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Perspective article

Mice in translational neuroscience: What R we doing?

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ABSTRACT

Animal models play a pivotal role in translational neuroscience but recurrent problems in data collection, analyses, and interpretation, lack of biomarkers, and a tendency to over-reliance on mice have marred neuroscience progress, leading to one of the highest attrition rates in drug translation. Global initiatives to improve reproducibility and model selection are being implemented. Notwithstanding, mice are still the preferred animal species to model human brain disorders even when the translation has been shown to be limited. Non-human primates are better positioned to provide relevant translational information because of their higher brain complexity and homology to humans. Among others, lack of resources and formal training, strict legislation, and ethical issues may impede broad access to large animals. We propose that instead of increasingly restrictive legislation, more resources for training, education, husbandry, and data sharing are urgently needed. The creation of multidisciplinary teams, in which veterinarians need to play a key role, would be critical to improve translational efficiency. Furthermore, it is not usually acknowledged by researchers and regulators the value of comparative studies in lower species, that are instrumental in toxicology, target identification, and mechanistic studies. Overall, we highlight here the need for a conceptual shift in neuroscience research and policies to reach the patients.

1. The value of animals in research

Laboratory animals provide a complex biological system in which we can control and standardize the genetic and environmental conditions, intervening and sampling when it is needed. The use of vertebrates and cephalopods for scientific purposes is regulated by law, based on Replacement, Reduction, and Refinement (3Rs) (Russel and Burch, 1959). At a time when the European Union (EU) members of parliament have voted to adopt a Resolution (RSP 2021/2784) calling for a '*coordinated Union-level action plan to facilitate the transition to innovation without the use of animals in research, regulatory testing, and education*', we join other voices in academia in defending the value of animal research (Homberg et al., 2021). Yet, we need to acknowledge an overuse that requires a sober reassessment of its value.

It is certainly irresponsible to suggest that animal research is not useful or that human-derived cellular models and bioinformatics/artificial intelligence could substitute them in the near future. This is perhaps a "*reductio ad absurdum*" argument, as it is unlikely that a regulatory agency would allow embarking on a clinical trial without some in vivo evidence of safety and efficacy; however, we are witnessing rapid progress on organ-on-chip acceptance for toxicology data (Cohen et al., 2021) – and thus, it is timely to ask precisely what animal research is useful for (Bale et al., 2019).

In translational research, preclinical studies in animals remain central to European Medicines Agency (EMA) and United States (US) Food and Drug Administration (FDA) regulatory agencies' guidelines for testing new treatments based on drugs, and genetic solutions, or regenerative products. The goal of these studies is to establish the scientific rationale of the proposed approach, ensure human safety, establish a starting clinical dose, dose-escalation scheme, and dosing regimen and identify potential toxicity along with safety biomarkers that can be monitored in the clinic, following Good Laboratory Practices (GLP). However, regarding both scientific rationale and toxicity, it has been estimated that more than 80% of compounds entering human trials fail (Paul et al., 2010; Perrin, 2014; Van Norman, 2019), a reason why many pharmaceutical companies have lately disinvested in animal research (Hunter, 2011; Kaiser and Feng, 2015). At the regulatory level, "The Food and Drug Amendments of 2022" passed by the US House of Representatives (H.R.7667, USCONGRESS, 2022) incorporates **animal testing alternatives** in the new drug approval process, allowing an

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applicant for market approval to use methods other than animal testing to establish the drug's safety and effectiveness.

Here, we highlight the need to reassess and redefine the value of mice in translational neuroscience research which has a famously high attrition, or failure rate. The neuroscience community is aware of this problem, as reflected in the ongoing debate about the predictive value of mouse strains in basic and regulatory studies (Dawson et al., 2018; Garner, 2014; Gururajan et al., 2019; Kafkafi et al., 2018a; Morrissette et al., 2009; Nestler and Hyman, 2010; Perlman, 2016; Perrin, 2014; van der Worp et al., 2010).

We have stratified factors contributing to the poor translation of animal models in three levels (Fig. 1). The many problems identified in the translatability of **preclinical data** have been extensively discussed (An, 2018; Begley and Ioannidis, 2015; Garner, 2014; Goodman et al., 2016; Ioannidis, 2005; Kafkafi et al., 2018b; Macleod et al., 2014; Richter et al., 2010, 2009). To name a few, highlighted for their contribution to the reproducibility crisis, are the lack of training, un-rigorous science, poor experimental design and analysis, small sample size, and, overstated claims (favored by a system that overly rewards positive results). Initiatives have been launched to encourage the use of good practices and more accurate animal models in academia and industry in order to mitigate these issues (EMA, 2017; FDA, 2015; Garner et al., 2017; Gurusamy et al., 2021; Percie du Sert et al., 2020; Ritskes-Hoitinga et al., 2020). Yet, another reason for the high failure rate is the poor predictive translational power of the **animal models** themselves (Akhtar, 2015; Garner, 2014; Garner et al., 2017; Shanks et al., 2009). Modeling human brain disorders in animals is extremely challenging. The strategy often followed has been to deconstruct these disorders into more straightforward and easily quantifiable phenotypic units or endophenotypes (Gould and Gottesman, 2006; Lenzenweger, 2013). However, this approach reduces the efficacy and predictive value of the outcomes since they rarely cover all the symptoms of a disease (Al Dahhan et al., 2019). Thus, a major challenge when developing a model is either to target the entire spectrum of the brain disorder (Kalueff and Stewart, 2015) or to interpret the model accordingly to the limitations of the chosen endophenotype. The quality of an animal model is measured by its validity, which should be established for several aspects related to content and applicability. In general, a model has '*face value*' if it appears outwardly similar to what it is supposed to model, '*predictive value*' when it actually predicts the supposed outcome(s), and '*construct value*' if it involves the supposed disease mechanisms. We can also assess its '*internal validity*' or consistency with both the theory and existing data and its '*external validity*' which means that the results are broadly applicable and not limited to our experimental setup. Finally, *convergent* validity and *divergent* (or discriminant) validity inform us about the confirmatory and discriminant capacity of our model relative to other models. Some ongoing initiatives promote a more sophisticated way of delivering both construct and face validity, but the failure of mouse models to predict human outcomes is more often a failure of predictive, external, and convergent validity (Garner, 2014). For example, genetically modified mice have, in general, good construct value (supposed mechanism) and aim for good face value (phenotypic resemblance) but results are rarely predictive of the human outcome and seldom applicable to other models or correlated with other measures. Predictive value does not require a phenomenological resemblance to the human condition, and, indeed, some simple model organisms that have little face value turn out to be more insightful, because of the lack of assumptions. In translational research, predictive validity (translatability) is the ultimate proof of a model's value and can be calculated retrospectively, after obtaining data from humans (Willner, 1991). Reverse translation can improve the model value by adopting human biomarkers known to have clinical implications (in terms of disease development, prognosis, diagnosis, or drug response) (Garner, 2014; Venniro et al., 2020). In brain disorders, there has been a lack of biomarkers and objective diagnostic tests that could enable reverse translation (Nestler and Hyman, 2010), but lately, refined technologies have allowed validating several molecules as useful biomarkers (Khalil et al., 2018; Lleó, 2021). Thus, a critical step in translational neuroscience preclinical studies is to select a reproducible and predictive animal model. Notwithstanding, some argue that the translational problem is a level above, at the **interspecies translation** (Van Norman, 2019), given the notable differences between the rodent and the human brains, particularly in circuits underlying cognition and complex behaviors.

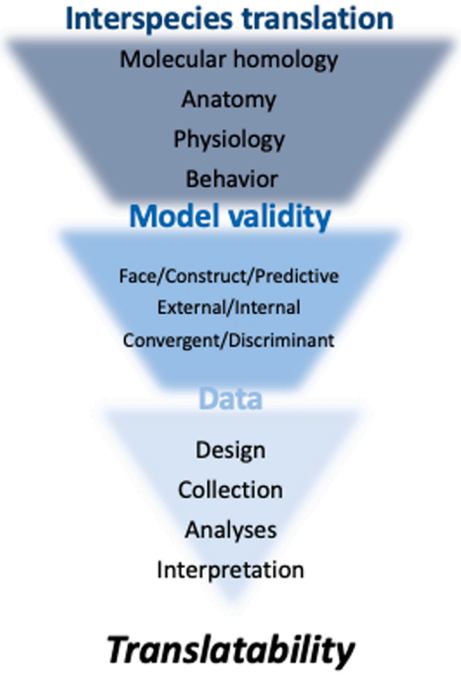

Fig. 1. Translatability in neuroscience research. Interspecies differences at molecular, anatomical, physiological and behavioral levels need to be considered when choosing a species to model a human disease. Next, the validity of an animal model should be considered in three independent dimensions 1) face/construct/predictive; 2) internal/external; and 3) convergent/discriminant. Lastly, the quality of the non-clinical data is critical for translation. Frequent problems are found in the *design* -no blinding or randomization, lack of input from clinicians-, *execution* and *collection* -insufficient training, inconsistent methodology, lack of reproducibility-, *analyses* -definition of endophenotypes, surrogate endpoints, statistics- and *interpretation* -tendency to anthropomorphize results instead of extrapolate them based on the physiology of each species.

In this perspective, we would like to highlight that there are many models, simple and complex, which can be useful in neuroscience translational studies if properly applied, and, in parallel, raise awareness of the overuse of mouse models without an in-depth analysis of their adequacy to the specific research question.

2. Selection of the species

The careful selection of the most informative species for an animal model is critical in order to replicate the disease completely and optimize its validity (Varga, 2012). A fundamental aspect is to find those species from which translation of results to humans is most straightforward. The selection of a species should not be based solely on availability, familiarity, or cost, yet, unfortunately, a long-standing problem is that when a scientific question can be studied in different species, researchers mostly prefer the cheaper and/or well-established animal model (Coid, 1978).

The selection of the most suitable animal for modeling a disease requires preclinical and clinical experts - veterinarians, neuroscientists, biologists, electrophysiologists, psychiatrists, psychologists, and bioinformaticians, among others - working together to establish a set of

scientific criteria, which the model must meet. This multidisciplinary team of specialists must take into account, not only the financial feasibility but also the biological characteristics, the available imaging, and molecular techniques, the results of previous experiments, and also the ethical issues for a given species (Ericsson et al., 2013; Walker and Eggel, 2020). In this regard, 66% of Europeans were found to feel that experimentation using mice is acceptable if this leads to improvement in human health and wellbeing, but only 44% agree, and 37% disagree, with the use of dogs or monkeys for the same purpose (EC, 2010). Likewise, in a recent survey in Spain, we observed that the percentage of people opposing the use of dogs or monkeys in research was higher than that against the use of mice, and that the vast majority of people working with laboratory animals considered their job a socially sensitive issue (Goñi-Balentziaga et al., 2021, 2022). In the US, Pew Research Center poll found that 47% favor the use of animals in scientific research, while 52% oppose it, but most Americans accept genetic engineering of animals that benefits human health (Funk and Hefferson, 2018). Overall, these results support the idea that the use of animals in research is based on utilitarianism (Singer, 1975) and on the assumption that animals with lesser capacities are considered to have lesser moral status (Walker, 2006).

3. Mice in translational neuroscience research

In 2017 and 2018, the Member States of the EU used 18,309,920 animals for the first time in research and testing. Of them, 56.7% (~ 10.37 M) were mice (*Mus musculus*) and 10.8% (~ 1.9 M) rats (*Rattus norvegicus*) (EC, 2019, 2021b) and both in translational and basic research, neuroscience applications occupied the top positions. There are no official statistic regarding the use of rodents in the US, but it has been estimated that 44.5 million mice and rats underwent potentially painful experiments during the same period (Carbone, 2021). The rapid development of technologies to manipulate the mouse genome (Gurumurthy and Lloyd, 2019) has facilitated the creation of multiple mouse models to study genetic factors in complex disorders, including many brain disorders (Kas et al., 2007). Preferred mouse strains are highly inbred, providing uniformity to easily reproduce an experiment and achieve statistical significance (Casellas, 2011). However, it is important to note that this genetic standardization is far from optimal to model human genetics and, in practice, it is not always conserved (Crusio, 2004; Crusio et al., 2009; Wolfer et al., 2002). Similarly, it is noteworthy the negative impact of environment standardization on external validity (Voelkl and Würbel, 2021).

Another approach to improve in vivo preclinical studies has been the generation of humanized mice or mouse-human chimaeras (Morata Tarifa et al., 2020; Shultz et al., 2007). Different laboratories have generated humanized chimeric mice with human neuronal and glial progenitors for the study of human neuronal development (Chen et al., 2016), to study progressive multifocal leukoencephalopathy (Kondo et al., 2014), and Huntington's disease pathogenesis (Osipovitch et al., 2019), and for the treatment of congenital hypomyelination (Han et al., 2013; Wang et al., 2013; Windrem et al., 2008).

Mouse behavioral assays have been developed to analyze the consequences of genome manipulation and to evaluate proposed therapeutics in preclinical studies (Bucan and Abel, 2002; Sukoff Rizzo and Crawley, 2017). Although somewhat useful in screening studies, this approach alone is a poor strategy for translational neuroscience. Moreover, there is a strong tendency in neuroscience to use relatively simple, quick, and seemingly easy tests performed with no formal training in behavioral sciences (Garner, 2014) with lamentable results. In an effort to increase reproducibility, the use of more automated behavioral analysis systems has been promoted (Quinn et al., 2006; Van de Weerd et al., 2001), but this does not address the systematic tendency to overinterpretation and anthropomorphizing of mouse behaviors, an ingrained issue in neuroscience research, more difficult to correct.

The rodents are better for modeling those aspects of human disorders related to the primary motor or sensory areas, not to associative areas. Indeed, most success in forward translation (Venniro et al., 2020) is found in addiction research, in which three approved medications — acamprosate, naltrexone, and nalmefene — were developed by means of animal models (Spanagel, 2017). Overall, motor behavior is more phylogenetically conserved among species than cognitive abilities. Rodent models that reproduce the lack of dopamine in Parkinson's Disease are useful for pharmacological screening and other approaches aiming for dopamine replacement, even if they are not useful for identifying disease-modifying therapies, as the mechanisms are not the same (Bankiewicz et al., 2001). On the other hand, transgenic mice based on human mutations in *PARK* genes (construct value) have been of little value (Blesa and Przedborski, 2014). Perhaps, novel models could be more predictive for such approaches (Nuber et al., 2018). However, there is a tendency to look for models that closely resemble the human phenotype (face value), notwithstanding the obvious differences in bipedal gait generation and fine motor skills, among others.

Nevertheless, most problems arise when modeling complex brain disorders, such as Alzheimer's disease (AD), and, in fact, AD transgenic mice generated so far are a prototypical example of poor translatability. None of AD transgenic mice has been able to recapitulate the neuropathology associated with the disease (Dawson et al., 2018), which is not surprising given the enormous species differences spanning from brain anatomy (Wise, 2008) to molecular isoforms and splicing variants (Leung et al., 2021), including tau isoforms (McMillan et al., 2008). The consortium MODEL-AD (www.model-ad.org) was created to develop the next generation of in vivo AD models. Current transgenic models use genome editing to better recapitulate human traits (Hosokawa et al., 2021), but we do not know whether they will be more predictive in translation.

Although useful to identify basic pathogenic mechanisms in some brain disorders, mouse models are limited by gross anatomical and connectivity differences, given that rodents lack certain cortical areas, such as 'granular' homotypical cortex in multiple functional areas including the dorsolateral and ventral prefrontal, orbitofrontal, and the frontopolar cortex that appeared during primate evolution (Wise, 2008). As mentioned above, a recurrent problem in complex brain disorders is the overinterpretation of cognitive/behavioral phenotypes arising in mice from different brain circuits. For example, a recent study of Fragile X syndrome in human brain organoids revealed no alteration of metabotropic (m)GLUR5 receptors, a promising target in mouse preclinical studies that had failed to translate in clinical studies (Kang et al., 2021).

4. Alternative approaches using large animals

Large animals more closely match human biological, behavioral, and/or genomic features. They are reasonably outbred and long-lived, allowing for longitudinal studies, and are more similar in size to a neonate or small child, providing an opportunity to address issues related to scaling up therapy as well as developmental and age-related features. Many anatomical and physiological parameters are more similar to those in humans (versus those in mice), and have demonstrated better suitability for translation into humans (Casal and Haskins, 2006; Hein and Griebel, 2003; Ribitsch et al., 2020).

Moreover, large animals have the potential to be naturalistic disease models of human brain diseases that can benefit from clinical veterinary studies. For example, dogs (*Canis familiaris*) present common behavioral problems such as anxiety, compulsive disorders, or age-related cognitive dysfunction (Azkona et al., 2009; Overall, 2000). In the same way, the study of neurodegenerative diseases may benefit from studies in aged large mammals (Danek et al., 2017; Eaton and Wishart, 2017; Emborg and Kordower, 2002; Moreno-Gonzalez and Soto, 2012; Ruple et al., 2022). For these studies, creating a strong, high-performing team of clinicians, scientists and veterinarians would improve productivity as recently remarked (Ober et al., 2022).

In addition, genetically altered large animals, made possible by the advances in transgenic technology, may lead to animal models with higher face and construct validity than rodents. The generation of genetically edited pigs (*Sus scrofa domestica*) (Lillico et al., 2013) and rhesus monkeys (*Macaca mulatta*) (Chen et al., 2015) represented an important step forward in preclinical studies. Besides, the ability to engineer the same disease mutation into several species to compare the different models against the observed human pathology is a powerful strategy to advance new treatments (Whitelaw et al., 2016).

Notwithstanding, in the EU and Norway the use of pigs, dogs and non-human primates (NHP) represented only 1% of total animals used for scientific purposes, although the use of NHP has increased slightly (4%) in 2018 (EC, 2021b). In the US the number of monkeys used in biomedical research reached an all-time high in 2017 (75,825), although their use has decreased by around 10% in the last two years (USDA, 2017, 2018, 2019). For complex traits, neuroscience researchers are favoring the use of NHPs given the profound differences in cognition and behavior between rodents and primates, and the underlying anatomical and molecular differences (Scott and Bourne, 2021). Primates have disproportionally enlarged neocortices and relatively higher proportion of interneurons which are increasingly identified as pathogenic players in neuropsychiatric disorders. The expansion relative to other mammals occurs mostly in the association cortices in which primates have a higher proportion of interneurons compared with primary sensory areas (28.5% vs 16% in humans) while in mice the proportion is closer (14.5% vs 12.5%). At the subcortical level, primates also have a distinct type of striatal interneurons that has no counterpart in mice (Krienen et al., 2020). Interneurons shape the properties of local circuits and are instrumental in maintaining the excitatory/inhibitory balance, providing greater control over integrative functions underlying complex behaviors. Interestingly, a recent study has described a 10-fold expanded interneuron-to-interneuron network in the human cortex that is sparsely present in mouse (Loomba et al., 2022). A new type of dopamine neuron that could project directly to the cortex and has no counterpart in mice has also been recently described in the dorsal tier of the substantia nigra of humans and monkeys, which is also considerably expanded relative to rodents (Kamath et al., 2022).

Therefore, there are specific research areas where the use of monkeys may be indispensable, such as opioid addiction research (Venniro et al., 2020) and complex brain disorders (Scott and Bourne, 2021).

5. Why is it so difficult to implement the use of large animals in translational neuroscience?

It is noteworthy that the main reasons for using rodents instead of large animals are often not scientific. Large animals are pricey and require bigger space and dedicated facilities to maintain them (Goodman and Check, 2002; Hagen et al., 2012). In a recent survey, mouse researchers most commonly selected practical constraints (79%), such as the ease of procuring animals, cost, vivarium space or the availability of research tools as informing their species choice. By contrast, only 14% of NHP researchers and 15% of researchers using mammals other than rodents or NHPs selected practical constraints (Walker et al., 2022). Besides, developing animal models in large animals requires expertise, not only as a researcher but also as a surgeon or anesthetist, thus people with no formal training in veterinary medicine cannot do studies in large animals (as they do in rodents). Nor can we ignore the fact that working with large animals can be emotionally demanding, as it is easier to bond with them.

Nevertheless, although using large animals could significantly increase the quality of the preclinical data and achieve comparable scientific progress with fewer animals, the use of companion animals, such as dogs, and the use of NHPs in research is a very sensitive issue. Good communication and engagement with stakeholders can facilitate progress in this regard (Mendez et al., 2022). However, there is a strong rejection from part of the society and, therefore, governments in Europe are opting to legislate to end experiments, instead of promoting scientific culture and educating the society to appreciate the benefits of using predictive animal models in biomedical research. For example, European legislation (Directive 2010/63/EU) states that the use of NHPs should be permitted only in biomedical areas essential for the benefit of human beings. This is undisputable for great apes. However, for other primate species, such restrictive legislation motivates researchers to conduct primate experiments in more permissive countries (Hao, 2007), in which even highly controversial human-primate chimera experimentation is permitted (Tan et al., 2021b). The airlines' decision to end monkey transport will create additional problems for biomedical research (O'Grady, 2022).

More resources for training, education, dissemination, husbandry, and data sharing, including the creation of multidisciplinary teams, in which veterinarians need to play a pivotal role, are urgently needed. Regulatory, financial, and scientific policies would be instrumental to improve translational efficiency in neuroscience research. To this end, it would be important to incorporate welfare and modeling experts into grant panels and decision-making committees. Recent strategies such as the BRAIN initiative (www.braininitiative.nih.gov) are promoting collaborative primate sharing resources like PRIME-DRE to advance NHP neuroimaging as an integrative approach for multiscale neuroscience (Consortium, 2021) and to extend data access to researchers, independently of their budget, location, training or facilities. A similar approach has been taken to share electrophysiological data in macaque monkeys (Wild et al., 2022).

6. Alternative species

Less complex model systems utilizing a richer diversity of animal model systems, in particular species with the lowest capacity to experience pain, suffering, distress and lasting harm, could be useful models to discover fundamental molecular and physiological principles essential for nervous system function, as perfectly illustrated by Kandel's studies on learning mechanisms in *Aplysia californica* (Kandel and Schwartz, 1982). Without being exhaustive, studies in invertebrate animals, like the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, have provided a means to link neural mechanisms to behavioral plasticity (Holden-Dye and Walker, 2018). These species provide the opportunity to do not only reverse genetics but also forward genetics, which is a phenotype-driven approach that involves the phenotypic screening of organisms with randomly induced mutations followed by subsequent identification of the causative mutations (i.e., those responsible for phenotype) (Sin et al., 2014). Simple models with little face value but good construct value may provide reliable insights and lead to more successful approaches, having, in many instances, higher predictive value than standard mammalian models. Research in tadpoles (*Xenopus tropicalis*) has provided mechanistic insight into the sex bias in autism (Willsey et al., 2021). This is another example of the use of a simple model (with no face value) to easily study mutations in multiple genes to identify a pathway that can be later validated in human organoids. Zebrafish *(Danio rerio)* is considered an emerging successful model for translational neuroscience in which to study novel candidate genes and for high-throughput screening (Stewart et al., 2014). Currently, many more species are being sequenced, and the scientific community has the potential to generate genetically modified lines of a wide range of species.

In summary, comparative studies of strategically chosen non-mammal species can perhaps replace mouse research in some instances and address some of the limitations discussed previously (Keifer and Summers, 2016). Thus, the combination of a comparative approach with the advantages of model systems would lead to more rigorous research in neuroscience (Brenowitz and Zakon, 2015; Maximino et al., 2015). Unfortunately, the potential of these species has been often underestimated, both by funding agencies and journal editors. We believe that the neuroscience community needs to educate not only

young researchers but also policy and financing bodies to promote a critical but fair appraisal of alternative, non-traditional modeling approaches.

7. Towards the first R

Replacement is still the most challenging of the 3Rs in terms of the technical and strategic nature of the research that is needed (Brock et al., 2004). In 2006, 79% of European citizens claimed that there was not enough public funding for the development and validation of alternative methods to replace animal experiments (EC, 2006). Among them, the use of human iPSC-derived neurons and brain organoids is rapidly gaining traction (Costamagna et al., 2021; Tan et al., 2021a). As mentioned above for Fragile-X syndrome, findings in simple model organisms can be complemented with data from human brain organoids (Kang et al., 2021). Moreover, it would be desirable to limit in vitro experiments with mouse and rat primary neurons or neuron-like lines, as primate and human cell lines are currently available.

The EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) is working to validate regulatory requirement tests to replace animals. Recently, EURL ECVAM and the European Commission's Joint Research Centre conducted a survey to investigate stakeholder opinions and perceived needs for the successful implementation and acceptance of complex in vitro models (CIVMs). The outcome of the survey showed that there is high interest in establishing mechanisms for adequate CIVMs for their use in regulatory and research studies. However, they are still underdeveloped and not standardized enough to allow proper assessment in regulatory terms (Batista Leite et al., 2021). As a first step, this year, the EU Commission implementing regulation (2021/1709) ruled out the use of the mouse bioassay for the detection of Paralytic Shellfish Poisoning toxins, as the Standard EN 14526 is available as an alternative method, complying with the current European legislation (EC, 2021a). In the US the FDA Modernization Act shall end the mandatory request of animal studies for the approval of new drugs. Moreover, we cannot ignore that during COVID-19 pandemia we have witnessed a dramatic acceleration in translation, partly by allowing human studies to begin before all standard animal tests of the vaccines had been concluded. This should help bring about a much-needed change in the perception of the irreplaceability of animal tests (Ritskes-Hoitinga, 2022).

8. Conclusion

Steps are being taken, if small, towards the total replacement of non-essential animal studies in biomedical research. Animal experimentation is still required to advance knowledge and therapies for human diseases. However, it is time for a conceptual change in neuroscience research, and we want to emphasize that the mouse is not the only, nor often the best, species in which to model human brain disorders for translation. Among large animals, NHP are better positioned to provide relevant information because of their higher brain complexity and homology to humans. To broaden NHP use in research we need to ensure that this does not compromise their wellbeing. Restrictive legislation is hardly going to improve it as it often promotes outsourcing studies to countries with less stringent laws. More resources for training, education, husbandry, and data sharing, including the creation of multidisciplinary teams, in which veterinarians need to play a pivotal role, are urgently needed. Regulatory, financial, and scientific policies would be instrumental to improve translational efficiency in neuroscience research.

Conflicts of Interest

The authors declare no conflict of interest.

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