People for the Ethical Treatment of Animals (PETA) Foundation – Written evidence (STS0023)

People for the Ethical Treatment of Animals (PETA) Foundation is grateful for the opportunity to submit evidence in response to the inquiry on Delivering a UK Science and Technology Strategy. As one of the largest animal protection organisations in the UK, we are submitting these comments on behalf of our 1.3 million members and supporters. The scientists and policy experts who work for PETA Foundation and PETA entities have a proven track record of productively assisting many international regulatory and government agencies and companies. This assistance includes providing expert opinions, regulatory advice, and technical support in a broad range of fields. Given the breadth and depth of our expertise, we believe that we can make a valuable contribution to this inquiry.

Summary

- In this submission we identify the barriers to the UK becoming a "science superpower" and the opportunities for the UK to realise its research investment in the life sciences.
- We identify the scientific, economic and public health opportunities for encouraging and supporting the progression of scientists who focus on innovative mechanistic methods including *in silico*, *in vitro*, and *in chemico* models, which overcome some of the translation issues of using animals to model human biological processes. While the UK has provided valuable leadership concerning the replacement of animals used in research, and in ensuring the promotion of new technologies – as evidenced by the cosmetics testing and marketing bans, which have led to innovation of new testing methods and changes in policy worldwide – there are many opportunities that the UK has yet to exploit.
- We draw the Science and Technology Committee's attention to areas where we should build on skills to achieve a "high-tech economy, and outline relevant international initiatives where the Government must ensure that the UK does not miss out on opportunities to lead in these areas. We outline how the Government can integrate the prioritisation of funding to help realise the scientific, economic and public health opportunities laid out in the 2015 Innovate UK report A Non-Animal Technologies Roadmap for the UK, ensuring that the UK is at the forefront of global scientific advancements in humanised biomedical research.
- Finally, we provide a framework for a national science and innovation strategy that can help the UK to achieve its goal of becoming a "science superpower".

Barriers to the UK becoming a "science superpower"

To achieve the Government's aims for UK science, UK research, development and innovation institutions need reform – in particular, the UK's life sciences, one of the priority areas of the National Science and Technology Council (NSTC). As identified in a recent Science and Technology Committee inquiry, the integrity of research is facing a reproducibility crisis, and addressing this is vital to the future of the UK life sciences, particularly in light of economic recovery from the global pandemic.[1] It is

estimated that between 50% and 89% of preclinical research is not reproducible, with the use of animal models frequently highlighted as a serious problem area.[2,3] Francis Collins, director of the US National Institutes of Health, has noted that "[p]reclinical research, especially work that uses animal models, seems to be the area that is currently most susceptible to reproducibility issues".[4] However, as UK Reproducibility Network recently highlighted, the issue of reproducibility in UK science is an opportunity, as opposed to a crisis, to address new ways of working and how UK research can be improved.[5]

For decades, extensive research has demonstrated the poor translation of basic and applied research, and predictive failures in safety and efficacy testing, from using animals to understand human disease and test therapeutics. Inherent species differences mean that other animals cannot reliably serve as analogues for understanding human disease and developing safe and effective treatments for humans.[6] Systematic reviews published in peer-reviewed journals document the limitations in translating results from studies using animals into treatments for humans in numerous disease areas. Some examples include cancer,[7] cardiovascular disease,[8] diabetes,[9] HIV/AIDS,[10] immunology,[11] nerve regeneration,[12] neurodegenerative disease,[13] sepsis,[14] and stroke.[15] The majority of "highly

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[1] Reproducibility and research integrity: Inquiry. Science and Technology Committee. UK Parliament. Published 2021. https://committees.parliament.uk/work/1433/reproducibility-and-research-integrity/publications/ Accessed 15 March 2022.

[2] Freedman LP, Cockburn IM, Simcoe TS. The economics of reproducibility in preclinical research. *PLoS Biol*. 2015;13(6):e1002165. doi:10.1371/journal.pbio.1002165.

[3] Torrington E. Reproducibility, scientific rigor and responsibility. *BioTechniques*. 2021;71(2). doi:10.2144/btn-2021-0066.

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[14] Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A*. 2013;110(9):3507- 3512. doi:10.1073/pnas.1222878110.

[15] Sommer CJ. Ischemic stroke: experimental models and reality. *Acta Neuropathol*. 2017;133(2):245- 261.

promising" basic science discoveries are based on animal studies, but it is estimated that fewer than 10% of these enter clinical use within 20 years.

The poor translation of results from animals to humans is further undermined by factors such as poor study design, publication bias and compounding effects inherent within the laboratory environment. For example, University of Oxford scientists found that a lack of measures to reduce bias in animal experiments likely results in an overestimation of the benefits of the treatment studied, thus compounding the trustworthiness and the rationale given for justifying further research using animals.[16] Despite the so-called reproducibility crisis having been heavily discussed in the scientific literature, measures applied to improve experimental design have been unsuccessful.[17,18,19,20]

Unsurprisingly, weaknesses of animal experiments cannot be overcome by simply improving study design, because external validity, or the "extent to which research findings derived in one setting, population or species can be reliably applied to other settings, populations and species",[21] can never be achieved. Inherent species differences mean that non-human animals cannot serve as analogues for understanding the specific biological details necessary to develop safe and effective drugs for humans. Indeed, animal 'models' are often considered a black box and their predictive value has been challenged on a number of fronts. In terms of effectively directing resources to deliver an effective science and technology strategy, it is worth considering that whilst humans are animals, are animals human enough?

In the field of regulatory toxicology and environmental protection, continued dependence on unreliable animal tests lessen the level of protection that can be afforded. Since tests on animals are known to lack reliability, relevance, and – in the case of those designed to detect certain carcinogens and endocrine disruptors – validation to modern standards, basing regulatory and chemicals management decisions on the results of such tests could lead to the misclassification of substances with damming consequences for the protection of humans, the environment, and animals. Animal tests are designed to measure the effects of large doses of single substances administered to small animals with short lifespans.

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They cannot address the long-term effects of the cocktail of low doses of chemicals to which human beings – large animals with long lifespans – are exposed. In addition, species differences render animal tests intended to identify subtle effects such as disruption to human endocrine or immunological systems or neurobiology, especially from low doses of substances, highly unlikely to meet their intended objective. Consider, for example, studies conducted using rats or mice to assess whether a chemical causes cancer in humans or not. The rodent cancer bioassay has come under scrutiny since the 1970s for its inability to predict human outcomes. Two assumptions underlie the bioassay: (1) rodent carcinogens are human carcinogens, and (2) high-dose chemical exposure in rodents is indicative of an environmentally relevant dose.[22] Both assumptions have been proved incorrect by 50 years' worth of data. The test also lacks predictivity and is poorly reproducible, with factors such as stress, differences in diet, and even the strain or sex of test animals likely to affect results.[23,24,25] One review found a concordance of only 57% in carcinogenicity classifications for duplicate studies.[26] Moving away from the current research paradigm using animals is imperative, not only on moral and ethical grounds, but also to improve the predictive value of safety and efficacy tests.

In its current form, the UK Government does not have a strategy and sufficient existing policies to achieve its aims for the UK to become a "science superpower" in the life sciences. As stated above, there is mounting evidence that animals are not reliable models of human diseases and cannot be accurately used to predict human responses. As a consequence, data derived from animal studies may be viewed as a significant barrier to drug development or safety assessment and thus delay public access to potential new therapeutics. In a recent paper co-authored by scientists from the UK Medicines and Healthcare products Regulatory Agency, it was reported that the forced swim test – a test purportedly designed to gauge the antidepressant qualities of drugs – and equivalent tests cannot predict the efficacy of potential new antidepressant drugs, and could rule out effective new drugs for humans.[27] Transitioning towards human-relevant methods will likely improve patient access to treatments who need them more safely and in less time.

If finite public funds are to be used responsibly, they must fund research that leads to effective treatment for humans.

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Opportunities for UK to realise its research investment in the life sciences

Recent studies report that the pharmaceutical industry is reducing its reliance on animal tests because of the extensively documented difficulties in applying results from other species to humans.[28, 29] It has been estimated that from 2005 to 2008, European pharmaceutical companies have decreased their use of animals by more than 25%.[30]

A 2018 academic report of the economic landscape of non-animal methods states it clearly: "Many animal tests are simply too costly, take too long, and give misleading results."[31] Of more than 1,000 compounds tested on animals for improving stroke outcome, many of which reduced brain damage in rodents, none that reached clinical trials in patients improved stroke outcome.[32] Speaking about Alzheimer's disease, the chief science officer of the Alzheimer's Drug Discovery Foundation has commented, "We've cured mice engineered with this disease over 500 times. The mouse models don't translate into humans."[33] At the most conservative US estimate, the failure to reproduce preclinical research equates to approximately $28 billion per year on misleading experimentation,[34] not to mention the costs to society of frustrating the development of effective treatments and disregarding potentially helpful therapies and interventions.

There is growing scientific consensus that there is much to be gained from enhanced support for human-relevant research methods and technology that are better suited to solving human biomedical and regulatory assessment paradigms than from reliance on animal studies. For example, it is estimated that organ-on-a-chip technologies, which emulate tissue and organ physiology *in vitro*, could reduce total drug development costs by up to 25%, saving approximately US$700 million (£512 million).[35]

The Department for Business, Innovation & Skills (now the Department for Business, Energy & Industrial Strategy),[36] Innovate UK,[37] and the Medicines

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[36] Home Office, Department for Business, Innovation & Skills, Department of Health. Working to reduce the use of animals in scientific research. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/277942/bis-14-589-working-to-reduce-the-use-of_animals-in-research.pdf Published February 2014. Accessed 15 March 2022

Discovery Catapult and BioIndustry Association[38] have published reports that highlight concerns around the translation of animal models to human clinical benefits, alongside the potential business opportunities for human-relevant non-animal research methods in the UK. Additionally, Innovate UK has identified non-animal technologies "as one of a series of emerging technologies with the potential to drive future UK economic growth" and attract international investment. The report outlines how the UK's strengths – namely its pharmaceutical sector, consumer goods and personal care companies, contract research organisations, and academic researchers – have the ability to deploy non-animal technologies and position the nation as the a "global powerhouse in this area". So by facilitating their development and use, the UK will be in a position to drive economic as well as scientific progress. However, to date, the Government has done little to implement the recommendations of these reports to humanise biomedical research in the UK. It is vital that the recommendation from Innovate UK's 2015 Non-Animal Technologies Roadmap for the UK are implemented, and the recognition that the "market potential for non-animal technologies is huge [. . .] one of a series of emerging technologies that could drive future UK economic growth" is acknowledged and incorporated into all life sciences strategies. Alongside this, the Governments previous 2014 UK Delivery Plan[39] and subsequent 2015 publication,[40] "Working to Reduce the use of Animals in Scientific Research" must be updated, and more ambitious goals set in line with international scientific and policy developments since their publication.

Biomedical research, drug/therapeutic development, and other areas of pharmacology and medicine can benefit from modern applications such as artificial intelligence, simulations and mathematical modelling combined with systems elements based on *in vitro* methods and clinical studies that can derive data at the cellular, tissue, organ, body, and population level. By mandating a move away from animal experimentation and towards more advanced human-relevant scientific methods, the UK has the opportunity to expedite the development of new technologies that will streamline drug development, making the process safer, cheaper, and more effective. Developing these technologies also allows for the creation of interdisciplinary research teams that will be fundamental in creating the "human disease models of tomorrow".[41]

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[37] Innovate UK. A non-animal technologies roadmap for the UK: advancing predictive biology. https://www.ukri.org/wp-content/uploads/2015/11/IUK-071221-RoadmapNonAnimalTech.pdf Published November 2015. Accessed 15 March 2022.

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The Government does not currently have a strategy to support and incentivise biomedical research and innovation without animals, and thus the UK is missing out on a major economic opportunity. Dedicated funding is need to support UK researchers in the use and development of advanced human-relevant research and testing methods that do not use animals; resources from animal experiments should be redirected towards non-animal models of human biology and disease. Such research could build upon and complement the already impressive array of technologies available – including organs-on-chips, organoids, and *in silico* modelling – and offer tangible benefits to society by addressing the reproducibility crisis and high attrition rate in drug development.

Furthermore, companies and researchers with the potential to develop new therapeutic products would benefit from regulatory changes to allow greater use and acceptance of non-animal preclinical pharmacology and toxicology testing. Currently, researchers developing therapies that show promise in non-animal models of disease, for instance by producing changes in human-relevant models at the cellular or molecular level, may be presented with a restrictive choice between demonstrating the effect in an animal model (that may poorly predict effects in humans, see appendix) or not taking their project forward. Scientists using animal-free methods are also often pushed to test on animals by funding bodies, journal reviewers, as well as the regulatory authorities. For example, the Coalition Government's Delivery Plan "Working to Reduce the Use of Animals in Research" noted that conservatism among scientific journal editors and peer reviewers is a barrier to the uptake of non-animal methods, as publications tend to downplay the significance of non-animal research.[42]

When shifts away from using animals are initiated at government level, we see a thriving expansion in innovative, humane non-animal approaches that can have numerous applications, as evident when the European cosmetics animal testing ban came into effect; which it should be noted, was implemented irrespective of availability for non-animal replacement methods for all human health endpoints. In the advent of the testing ban, Europe invested heavily in the development of non-animal testing methods with fantastic returns. For example, scientists may now use high-tech, sensitive tests such as 3-D tissue models produced from human cells to evaluate whether chemicals irritate the skin and eyes. These humane tests are a great success story, not only in reducing suffering to animals but these tests have been found to produce more accurate, human-relevant results in comparison to tests on animals.[43] An impact assessment published by the European Commission

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[41] hDMT Institute. White Paper: Towards Precision Medicine in Future Healthcare: Organ-on-Chip Technology and hDMT. 2016.

[42] Department for Business, Innovation & Skills, Department of Health, and Home Office. Working to reduce the use of animals in research: delivery plan. Retrieved from https://www.gov.uk/government/publications/working-to-reduce-the-use-of-animals-in-research-delivery-plan. Published 2014. Accessed 15 March 2022.

[43] Joint Research Centre of the European Commission. *EURL ECVAM Progress Report on the Development, Validation and Regulatory Acceptance of Alternative Methods (2010-2013).* https://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-status-reports/files/eurl-ecvam-report-cosmetics-2013. Published 2013. Accessed 15 March 2022.

recognised that the provisions of the cosmetics animal testing ban were "generally seen as a crucial accelerator of research and validation of alternative methods by all stakeholders".[44] In addition, it was also stated within the report that "The search for alternative methods is by now also more and more recognized as the search for better science and forms part of an overall shift of paradigm in safety assessment". Indeed, the cosmetics testing and marketing ban, was first implemented in the UK as a voluntary ban,[45] and since then it has been influential internationally, with cruel cosmetic tests now illegal or policies in development to ban such practices across numerous countries. The UK has the opportunity to lead by example in other areas of biomedical research and testing.

The future of science lies in humane and human-relevant technology such as organs-on-chips, micro-models of the brain, and computer models that can more accurately predict what happens in human beings than tests on animals do. It is time for the UK Government to make its position clear on how the UK life sciences will be an international leader in these technologies.

What can the UK learn from other countries?

The UK's reliance on animal-based research is a significant obstacle to our becoming world leaders in the life sciences sector. Many of the world's leading scientists are now focusing on non-animal human-relevant research, due to the overwhelming evidence that tests using animals do not provide results that are applicable to humans.

The transition away from using animals to model human disease or as tools to predict human responses to drugs and towards human biology-based methods is changing policy around the world:

- In September 2021, Members of the European Parliament almost unanimously supported a Motion for a Resolution calling on the European Commission to develop an action plan, with timeline and milestones, to phase out experiments on animals and accelerate the transition to innovation without the use of animals in research, regulatory testing, and education.[46]
- The Netherlands has initiated the government-coordinated Transition Programme for Innovation without the use of animals (TPI) to help fulfil the country's ambition to be a frontrunner in innovation without animal testing. The TPI brings together regulators, scientists, funding bodies, and industry to offer them a

[44] European Commission**.** Commission Staff Working Document Impact Assessment on the Animal Testing Provisions in Regulation (EC) 1223/2009 on Cosmetics Accompanying the Document Communication from the Commission to the European Parliament and the Council on the Animal Testing and Marketing Ban and on the State of Play in Relation to Alternative Methods in the Field of Cosmetics. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013SC0066. Published March 2013. Accessed 15 March 2022.

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[46] European Parliament. Motion for a Resolution. https://www.europarl.europa.eu/doceo/document/B-9-2021-0425_EN.html. Accessed 15 March 2022.

platform for identifying and developing innovative activities within their fields that will increase the pace of the transition to animal-free research.[47]

- The US Environmental Protection Agency (EPA) released the first update to its New Approach Methods Work Plan for reducing the use of animals in testing. The plan lists concrete steps that the agency will take in the coming 3 years to reduce tests on vertebrates for pesticides and chemicals, including establishing metrics to monitor the agency's progress; developing, establishing confidence in, and accepting non-animal tests; offering educational opportunities on the use of non-animal methods; and engaging with stakeholders. The EPA work plan highlights that non-animal methods have the potential to increase the "rigor and sophistication" of chemical assessment by the agency.[48]
- Also in the US, the Food and Drug Administration Modernization Act of 2021 proposes to amend the Federal Food, Drug, and Cosmetic Act to lift the compulsory requirement to test all new drugs on animals in favour of "alternative testing methods".[49]

It is crucial the UK does not fall behind international developments and the Government upholds its manifesto commitment[50] to lead in animal welfare and science. As a recent UK industry report emphasised, the time has come for the UK to humanise drug discovery and toxicology[51] – this must be part of the Governments strategic direction for the UK life sciences. Now is the time for the UK government to make a commitment to develop a strategy for ending experiments on animals and prioritise funding for sophisticated non-animal methods.

The predominant Government-supported funding for the development of non-animal methods is through the National Centre for the Replacement, Refinement & Reduction of Animals in Research, which has provided £100 million in funding since its launch in 2004.[52,53] Considering this total spans almost two decades and comprises research on reduction and refinement as well as replacement of animals, this is an inadequate investment for UK science. Similarly, between 2015 and 2019, the Biotechnology and Biological Sciences Research Council spent only around £7 million of its research budget on developing innovative methodologies for studying human (and animal) physiology.[25,54] Its annual research budget is around £364

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[47] TPI. Increasing the pace of animal-free innovation. https://www.transitieproefdiervrijeinnovatie.nl/english/tpi%E2%80%99s-aim. Accessed 15 March 2022.

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[51] BioIndustry Association, Medicines Discovery Catapult. State of the Discovery Nation 2018 and the role of the Medicines Discovery Catapult. https://md.catapult.org.uk/resources/report-state-of-the-discovery-nation-2018/ Published January 2018. Accessed 15 March 2022.

[52] Freeman, G. Animal experiments. Parliament: Written Answer. HC 59104. 19 October 2021. https://questions-statements.parliament.uk/written-questions/detail/2021-10-19/59104. Accessed 23 November 2021.

[53] Freeman, G. Animal experiments. Parliament: Written Answer. HC 63808. 26 October 2021. https://questions-statements.parliament.uk/written-questions/detail/2021-10-26/63808. Accessed 23 November 2021.

[54] Freeman, G. Innovation and Research. Parliament: Written Answer. HC 59833. 20 October 2021.

million.[55] The UK must prioritise and redirect funds from animal studies to non-animal methods.

UK research needs modernising to keep pace with scientific advancements, and our policies must reflect this. Central to the Animals (Scientific Procedures) Act are the 3Rs principles of replacement, reduction, and refinement. This concept was developed over 50 years ago to benefit individual experimental design and not to address the need for understanding, and developing treatments for, many human diseases. A 3Rs policy is not fit for the purpose of meeting the need to develop a strategy to innovate scientific progress without using animals.

The British public want to see greater investment in non-animal methods. For example, 75% of respondents to an Ipsos MORI poll backed increased efforts to develop alternatives to animal use.[56] Particularly in light of the UK's exit from the EU, it is vital that the UK keeps pace with scientific advancements and that our evolving policies reflect this. Redirecting resources away from unreliable research on animals and instead prioritising investment in superior, non-animal methods will benefit humans, animals, and the future of science, and will allow the UK to boost its status as a world leader in science, research, and innovation.

Investment in skills to achieve a "high-tech economy" for the UK

As the fields of animal-free research and testing continue to expand, increased education and hands-on training will accelerate the transition to these methods. However, in deploying such initiatives, it is important to recognise that barriers can exist to adopting new technologies and therefore efforts to build confidence are needed. For example, Innovate UK, has recognised that overcoming scepticism about the ability of non-animal methods to model biological processes will help to overcome a major barrier to the uptake of these methods. Furthermore, conservatism and inertia to move away from animal-based methods can be overcome by encouraging scientists "to think beyond their immediate research areas to how their skills, technology and "know-how" can be leveraged and exploited to accelerate the development and adoption of" advanced non-animal methods.[57] It is vital that such educational initiatives be adopted and given ample financial support across the whole research and testing sector, from academia,

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https://questions-statements.parliament.uk/written-questions/detail/2021-10-20/59833. Accessed 23 November 2021.

[55] UK Research and Innovation. 2021/22 budget allocations for UK Research and Innovation. UKRI. https://www.ukri.org/wp-content/uploads/2021/05/UKRI-270521-UKRI-Allocation-Explainer-2021-22-FINAL-PDF.pdf. Published May 2021. Accessed 23 November 2021.

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[57] Innovate UK. A non-animal technologies roadmap for the UK: advancing predictive biology. https://www.ukri.org/wp-content/uploads/2015/11/IUK-071221-RoadmapNonAnimalTech.pdf. Published November 2015. Accessed 15 March 2022.

scientific and funding communities, industry and regulators, and from future scientists to established professionals.

Similarly, there is a need for additional education and hands-on training on non-animal methods. Students and early career scientists must be provided opportunities to develop the skills necessary to contribute to this research field so that the UK can compete with international developments. Because many study programmes lack sufficient courses about animal-free methods, supplemental training programs have been developed. For example, in the EU, the European Commission's Joint Research Centre (JRC) hosts a summer school on non-animal approaches.[58] Similar programmes could be replicated at national level, particularly now the UK is no longer party to the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM). In Canada, the University of British Columbia has accepted a new undergraduate module offered by the Society for Humane Science on 'New Approach Methods in Biomedical Science' that focuses on training students in animal-free methods for research and testing.[59] Many online resources featuring experts from the field also exist, including those offered by PETA Science Consortium International e.V.[60] and the Physicians Committee for Responsible Medicine.[61] Thus, information on animal-free research and testing is available and should be a component of all biomedical education.

Awareness among scientists about animal-free methods may be increased through the creation of a national centre of competences for animal-free research and testing, animal-free research officer positions to advise professors, staff and students, and tenure tracks and professorships based on non-animal methods. Universities and other academic institutes could also be encouraged to develop a departmental body with regard to the transition to animal-free research and testing that can work and advise across different departments. Such bodies could help organise PhD/postgraduate programmes that use only non-animal methods as well as workshops, seminars, and summer schools on *in vitro* and *in silico* methods. The Government funded UKRI[62] is in perfect position to provide leadership, and dedicated funding, for such opportunities through their research councils.

Because non-animal science and technology are rapidly evolving, it is not only education and training at universities that is needed. The curriculum for registered professions, such as the European Registered Toxicologist, should also include mandatory courses on new approach methodologies, *in vitro* to *in vivo* extrapolation, systematic reviews, and AOPs. Further, established researchers and

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[58] EU Science Hub. JRC Virtual Summer School on "Non-animal Approaches in Science: The Three R...evolution". https://ec.europa.eu/jrc/en/event/conference/jrc-summer-school-non-animal-approaches-science-3. Published 2021. Accessed 03 December 2021.

[59] Society for Humane Science. University Education. https://www.forhumanescience.org/influencing-science-culture/university-education/ Accessed 03 December 2021.

[60] PETA Science Consortium International e.V. Training Opportunities. https://www.thepsci.eu/our-work/training/ Accessed 03 December 2021.

[61] Physicians Committee for Responsible Medicine. NAM use for regulatory application. pcrm.org. Updated 2022. Accessed 17 March 2022. https://www.pcrm.org/ethical-science/animal-testing-and-alternatives/nura

[62] UKRI: UK Research and Innovation. https://www.ukri.org/

regulators using animal-based methods should be provided *re*-training opportunities as well as encouraged to forge multidisciplinary collaborations to evolve their skills and establish new and innovative ways of asking research questions and the methods used for answering them. For example, the Dutch TPI created a series of "helpathons", action-orientated workshops built around a specific question that encourages researchers through a community forum to think creatively and harness the power of coincidence in the discovery of new opportunities with regard to non-animal approaches. [63]

Funders may also require intermittent training, to identify the most promising advanced animal-free methods that could pose commercial potential. Similarly, regulators responsible for authorising experiments on animals, and those requiring testing data to meet legislative requirements (e.g., for medicinal and veterinary products, chemicals, biocides and pesticides), should partake in compulsory training in advances in animal-free science as part of their continuing professional development.

As the field of animal-free testing methods continues to expand, researchers and regulators must keep pace with these pivotal developments. Increased education and training initiatives are urgently required to gain more confidence in reliable and relevant non-animal methods that can best protect human health and the environment.[64]

A national science and innovation strategy

The work of PETA entities around the world to end the use of animals in several specific areas of experimentation has been met with success. PETA entities have developed the Research Modernisation Deal (RMD), [65] which maps out a strategy for ending the use of animals in biomedical research and regulatory testing and highlights the economic, public health, and animal welfare benefits of applying and developing advanced animal-free methods. The RMD is available at https://www.peta.org.uk/features/research-modernisation-deal/ or on request.

In order to end the use of animals in experiments and prioritise investment towards non-animal methods, the RMD recommends the development of a strategy, which can be integrated into Government policy, that includes the following critical steps:

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[63] TPI. Increasing the pace of animal-free innovation. https://www.transitieproefdiervrijeinnovatie.nl/english/tpi%E2%80%99s-aim. Accessed 15 March 2022.

[64] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. Article 38. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063. Published 22 September 2010. Accessed 15 March 2022

[65] People for the Ethical Treatment of Animals Foundation. The Research Modernisation Deal. https://www.peta.org.uk/wp-content/uploads/2020/05/PETA-Research-Modernisation-Deal-UK-EU-V1.3.pdf. Updated March 2020. Accessed 15 March 2022.

Strategic Priority #1: Immediately eliminate animal use in areas for which animals have already been shown to be poor and unreliable predictors for humans and have impeded progress

Where multiple reviews have documented the overwhelming failure of animal use to benefit human health in specific areas, these should be ended as soon as possible and replaced with more effective and efficient non-animal research methods. Some examples include cancer,[66] cardiovascular disease,[67] diabetes,[68] HIV/AIDS,[69] immunology,[70] nerve regeneration,[71] neurodegenerative disease,[72] neuropsychiatric disorders,[73] sepsis,[74] and stroke.[75] A full review, including specific methods of toxicity assessment, is provided in the RMD.

Strategic Priority #2: Conduct critical scientific reviews to identify the areas in which the use of animals can be ended

For those areas of investigation where there is still some question as to whether the use of animals is beneficial, a thorough systematic review should be conducted to determine the efficacy of using animals. Article 58 of Directive 2010/63/EU mandates that the European Commission conduct periodic thematic reviews concerning the use of animals in scientific procedures, thus providing a clear mechanism for advancing the replacement of animals in science.[76] While it was not a requirement for Article 58 to be transposed and is therefore not in the Animals (Scientific Procedures) Act 1986 (ASPA), the Animals in Science Regulation Unit (ASRU) of the UK Home Office has noted in "Guidance on the Operation of the Animals (Scientific Procedures) Act 1986" that "similar reviews can play an important part in ensuring the effective operation of ASPA" and proposes carrying

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[66] Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. *Am J Transl Res*. 2014;6(2):114-118.

[67] Chandrasekera PC, Pippin JJ. The human subject: an integrative animal model for 21st century heart failure research. *Am J Transl Res*. 2015;7(9):1636-1647.

[68] Wang B, Chandrasekera PC, Pippin JJ. Leptin- and leptin receptor-deficient rodent models: relevance for human type 2 diabetes. *Curr Diabetes Rev*. 2014;10(2):131-145. doi:10.2174/1573399810666140508121012.

[69] Girard M, Habel A, Chanel C. New prospects for the development of a vaccine against human immunodeficiency virus type 1. an overview. *C R Acad Sci III*. 1999;322(11):959-966. doi:10.1016/s0764-4469(00)87193-0.

[70] Bouvier NM, Lowen AC. Animal models for influenza virus pathogenesis and transmission. *Viruses*. 2010;2(8):1530-1563. doi:10.3390/v20801530.

[71] Angius D, Wang H, Spinner RJ, Gutierrez-Cotto Y, Yaszemski MJ, Windebank AJ. A systematic review of animal models used to study nerve regeneration in tissue-engineered scaffolds. *Biomaterials*. 2012;33(32):8034-8039. doi:10.1016/j.biomaterials.2012.07.056.

[72] Potashkin JA, Blume SR, Runkle NK. Limitations of animal models of Parkinson's disease. *Parkinsons Dis*. 2010;2011:1-7. doi:10.4061/2011/658083.

[73] Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. *Nat Neurosci*. 2010;13(10):1161-1169. doi:10.1038/nn.2647.

[74] Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A*. 2013;110(9):3507- 3512. doi:10.1073/pnas.1222878110.

[75] Sommer CJ. Ischemic stroke: experimental models and reality. *Acta Neuropathol*. 2017;133(2):245- 261. doi:10.1007/s00401-017-1667-0.

[76] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. Article 54. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063. Published 22 September 2010. Accessed 15 March 2022

out its own thematic reviews in consultation with the Animals in Science Committee (ASC).[77] To date, there has been no progress on thematic review at UK nor EU level.

Strategic Priority #3: Implement transparent, robust prospective and retrospective evaluations for all projects, allowing for a public commenting period so that external experts can contribute to them

To increase scientific scrutiny of research proposals and to identify failing animal models, we recommend that the UK Government develop and implement a more robust and transparent schedule of prospective and retrospective evaluations for all projects. Such an evaluation should not only be a pre-requisite at the licensing level but also at the funding level where public funds are being invested. To increase the transparency and accountability of the regulatory process further, project licence applications should be made available for a public commenting period, through which experts in non-animal methods have the opportunity to provide guidance, and associated retrospective evaluations should be published and linked to the original application. Such changes will help ensure the accuracy of the harm-benefit analysis process and its relevance to human clinical outcomes.

Strategic Priority #4: Harmonise and promote international acceptance of non-animal testing methods for regulatory toxicity testing requirements

To implement the vision of a more sophisticated approach to toxicity testing that will more adequately provide safety information on all chemicals in commerce, we further recommend that regulatory and government agencies enforce the existing UK legal requirement that a scientifically satisfactory method or testing strategy not entailing the use of live animals be used instead of a procedure involving animals wherever possible. In addition, we recommend that a public-private centre for predictive animal-free toxicology be established. Such a centre would help transform the science of safety assessment, with new tools to guide industry, government, consumers, and international trade partners to adopt best practices.

Strategic Priority #5: Increase funds for non-animal studies and decrease funds for animal studies

Poor predictivity of preclinical experiments on animals for toxicity and efficacy in humans has led to high attrition rates in the development of new therapies and is likely the cause of poor investment in the life sciences. The UK should focus on driving economic growth by prioritising investment in and development of inventive, intelligent technology that can also encourage outside investment in the life sciences. As described above, non-animal techniques are one of the emerging fields with growing economic potential, and investment in them could increase returns and, in turn, encourage new investors and collaboration opportunities.

Strategic Priority #6: Educate and train researchers and regulators on the benefits of and how to use non-animal research and testing methods

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[77] ASRU. ASRU Change Programme: Questions and Answers. Home Office. https://www.lasa.co.uk/wp-content/uploads/2021/07/ASRU-Change-Programme-Questions-and-Answers-Updated-May-29-20211.pdf. Updated 29 May 2021. Accessed 15 March 2022.

As outlined above, there is a need for additional education and hands-on training in non-animal methods. Students and early career scientists must be provided opportunities to develop the skills necessary to contribute to this research field so that the UK can compete with international developments. Alongside challenging scepticism about the ability of non-animal methods to model biological processes to help to overcome any barriers to the uptake of these methods.

For the UK to maintain its position at the forefront of global science and innovation, it must embrace scientific and technological progress and have the courage to challenge the status quo. Now is the time to take the next step and formally commit to the ultimate goal of ending animal use in biomedical research and testing. The Research Modernisation Deal offers a strategy for reaching this goal.

We hope the Research Modernisation Deal will be a useful tool for your reference and decision-making on Delivering a UK Science and Technology Strategy.

24 March 2022