markers of effect in endocrine disruption: How to link a functional assay to an adverse outcome pathway. *Ann Ist Super Sanita 51*, 167-171. doi:10.4415/ANN_15_02_16

Madia, F., Worth, A., Whelan, M. et al. (2019). Carcinogenicity assessment: Addressing the challenges of cancer and chemicals in the environment. *Environ Int 128*, 417-429. doi:10.1016/j.envint.2019.04.067

Acknowledegments

The Italian Platform on Alternative Methods (IPAM) is thanked for organizing the *ecopa* Symposium 2019. The scientific support of Umberto Agrimi is acknowledged. The authors thank the Istituto Superiore di Sanità (ISS, Italian National Institute of Health, Rome, Italy) for the logistic support as well as Paola Patrignani, Mariachiara Petrassi and Valentina Prota.

Stefano Lorenzetti[1], Gabriele Aquilina[1], Francesca Caloni[2], Eliana M. Coccia[1], Pietro Cozzini[3], Gabriele Cruciani[4], Alexandre Fouassier[5], Andrea Gissi[6], Laura Goracci[4], Tuula Heinonen[7], Philippe Hubert[8], Federica Madia[9], Francesco Nevelli[10], Alberto Rainer[11], Costanza Rovida[12], Augusto Vitale[1] and Isabella De Angelis[1]

[1]Istituto Superiore di Sanità, Rome, Italy; [2]Università degli Studi di Milano, Milan, Italy; [3]Università degli Studi di Parma, Parma, Italy; [4]Università degli Studi di Perugia, Perugia, Italy; [5]Ncardia BV, Leiden, The Netherlands; [6]European Chemicals Agency, Helsinki, Finland; [7]Finnish Centre for Alternative Methods, Tampere, Finland; [8]French National Institute for Industrial Environment and Risks, Verneuil-en-Halatte, France; [9]European Commission Joint Research Centre, Ispra, Italy; [10]Merckgroup, Ivrea, Italy; [11]Campus Bio-Medico University of Rome, Italy; [12]Center for Alternative to Animal Testing in Europe, University of Konstanz, Konstanz, Germany

Meeting Report

3R-related Research Funding: Insights from a Meeting Hosted by the German Centre for the Protection of Laboratory Animals (Bf3R)

doi:10.14573/altex.2002201

Introduction

In spite of extensive efforts towards implementation of the 3R principle, including the establishment of 3R centers and tightening of legislations on animal welfare, the overall number of animals used for scientific purposes remains high in Europe. One of the fundamental goals of 3R research foundations is to significantly reduce this number by promoting the further development and acceptance of alternative methods to animal experimentation. The different measures proposed to reach this objective must meet two main prerequisites: I) Transparent knowledge transfer between scientists and funders regarding funding opportunities and II) definition of criteria for assessing the success of funding.

With this in mind, the German Centre for the Protection of Laboratory Animals (Bf3R) at the German Federal Institute for Risk Assessment (BfR) held a symposium in Berlin on September 20, 2019, focusing on 3R-related research funding. The agenda included short lectures on nationwide funding programs, keynote lectures addressing particularly illustrative examples of third party-funded 3R research as well as current strategic challenges concerning open science, a world café, and a poster session. In addition to these events, which were open for all participants, the symposium also included a separate session for representatives of the funding institutions, academic and research institutes, and the Federal Ministry of Food and Agriculture. Here, topics such as measures for attracting promising project ideas, strategies for assessing the success and impact of funded projects, and incentives for the publication of negative results or replication studies were intensively discussed.

Information on 3R funding opportunities in Germany

The first thematic block included short presentations on current 3R-related research funding programs in Germany. The representatives portrayed the cornerstones of their funding programs, including information on the frequency of the calls for proposals, deadlines, structure and length of the application, and possible funding volume, as well as hints for a successful application. The participant institutions were the German Federal Ministry of Education and Research (BMBF), which was represented by the

project management Jülich[1], the German Research Foundation[2] (DFG), the set Foundation[3], the Federal State of Baden-Wuerttemberg, the Federal State of Rhineland-Palatinate, and the German Centre for the Protection of Laboratory Animals[4]. Several representatives of the above-mentioned institutions were also available for questions and provided information material on the respective programs during the poster session (see below).

Keynote lectures on 3R research projects and strategies of knowledge dissemination

As the first keynote speaker, Dr **Holger Breithaupt**, Senior Editor at EMBO Press Journals, where he is responsible for "Science & Society", outlined the relevance of open science and the dissemination of knowledge. He explained why the high-pressure, metrics-centered publishing culture is a root cause of missing research integrity and how the scientific community is faced with the great challenge of making research data accessible and affordable for all scientists – not only to overcome the reproducibility crisis. It became clear that journals and institutions must take action to encourage open science and incentivize the publication of negative or confirmatory results.

The next two keynote lectures focused on third-party funded research projects. Prof. **André Bleich** (Hannover Medical School) presented the research unit "Severity Assessment in Animal-Based Research", which was launched in the spring of 2017. Within the interdisciplinary consortium, funded by the DFG, various research groups are working to establish a severity assessment framework for different animal species[5]. In his talk "Development of the Hamburg Anatomical Neurointerventional Simulator – Replacement of Animal Experiments", Prof. **Dieter Krause** (Hamburg University of Technology) presented the BMBF-funded development of a method for replacing animal experiments in the area of stroke research and for the training of medical doctors. Besides introducing the scientific background and presenting preliminary data from their projects, both speakers shared their experience regarding the application and review processes.

Poster session

To give insights into current activities regarding 3R research and to enhance the interaction between all participants, information booths were provided by representatives of the funding institutions parallel to a poster session. Here, participants could present their current 3R research or intended projects – with topics ranging from *in silico* methods to cell culture-based organoids. This gave research funders the opportunity to identify interesting projects; at the same time, scientists could initiate possible collaborations. All attendees had the opportunity to vote for the best poster presentation. The young investigator Dr **Niklas Schwarz** (Hertie Institute for Clinical Brain Research, University of Tübingen) won an award for his poster entitled "Long-term adult human brain slice cultures – a new model system to study human CNS circuitry and disease".

World café

As one of the first 3R centers in the EU, it is the Bf3R's fundamental goal to further shape the 3R research landscape. For this purpose, we identified a world café as the perfect opportunity to talk to scientists about important 3R-related topics. At four discussion tables, each under the curation of two BfR employees, questions, concepts and ideas regarding the following themes were intensively discussed:

1) *How is the 3R principle implemented at my home institution: problems and perspectives*. Participants at this table said they would like to see institutes and faculties building up a better in-house 3R culture, with clear information structures and contact persons. Further integration of the 3Rs into teaching was identified as an indispensable step towards their acceptance within the scientific community. Progress has been made in this area in recent years. For instance, the Max Planck Society, one of Germany's most important research organizations, has committed itself to a fourth "R" of "responsibility".
2) *Can the pre-registration of animal experiments contribute to a better planning of experiments, increase their transparency, and improve the quality of the obtained data?* From the discussion at this table it became clear that many researchers are not aware of the possibility to register their studies in publicly accessible databases. Study registries such as the animal study registry of the German Federal Institute for Risk Assessment[6] can increase transparency and reproducibility, improve the quality of study designs, and prevent selective reporting. Many journals and research funders have already implemented preregistration of studies as a prerequisite in their submission process, but scientist must be better informed about the benefits.
3) *What are appropriate measures of research quality: instruments, their pros and cons, and possible alternatives*. Participants at this table first defined quality research as a gain of knowledge. In this context, they named the reusability of study results as an important quality feature. Research data must be available in a suitable technical and content-related manner, and raw data should be openly accessible. Here, dependence on private companies was considered problematic

[1] http://www.ptj.de
[2] http://www.dfg.de
[3] http://www.stiftung-set.de
[4] http://www.bf3r.de
[5] http://severity-assessment.de/
[6] https://www.animalstudyregistry.org

Impressions from the symposium held in Berlin

due to different data formats, which might impede direct reading of metadata. The impact of research results on the reduction of experimental animal numbers was mentioned as another quality feature, but assessing such numbers from databases was considered difficult. The elimination of subjective influences distorting study results was named as a further quality measure. Due to legal requirements and ethical reasons, this applies in particular to animal experiments. Automation processes were also found to be important in this regard.

4) *How to improve the use and comprehensibility of research data? How can funding agencies incentivize "open science"?* Promoting open data and registration of studies was discussed at this table, because failure to reproduce results was deemed one of the major challenges in today's research. Participants discussed whether certified quality management is a hindrance to free research due to its high administrative effort. They felt that good study planning needs to be part of teaching at universities and the use of tools such as the Research Data Management Organiser[7] (RDMO) for creating data management plans should be the standard. Against this background it seems vitally important to introduce early-stage researchers to the topic of data management and to further foster interdisciplinary know-how transfer – data specialists and statisticians are indispensable in today's biomedical research.

Parallel session of funding institutions

In a separate session, related topics were intensely discussed by representatives of the funding institutions, academic and research institutes, and of the Federal Ministry of Food and Agriculture. The fundamental question was: How can funding strategies for 3R research be improved in order to decisively contribute to the implementation of the 3Rs? The debate focused on the following key topics:

Definition of criteria for assessing the success of funding. Here, there was consensus that classical parameters such as the number of publications resulting from a project, the impact factor of the journal in which they were published, or the number of citations these publications receive, do not necessarily reflect a concrete benefit for the animals and are therefore not appropriate for assessing the success of the funding. In the toxicological field, in which animal experiments are largely standardized and follow pre-defined guidelines, a good indicator would be the implementation of a newly developed method as, for instance, an OECD test guideline. In basic biomedical research, which is less regulated, the situation is more complicated. The creation of a "3R label" for tried and trusted methods or the availability of search tools or databases to identify widely used alternative methods could help solve the problem. Another component of a "successful" 3R project is the response it evokes in the general public and scientific communities towards an intensive debate and dialogue on animal experiments and alternative methods. An important development would be the follow-up financial support for a formal validation of novel regulatory methods, which is a pre-requisite for their acceptance and widespread use and is usually associated with high costs.

How to increase the attractiveness of 3R research and its acceptance in the scientific community. Several participants argued that many established scientists still regard the field of alternative methods as less scientific, and 3R research less worth pursuing. It was also noted that numerous top-class scientists actually work on alternative methods (for instance those working on organoids or tissue engineering), but that the 3R aspect of their work is not immediately apparent. It seems that the image of the 3Rs needs to be further burnished, for instance by emphasizing their appropriateness for improving the translational value of basic research or for reforming cumbersome toxicological test strategies based on animal experiments, instead of focusing on ethical aspects. Another point was the importance of attracting young re-

[7] https://rdmorganiser.github.io/

searchers to the field, a comment that also came up several times during the world café. Knowledge on the 3Rs should be better integrated into teaching. Funding institutions might also consider bringing young scientists together in a kind of 3R research retreat to strengthen scientific exchange, build a network, and create a fruitful and open atmosphere.

Outlook

With around 150 participants, three keynote speakers, and the support of six funding institutions, the first symposium on 3R funding can be considered a success. While focusing on research possibilities in Germany, the symposium also addressed various interesting questions regarding the promotion of 3R research with important implications for the European and worldwide funding landscape. Research funders agreed that networking, also among themselves, is enormously important, because all players are struggling with the same obstacles to attract novel ideas and high-quality applications in which the 3R aspect is not just a by-product but an original goal. The main conclusion was that accurate study planning and management, enhancement of research transparency, and the interdisciplinary training of young scientists are central to achieving a reduction of animal testing.

Acknowledgements

The authors thank the representatives of the funding institutions, ministries, and academic research institutes as well as the keynote speakers and all participants for the lively discussion. Also, we thank our colleagues at the BfR who contributed to the success of the symposium.

Elisa Wistorf[1], Fanny Knöspel[1], Gilbert Schönfelder[1,2] and Marlon R. Schneider[1]

[1]German Centre for the Protection of Laboratory Animals (Bf3R), German Federal Institute for Risk Assessment (BfR), Berlin, Germany; [2]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

(marlon.schneider@bfr.bund.de)