Meeting Report

Science Instead of Animal Experiments

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On October 27, 2018 the German-based organisation Doctors Against Animal Experiments (*Ärzte gegen Tierversuche e.V.*) held its second congress "Science instead of Animal Experiments" (*WIST – Wissenschaft statt Tierversuche*) in Cologne, Germany with international speakers and around 200 participants on how valid animal experimentation is and which alternative approaches exist in human-based research, with a focus on neurological and psychiatric research.

Jarrod Bailey, PhD, Senior Research Scientist at Cruelty Free International and Fellow at the Oxford Centre for Animal Ethics, Hexham, UK, spoke on "Non-human primates in neuroscience research: The case against its scientific necessity". According to the speaker, the harm-benefit analysis is often distorted by researchers: the suffering of the animals is downplayed, while the alleged benefit is exaggerated. Deprivation of fluid and food, and fixation of the head may cause a state comparable with human post-traumatic stress disorder, which may influence the results. Differences between monkeys and humans include differences in genetics, eye movements, cerebral cortex structure, and cognitive functions. Human-based research techniques with imaging techniques, neuroimaging, and cognitive research, on the other hand, are powerful and relevant to humans.

Désirée H. Veening-Griffioen, Department of Pharmacological Sciences at the University of Utrecht, the Netherlands, held a lecture entitled "About mice and bad science: the failed construction of Alzheimer as 'drugable' disease". The speaker explained on the basis of data from her research that more and more studies on genetically modified or experimentally generated animal models are published, but that their predictive value is low, because the animal model mimics only one aspect of the multifactorial disease. She also spoke about the aim of the Netherlands to phase out animal experiments in drug development by 2025.

Gerry Kenna, PhD BSc Hons, Pharmaceutical Director of Safer Medicines Trust, Macclesfield, UK, spoke on "Overcoming obstacles to human relevant science". Of 578 withdrawn drugs, half had toxicological problems in patients despite extensive prior animal toxicity testing. *In vitro* tests have been developed that predict liver damage in humans better than animal studies carried out for regulatory approval. However, *in vitro* methods are often not readily accepted by the scientific community. Changing this requires education and cooperation with scientists and regulatory authorities. He called for increased funding of human-relevant test methods.

Ann Lam, PhD, of the Physicians Committee for Responsible Medicine (PCRM), Washington, DC and The Green Neuroscience Laboratory, Neurolinx Research Institute, San Diego, CA, USA, presented "Beyond opposition: Breakthroughs in human-based approaches to basic neuroscience and medical discovery". Decades of animal research in the field of dementia, for example, have not resulted in effective treatment. Animal-free research, such as working with xeno-free pluripotent human stem cells or human tissue derived from operations, provides more human-relevant data. Computer models can be used to simulate the brain structure and activities of nerve cells.

Thomas Hartung, PhD, Professor of Pharmacology and Toxicology at the University of Konstanz, Germany, and Director of CAAT US and Europe as well as Professor of Evidence Based Toxicology at Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA, gave a talk on "The study of neurological diseases with laboratory-grown mini-brains". He argued that there are also important economic and scientific reasons to move away from animal testing. For example, aspirin (acetylsalicylic acid), which was developed more than 150 years ago without animal testing, would not pass today's safety tests on animals. 97% of drugs tested on animals fail in clinical trials. One reason is that animal experiments are usually carried out on genetically identical mice, which do not reflect the diversity of human beings in their genetics, age, and disease structure. His team has developed "mini-brains" generated from human skin cells that can be used to investigate neurological diseases in a high-throughput or a patient-specific manner.

Katja Merschbächer, PhD, University of Saarland, Germany, explained in her talk on "Parkinson's Research and the Role of Brain Organoids" that animal models only mimic symptoms of Parkinson's disease, which does not occur naturally in any animals apart from humans. Induced pluripotent stem cells from patients are now being used for research on the disease and may be useful to test drug candidates and to develop personalised models for pre-clinical testing.

Markus Keller, PhD, German Institute for Alternative and Sustainable Nutrition (IFANE), and director of the Department of Vegan Food Management at the FHM College, Cologne, Germany, talked about "Brainfood instead of dementia? Opportunities and limits of nutrition". 80% of the studies Dr Keller evaluated showed that the consumption of fruit and vegetables has a positive effect on health. A plant-based or Mediterranean diet (which can include fish), which supplies high levels of beta-carotene, vitamins C and E, and secondary plant compounds, folate, mono-unsaturated fatty acids, and omega-3 fatty acids, has been found to reduce the risk of Alzheimer's disease by 33% to 65%. Vegetarians and vegans also have a lower risk of diabetes, cardiovascular disease, and high blood pressure.

The congress aimed at challenging animal experiments as the gold standard and addressed the public, academics, and regulators. Simultaneous translation was provided. Guests included numerous scientists, representatives of authorities, politicians, veterinarians, and physicians as well as interested persons from the animal protection movement and the public. WIST II was very well received by the participants and certainly helped to further stimulate the discussion about the validity of animal experiments.

Corina Gericke and Silke Strittmatter
Doctors Against Animal Experiments, Cologne, Germany

Meeting Report

Alternative Methods to Replace or Reduce Animal Models in Biomedical Research

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The first open meeting of the R2N consortium, Replace and Reduce (R2N) based in Lower Saxony, on alternative methods to replace or reduce animal experiments took place at the Hannover Medical School (MHH), in Hannover, Germany on November 6-7, 2018. The meeting was chaired by Prof. **André Bleich** (Director of the Central Animal Facility and Institute for Animal Sciences, MHH) and Prof. **Nils Hope** (Centre for Ethics and Law in the Life Sciences, Leibniz University Hannover). The gathering aimed to discuss the latest technologies and opportunities to replace and reduce animal testing as well as to encourage scientific exchange among industry, academia, and students. The meeting was opened by Prof. André Bleich, who highlighted the relevance of alternatives to animal experiments in all areas of biomedical science in order to reduce the number of animals used in research, and stated that such approaches are leading the science into a new era.

Prof. **Thomas Hartung** (Johns Hopkins Centre for Alternatives to Animal Testing, Baltimore, MD, USA) stressed the increasing need for more representative tests to predict human health threats. Given the limitations of animal-based toxicology and traditional human cell culture, the combination of the biomedical and bioengineering fields is the key to produce more reliable methods that better emulate the human *in vivo* environment. One of the solutions to testing the reaction of brain cells to foreign substances is the human iPSC-derived mini-brain. Another measure to reduce animal testing in toxicology is the software tool REACH*Across*™, which uses a large toxicological database (an *in silico* method) to predict the effects of substances based on chemical similarity to substances that have been characterized.

Dr **Sylvia Escher** (Fraunhofer ITEM, Hannover, Germany) presented the development of an animal-free testing strategy for risk assessment of inhalable compounds. The project "EXITOX II" develops an integrated approach for testing and assessment (IATA) of compounds which combines the outcomes of *in vitro*, *ex vivo*, and *in silico* models. The project also has developed two *in silico* models, i.e., a lung-PBPK (physiologically based pharmacokinetic) model that predicts the uptake and distribution of volatile chemicals in the human respiratory tract and a QSAR model that predicts plasma protein binding, an important input parameter for PBPK modelling. Both tools will be available for use in the near future for quantitative *in vitro* to *in vivo* extrapolation (IVIVE).

To overcome the limitations of single cell culture and the use of non-human species for testing of drug candidates, **Isabel Rütschle** (TissUse GmbH, Berlin, DE) presented the organ-on-a-chip model. Such chips are roughly the size of a credit card and house miniaturized organs. The system allows interactions between different organs via a microfluidic system driven by a peristaltic pump. Multi-organ-chips are being developed to replace animal use for pre-clinical testing of drugs as well as toxicological testing of cosmetic ingredients and chemicals. They can be used to model physiological and pathophysiological conditions, e.g., Type II diabetes and Alzheimer's disease.

PD Dr **Alexander Mosig** (University Hospital Jena, Jena, DE) introduced the *in vitro* gut-liver axis model. The system aims to investigate molecular and cellular mechanisms of inflammation-associated organ dysfunction in sepsis. To date, there is no specific anti-sepsis drug and the sepsis treatment relies mainly on early detection and symptomatic approaches. The *in vitro* gut-liver axis model is composed of parenchymal as well as circulating immune cells. Acute and chronic infection models are established to permit study of sepsis-associated multi-organ failure *in vitro*. The system has potential to reduce the number of experimental animals used for the study of sepsis.

Demonstrating the applicability of stem cell models developed in academia to pharmaceutical environments, Dr **Udo Kraushaar** (Natural and Medical Sciences Institute at the University of Tübingen, Tübingen, Germany) presented cell culture models of hiPS cardiomyocytes and neurons. Methods to differentiate somatic cells from human embryonic stem cells (hESC) and human induced pluripotent stem cells (hiPSC) now allow the use of human cellular material for compound screening and