide any insight into which proteins (genes) might be required for normal hearing.
- Human genomic sequence data is effective for identifying the causes of childhood deafness, but it provides limited insight into the mechanism of adult-onset hearing loss. Safe and effective translation can only be achieved by using animal research approaches to determine fundamental physiological mechanisms and validation. More broadly, Fellows agreed that significant progress is still required before findings from genome-wide association studies, RNA sequencing and whole genome sequencing can be translated effectively and safely.
- For hearing, mice appear to be well aligned with humans and mouse mutants seem to be good models, providing insight into treatment development. For example, the first gene therapy for childhood deafness was possible because of prior findings in mouse models.

The choice of cells used in replacement models is an additional challenge:

- For example, primary cells from different life stages could potentially behave differently. Within cardiovascular research, factors such as pulsation, oxygenation status and blood flow perturbations can also impact on the biology of the model, which add additional complexity.

- We don't yet know how to make or maintain the majority of cell types found in the body, including the immense number of cell types within the immune and nervous system. Models can only be created from known cell types, meaning that, by creating models only using cells we know about, we miss those that we haven't yet discovered. For example, earlier this year, an entirely new and unsuspected cell type was discovered in the cartilage of the mouse knee, by examining this tissue in mice. This is unlikely to have been identified solely by looking at in vitro models. Similar, undiscovered cell types likely exist in the brain.

Ongoing developments in replacement technologies

Our Fellows and grant awardees provided some examples of ongoing developments in replacement technologies within their respective institutions:

- One Fellow described their lab's current development of a virtual (AI/ machine learning) mouse that models aging and response to and resistance to, cancer treatment. Their recent paper demonstrated how this approach can identify biological shifts during cancer resistance to allow the selection of effective treatments that dramatically reduced mouse use. The paper suggests that this could be done on human tumours in trials to avoid excessive preclinical work. The Fellow provided the preview of the paper from the Journal (which is on the cover of Cancer Cell in September 2025.) A second, much larger paper, is in preparation.
- One grant awardee is working with colleagues at Keele University to develop a fully humanised blood vessel on a chip model for thrombosis research, a project supported by the NC3Rs. Their aim is to develop a platform to improve the identification of druggable targets using the model. There are two arms to the project: further development of the blood vessel side of the model and the other to develop ways that human platelets can be directly modified (as a replacement for transgenic mouse models.

The future of alternative models

We heard from Fellows that it could potentially take several decades for models for tissue–tissue or cell–cell interactions to replace in vivo models and around a decade for multiscale computational models of multiple organs to achieve sufficient complexity in predicting disease risk and drug response. Although Fellows were supportive of plans to reduce the unnecessary use of animals in research, many warned of eliminating their use too soon, or of eliminating them at all:

- Doing so may result in unexpected consequences to research and innovation. For example, within neuroscience, insights from animal studies generate the data and theories that inform computational models and drive advances in areas, such as AI. One Fellow predicts that future breakthroughs, both in medicine and machine learning, will emerge from studying real brain networks, not from in silico systems alone.
- Moving away from animal models can result in a loss of knowledge of biological mechanisms. This could limit our ability to generate knowledge on disease mechanisms.

- There is the risk that, if alternative technologies become part of the drug regulatory process without validation, patient lives will be put at risk, with drugs potentially being approved which cause severe toxicity in patients.
- New drug treatments may also be abandoned because in vitro systems suggest they may be toxic when they are not i.e. false positives.

Any movement away from animal models would require:

- Demonstration that replacements are as reliable and reproducible as existing animal models to build confidence for their adoption.
- Education and training in how replacements are viewed by regulatory bodies.
- Better links between industry, academia and drug regulators to co-develop models

Fellows have also highlighted practical barriers to adopting replacement technologies. For example, the lack of standardised protocols makes comparisons between labs and platforms challenging. Replacement approaches can also be time-consuming, potentially costly and technically challenging without the right training and financial support. It can be difficult to convince researchers that the benefits of implementing such approaches outweigh these barriers.

Fellows cautioned that, before moving away from animal models, it is important to ensure they are being used correctly to be fully effective and fairly assessed. This includes ensuring that appropriate models and correct trial designs and validation protocols (e.g. blinded studies) are used to minimise the risk of failures in drug translation. E.g.:

- Mouse models should reflect the genetic basis of the human condition it is trying to model.
- They should reflect human pathways of drug metabolism.
- Drugs should also be tested in the same treatment windows between mice and humans.
- Patients should be stratified into cohorts that have the same disease (or at least disruptions in the same pathological pathways) to ensure reliability when modelling in vitro and in vivo. Otherwise, effective drugs are ‘lost in the noise’ within unstratified trials.