akademien der wissenschaften schweiz
académies suisses des sciences
accademie svizzere delle scienze
academias svizras da las scienzas
swiss academies of arts and sciences

Monkey, Mouse or Zebrafish?

Ethical and scientific considerations in choosing model organisms for animal experiments

Symposium report

The symposium entitled "Monkey, mouse or zebrafish? Ethical and scientific considerations in choosing model organisms for animal experiments", organised by the Ethics Committee for Animal Experimentation (ECAE) of the Swiss Academies of Arts and Sciences (a+), was held online on 1 July 2021. This event attracted considerable interest, both in Switzerland and abroad, with over 400 people participating.

The aim of the symposium was to explore the scientific and ethical problems arising in connection with the choice of model organisms for animal experiments, and to raise awareness of these questions among researchers, animal welfare officers and regulators. In his introduction, **Professor Hanno Würbel**, director of the Animal Welfare Division at Bern University and chair of the ECAE, explained the importance of this topic. Under the Swiss Animal Welfare Act, experiments involving sentient animals may only be carried out if the expected gain in knowledge cannot be achieved using alternative (animal-free) methods or via experiments in "animal species that are lower on the evolutionary scale". This raises questions not only as to the assessment of the gain in knowledge but also as to the existence of a moral hierarchy among sentient animals.

In order to address these questions as concretely as possible and from a variety of perspectives, the topic of the symposium was discussed with reference to a specific research field – Alzheimer's disease. In the first part of the programme, the viewpoint of clinical research and practice was presented, and expectations concerning the use of animal models in preclinical research were defined. There followed an overview of animal models used in clinical research on Alzheimer's disease, with three researchers providing insights into the possibilities and limits of their work with, respectively, mice, zebrafish and non-human primates. The criteria applied in choosing model organisms were then examined from an ethical perspective. This was followed by a moderated panel discussion, including questions from the audience.

In his presentation on clinical research and practice, **Professor Jean-François Démonet**, Director of the Leenaards Memory Centre at Lausanne University Hospital (CHUV), emphasised the extraordinary complexity of Alzheimer's disease. This condition affects 47 million people worldwide and poses major challenges for the health system, as well as for patients, relatives and caregivers. Professor Démonet explained the role played in human pathophysiology by selected proteins and brain protein aggregates, inflammatory reactions and vascular factors. From a clinical viewpoint, he argued, one of the main difficulties for Alzheimer's research lies in the fact that the disease can only be understood as the overall product of changes on three different levels: progressive impairment of cognitive performance at the phenotypic level, functional changes in the brain and its plasticity, and – at the molecular level – changes in various molecules responsible for pathogenesis. But as regards understanding and treating the disease, the main problem, in his view, is that there is no clear connection between these three levels, and the causation is still not adequately understood. He concluded his talk by observing that what we need above all is a better understanding of the factors which account for the human brain's remarkable resilience against the development of the

Akademien der Wissenschaften Schweiz (a+) • Kommission für Tierversuchsethik (KTVE)
Haus der Akademien • Laupenstrasse 7 • Postfach • 3001 Bern • Schweiz
+41 31 306 92 70 • mail@samw.ch • samw.ch/tierversuche

disease. This will require further investigation of the interplay among microglia, neurons, astrocytes and microvessels, so as to improve our understanding of the inflammatory reactions associated with the disease.

In his presentation, **Professor Mathias Jucker**, Professor of Cell Biology of Neurological Diseases and a director at the Hertie Institute for Clinical Brain Research at the University of Tübingen, discussed the potential of animal models in translational research. In his view, two aspects are of central importance: firstly, a good animal model must have clinical relevance and, secondly, one must always be aware of the limits to the validity of animal models, which only provide a picture of what they actually model. An error frequently made is to disregard these limits, thus creating unrealistic expectations for translation. This is a consequence of the simple fact that the vast majority of animals – including mice and non-human primates – do not develop Alzheimer's disease as it occurs in humans. Accordingly, animal (e.g. transgenic mouse) models are created which only develop certain features, such as amyloid plaques or neurofibrillary tangles. If the conclusions drawn from the models are restricted to these specific pathological changes occurring in Alzheimer's disease, findings in transgenic mice can be said to have led to many important discoveries which are transferable to humans and are thus significant for clinical research.

These two general overviews were followed by three short presentations providing insights into mouse, zebrafish and non-human primate research. These contributions highlighted the fact that researchers have good reasons for choosing particular model organisms. First, **Dr Laure Verret**, Associate Professor of Neuroscience at the University of Toulouse, discussed her basic research, involving mouse models of Alzheimer's disease. Her discovery of epileptic episodes in transgenic mice with a mutation in the amyloid gene led to specific investigations in humans affected by the disease; it was thus demonstrated for the first time that epileptic episodes also occur in patients with Alzheimer's. Dr Verret's work illustrates the fact that research in mouse models can generate new knowledge leading to advances in clinical research.

Dr Caghan Kizil, a group leader at the German Center for Neurodegenerative Diseases (DZNE) in Dresden and Visiting Associate Professor at the Columbia University Irving Medical Center (New York), reported on his research in a non-mammalian model organism, the zebrafish. An important advantage of zebrafish, he explained, is that they can be readily modified genetically and are highly amenable to studies of development and regeneration. In his view, the physiological similarity of zebrafish and humans is sufficient to obtain clinically relevant findings. This applies in particular to reduced neurogenesis in patients with Alzheimer's. Dr Kizil emphasised that, given the marked neurogenesis observed in zebrafish, these animals are particularly suitable for studying the links between impaired neurogenesis and the development of Alzheimer's disease.

The third presentation dealing with a specific animal model was given by **Eric Rouiller**, emeritus Professor of Neurophysiology at the University of Fribourg, who discussed his research in macaque monkeys. He first emphasised the importance of the close relationship between non-human primates and humans in generating transferable findings, but also pointed out that this evolutionary proximity gives rise to particular ethical problems. While aware of these ethical problems, he defended the conduct of research in non-human primates to investigate questions which cannot be studied in other animal species. As examples, he mentioned studies of spinal cord injuries, cortical lesions and Parkinson's disease. In collaboration with Professor Martin Schwab (University of Zurich and ETH) – who had discovered the Nogo protein in mice, which plays an important role in inhibiting regeneration in the CNS – Professor Rouiller studied the potential of treatment with anti-Nogo antibodies to promote regeneration in macaques with spinal cord injuries. The success of these tests led to clinical studies, which are currently in Phase II.

After this tour d'horizon of biomedical research on Alzheimer's and other neurodegenerative diseases, the question of how decisions concerning the choice of model organisms are to be viewed from an ethical perspective was addressed by **Dr Samuel Camenzind**, a senior scientist in the Unit of Ethics and Human-Animal Studies at the Messerli Research Institute (MFI) in Vienna. His presenta-

tion focused on the question to what extent a moral hierarchy among different sentient animal species is justifiable. He first made reference to the Swiss Animal Welfare Act, which makes no distinction in principle and requires the dignity of all sentient animals to be equally protected; this entails protection of the inherent value of any sentient being. Dr Camenzind explained that the concept of dignity is based on a biocentric moral theory, which attributes moral value to the thriving of living beings. On the biocentric view, all living beings worthy of protection are in principle equal and are assigned the same moral value. To this extent, he argued, a hierarchy among vertebrates (e.g. a higher moral value for primates compared to mice, and for mice compared to fish) is not justifiable. While a hierarchy could conceivably be established on the basis of protection of animal welfare (a principle also enshrined, alongside dignity, in the Swiss Animal Welfare Act), Dr Camenzind noted that, as regards differences in sensitivity, the biological facts remain unclear. In his view, the moral gradation from non-human primates through mice to fish is ultimately due rather to our moral intuition and to our sense of closeness to these animals; however, this cannot be justified by objective ethical arguments within the framework of the existing Animal Welfare Act.

The concluding panel discussion, involving all the speakers, was moderated by **Dr Michaela Thallmair**, Animal Welfare Officer at the University of Zurich and a member of the ECAE. As well as the moral hierarchy among species, the question of a possible hierarchy of gains in scientific knowledge was also discussed. The researchers working on mice, for example, reported that, as a rule, their choice of animal model was not fundamentally questioned by the animal experimentation committee, whereas, according to Dr Kizil, certain funding agencies called into question the validity of zebrafish experiments and suggested that the proposed experiments be conducted in mice. Of interest in this context were the observations made by Professor Rouiller, as it is generally more difficult to obtain authorisation for experiments in primates than, for example, in mice. This trend, he said, had become increasingly pronounced in recent years; while the requirements for animal experiments had been tightened across the board, this was particularly true for studies involving non-human primates. This was reflected by the fact that experiments in non-human primates were increasingly being classified as SG3 (degree of severity 3). At the same time, however, he emphasised that, to date, discussions with cantonal veterinary offices and animal experimentation committees had always been very constructive.

Also discussed in this connection was the question why, in studies involving non-human primates, sample sizes are usually much smaller than in studies carried out on mice or zebrafish. Here, the question arises whether non-human primate studies are generally statistically underpowered or, conversely, mouse and fish studies tend to be overpowered. The panel was in agreement that a generalisation of this kind is not justified. The difference is probably partly due to differences in research questions and corresponding differences of approach. For example, non-human primates are usually subject to longitudinal studies, for which smaller sample sizes are required than for cross-sectional studies. Longitudinal studies are, however, increasingly also being carried out in other animal species; in some cases, this has only become possible as a result of technological advances (e.g. miniaturisation of probes). Nonetheless, there was a consensus that validity can be impaired if sample sizes are too small. With regard to the reservations expressed by Dr Camenzind concerning a moral hierarchy among different vertebrate species, it should at least be examined whether evaluations of appropriate sample size are not distorted by our moral intuitions, and whether adjustments would therefore need to be made, either in one direction (larger primate studies) or another (smaller studies in mice and fish).

In conclusion, Professor Würbel offered a personal assessment of the findings of the symposium. The researchers had strikingly demonstrated both the complexity of Alzheimer's disease and the multifaceted nature of research in this field. It had been convincingly shown that research involving animal models could yield important knowledge for human pathophysiology, provided that one remained aware of the limits of animal models and avoided unjustified extrapolations. For Professor Würbel, the question was not whether experiments involving animal models are of clinical relevance for humans, but what conditions need to be met to ensure that they are. However, with re-

gard to the implicit moral hierarchy among sentient animals and the importance of this for assessments of the degree of severity and evaluations of sample size for animal experiments, he wondered whether it would not be desirable to pursue detailed discussions with the authorities with a view to defining robust criteria. Finally, Professor Würbel stressed that addressing the topics covered by this symposium was important not least against the background of the forthcoming referendum on the popular initiative calling for a ban on animal experiments and clinical studies. For sound debate, it was important that all parties should be well informed, and therefore there was definitely a need for more events of this and a similar kind.

The ECAE would certainly be encouraged by the high level of interest shown in this symposium to organise further events designed to facilitate dialogue among the various stakeholders. This was in line with the overarching goal of the ECAE to promote high-quality, ethically responsible and scientifically valid research.