“Supporting Replacement in Academia: Exploring barriers around the acceptance and uptake of non-animal methods in science in UK Academia”, RSCPA report, sept. 2024

Summary

Although progress has been made over the last decade in the development of non-animal methods (NAMs), scientific and technological challenges remain. In addition to ethical issues, there is a growing awareness of the limitations of certain animal models, in terms of reproducibility, validity and transferability. Until now, the focus has been more on regulatory testing for new drugs, vaccines or chemicals than on academic research. However, in this field, there are sociocultural issues concerning the way science is currently done which act as barriers and brakes on the capacity and speed of replacement.

This report is based on a qualitative survey conducted in UK universities and medical schools among researchers and PhD students from all disciplines (32 in-depth interviews, including 8 PhD students). This study offers insights into key barriers around the use of NAMs and drivers of animal models in academia. 11 key themes arised, providing the basis for future multi-stakeholder work aimed at facilitating opportunities for overcoming some of the challenges and barriers identified.

1) Knowledge, expertise and experience

- It lacks ***skills required to make the transition to NAMs***at team level, both for the technical aspects and in terms of confidence in the reliability of these methods; there is a lack of procedural guides and standards, particularly for organoids; the risk of investing time in a new technique that may prove unsuitable or outdated is seen as an obstacle.
- The ***familiarity with animal models*** favors their continued use, whereas with NAMS, it's not clear how to calculate the cost of project, or whether we'll be able to publish (what are the right controls, etc.); using animals also allows us to compare our results with previous ones, giving an impression of security.
- ***The use of specific animal models***The use of specific animal models, requiring model-specific skills, is an incentive to continue using them. To publish and collect new data, it's easier to keep the same model. The time spent developing new approaches, relearning techniques, etc. is time not spent publishing. The practice of short contracts in universities, especially at the start of a career, favours this stability. Researchers who use both animal models and NAMs are rare.
- An important driving force behind the continued use of animal models is ***experience of the successes achieved*** with these models: positive results, publications, collaborations, obtaining funding, the possibility of using new techniques on these well-known models. Compared with *in vitro* models, animal models are considered to produce more results, and therefore more productive. All the more so as animal research is becoming increasingly standardized. All this leads to a downplaying of the urgent need to develop non-animal methods. Animal research is not seen as a real problem.
- The ***in vivo skills are considered sought-after by academia and industry alike*** (for example, in animal surgery). This makes it easier to find a job.

2) Training in NAMs

- ***Access to training*** on NAMs poses a problem. Training must be linked to project research, particularly during doctoral and post-doctoral studies. NAM training funds should be included in the budgets of projects using animals.
- We highlight ***the absence of formalized NAM training courses***. Training tends to be informal. On the other hand, for animal research, mandatory and organized training courses are planned.
- On the other hand, information is provided, but it's not enough. This has consequences for the confidence that researchers have in NAMs.

3) Funding

- To obtain funding for research and development in the NAMs, ***demonstrate prior experience and expertise***. You need to collaborate with researchers working on *in vitro* methods, or conduct a pilot study before project. This takes more time.
- Another obstacle is the ***duration of research funds***. If they are short-term funds, as is often the case in the UK, this is an obstacle to embarking on the development of new techniques. Efforts to change methods during the course of project are not encouraged if they do not produce results (and publications) within the allotted time.

4) Access to NAMs

- ***The high development costs of NAMs*** are cited as a major obstacle, particularly for organoids, compared with animal research. The perception is that small labs can't afford it. The balance of costs may shift in the future, but in the meantime, this is holding back the widespread adoption of NAMs.
- ***Access to the required infrastructure*** (space, equipment, expertise and support) is a key factor. And it's not easy when the all-important animal research infrastructure is already in place. Having these animal infrastructures in place, with animal facilities, technical support staff for animal care, training programs, the ability to generate genetically modified mouse lines, standardization... all encourage the pursuit of animal research. And this, even if it's not the best model in terms of transferability. Investing in NAMs requires institutional support, and cannot be the choice of a single researcher.

5) Career progression

- ***The pressure to publish*** favors the use of familiar models, because of the training and development time that a new model would require. It's too risky. Especially in a context of short-term contracts.
- In addition, the use of NAMs is constrained by the ***perception that any results will have to be validated in animal models*** to be accepted for publication in a reputable journal. Even though an *in vitro* model may prove more physiologically relevant than *in vivo* models. But there is a bias in favor of animal methods.

6) Communication and collaboration between those developing/using NAMs and those using animals

- ***Lack of communication*** (working in "silos") leads to everyone remaining in their own "bubble". Dialogue needs to be initiated in a non-confrontational way, between the two groups, without categorizing "animal users" and others. The aim is to share information, suggest potential alternatives and initiate collaboration. This dialogue would also enable us to find out more about the needs of animal researchers in terms of alternatives.
- ***The development of alternatives needs to be placed in the in vivo context***The development of alternatives needs to be placed in the in vivo context, for good communication and mutual understanding, for relevant implementation in human physiology, and to ensure that NAMs are adapted and relevant. *Ultimately,* the challenge is to find relevant models for patients.

7) Awareness of NAMs

- There's a need for ***better communication on the benefits and opportunities offered by NAMs***. Awareness is more than just information. We need to communicate on how to access NAMs, funding opportunities, the practical aspects of their use, and their scientific benefits. We need to create a community around NAMs, demonstrating all their advantages, in terms of both research and careers, to encourage researchers to train and use them. There needs to be a forum for dialogue and exchange on the needs and constraints of researchers using animals.
- ***The perception that replacement is more difficult to implement than reduction and refinement*** represents an imbalance in the promotion and implementation of the 3Rs. Replacement seems more abstract, more distant, more disruptive to established research processes.

8) Institutional commitment to replacing animals

- ***Ongoing investment in animal infrastructure and a lack of visible investment in support for NAMs*** are characteristic of institutions with a limited commitment to replacement. The initiative must then come from researchers, who must fund access to non-animal research infrastructures from their own funds. But commitment varies from one university to another.
- ***The implementation of and commitment to the 3Rs is sometimes perceived as merely symbolic*** both at institutional and researcher level. In such cases, the 3Rs are just "boxes to tick", and we "pretend we're making an effort" without making a serious commitment to them. This underlines the importance of deploying replacement strategies with action plans to create the conditions for real replacement in the future.

9) Use of NAMs in conjunction with animal models

- ***The use of NAMs is often seen as enabling more precise in vivo investigations, as well as reducing and refining the use of animals (rather than replacing them).*** NAMs enable questions to be better targeted in *in vivo* investigations, contributing to the reduction. They are also used to complement animal research, providing another way of answering a scientific question. However, there are also cases where NAMs enable new avenues of research to be developed, independently of animal research.
- ***Lack of confidence in the feasibility of a complete replacement*** is often mentioned. The importance of using a whole living organism, at least at one stage of the research, is

emphasized, especially in studies of complex physiological systems. One option, however, would be to develop *ex vivo* studies using animal tissue or, better still, human tissue. As a result, there is a risk that NAMs will develop alongside animal models, without replacement. To gain support for the transition objective, it is better to focus on cases where replacement is possible, while remaining open to technological advances that may emerge in the future. The principle of NAMs should be maintained as potential replacement possibilities rather than as complementary methods.

10) Perceived technological or scientific limitations of NAMs (excluding cultural aspects)

- ***The level of complexity achievable with current NAMs, in terms of representing the physiological characteristics of a living animal, is deemed insufficient*** The level of complexity achievable with current NAMs, in terms of representing the physiological characteristics of a living animal, is judged insufficient: for example, to take into account the variability of response to products, to correctly describe the biodistribution of a product in the organism, and so on. As a corollary, the need to deepen fundamental physiological knowledge of animal models is mentioned, to enable the development of more complex, relevant and precise NAMs.

11) The "established" nature of particular animal models

- ***The history of the use and characterization of certain animal models encourages their continued use.***. This is particularly true of the mouse, for which considerable knowledge has been accumulated on metabolism and genetics. Protocols are standardized, etc. Any new data is immediately contextualized within the known framework.
- ***These models have acquired the status of "gold standard*** within the research community in certain fields, which has an impact on the possibility of publishing, on research directions, on investment in infrastructures... hence the inertia.

Concluding remarks

For many researchers, the main driver for using NAMs is not the transition to non-animal research; they are seen as complementary methods. This makes it all the more important to assert the ethical imperative of replacement. However, the 3Rs are not a major source of motivation for researchers. Replacement is hampered by the need to develop new skills and collaborations, and is perceived as disruptive to traditional research directions. Researchers, moreover, are not encouraged to change by the way research is organized: short-term contracts, pressure to publish in good journals, the need to secure funding, especially at the start of a career.

Disseminating and raising awareness of NAMs must involve the creation of forums for dialogue and community-building, in phase with the academic research incentive system. The implementation of NAMs must not be detrimental to researchers' careers. We therefore need to take action to inform, raise awareness and build confidence in NAMs, to ultimately generate enthusiasm. We must remember that the barriers to transition are not only technical and scientific, but also sociocultural ("how science is done").