European Journal of Pharmacology 759 (2015) 1–2

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Editorial

European Journal of Pharmacology, Special issue on translational value of animal models: Introduction

ARTICLE INFO

Keywords:
Animal models
Translational research
3R

1. Introduction

The predictive value of animal models for a given clinical condition is getting increasing attention. Models in both large and small animal species have value for pharmacology and toxicology, including the first evaluation of adverse side effects and pharmacological efficacy of innovative disease intervention strategies, as well as the selection in a given therapeutic discovery program. Also, such models are helpful in elucidating pathways in physiological or pathological processes.

Evidently, opinions about the predictive value of animals models change over time, which is logical in view of changes in attitude of the general public, patients, scientists, health professionals, and regulatory authorities. The only way to address evolution in thoughts on how studies in animals can serve human health and disease is by a continued dialog, focusing on the usefulness and limitations of studies in animal models. Whether it being large or small animals, a main item in this dialog is nowadays how to properly balance animal well-being in experimental conditions with respect to the value of study results. This asks for models that yield reliable, reproducible and accurate output, and that are well tolerated by the animals. It asks the scientific community not only to consider the R of 'Reduction' but also the R of 'Refinement'.

Evidently, preclinical animal studies are performed with the understanding that animal modeling is required or indicated to enhance the knowledge database about clinical (disease) conditions, and to facilitate the clinical implementation of new medical entities. Obviously, for this purpose it is of extreme importance to know whether a given animal model has predictive value for the situation in men. Such insights prevent any unnecessary use of animals and prompt innovations in modeling to improve their translational value.

We thank the Editor of the European Journal of Pharmacology for opening the columns of the journal for a special issue on translational value of animal models. The series of 34 papers of excellent quality present a broad compilation of the various aspects of this topic: general approaches, methodological aspects, species-specific approaches, and the majority addressing disease-specific aspects. Most papers present an overview of the field, particularly manuscripts about disease-specific animal models. Some manuscripts present new data, which provides another—innovative—look at the use and interpretation of animal models. We also deliberately include papers from the toxicological field, to illustrate that issues regarding the translational value also exist in this discipline of biomedical research. As such, all manuscripts present and discuss relevant aspects of the translational value of animal models. Evidently, the field is too broad to present a comprehensive overview, but the series of papers in this special issue provide an excellent illustration of the relevant topics, which warrant their publication together in this issue.

The guest editors like to give in the following their impressions from reading the manuscripts in this issue.

First, it is clear that scientists in all fields of biomedicine wrestle with the translational value of animal models. This not only applies to disorders of the central nervous system, but essentially to all chronic diseases and diseases with a multifactorial pathogenesis. For most diseases, there is not one single animal model addressing all features of the disease. Animal models rather address certain aspects of the disease process, for instance the disease expression with organ/tissue damage. In addition, most models are applied in an acute rather than chronic setting. The pros and cons of these approaches are getting more and more attention, and several manuscripts have addressed these issues, which appear to be similar for different disease conditions. Scientists are becoming increasingly aware that not only the animal model itself, but also the time window used should be suited to test the hypothesis and to realize the aim of the proposed study. To conclude, it is of utmost importance that scientist ask the question about translational value upfront and collect proper data in as much detail as possible, in order to achieve the best outcome possible.

Second, there is increased attention for—and better application of—the 3R principles. The conduct of studies aimed to have a predictive outcome in humans has to be properly balanced with animal well-being. Besides investigators in research institutions, this is increasingly recognized by regulatory authorities. It is

http://dx.doi.org/10.1016/j.ejphar.2015.03.050

increasingly realized that animal well-being affects the outcome of studies. Noteworthy in relation to 3R principles, several manuscripts in this special issue mentioned that poor study design and poor reporting of both study methodology and data present a potential source for reduced predictability of animal studies. Evidently, this criticism directly affects any compliance with 3R principles. A better compliance with publication guidelines such as the ARRIVE guidelines could easily overcome these issues regarding design and reporting of studies. To conclude, it is of utmost importance to consider upfront that animal well-being is relevant in all phases of a given study, from study design and performance to interpretation of study data. As part of these considerations it should be considered whether the animal's well-being will affect the outcome of the study, and this should be done before initiating any study.

Third, most of the manuscripts on disease-specific models mention the combination of output parameters for efficacy and those for tolerability or adverse side effects. Combined efficacy/tolerability studies are increasingly accepted in testing Advanced Therapy Medicinal Products, such as cell and gene therapy products. Hence, in this arena of research, pharmacology and toxicology are coming more closely together. Regulatory authorities support this approach in the advanced preclinical stage of drug development. This approach fits with increasing awareness in the field of toxicology regarding the question whether regulatory toxicology studies should indeed be performed in naïve animals. To conclude, it is of utmost importance to start a dialog with regulatory authorities already in the advanced stage of preclinical development, so that the design and performance of studies in animal models can optimally serve the transition from preclinical to clinical development.

Fourth, some papers address outliers in animal studies. Outliers are often neglected in the interpretation of study data. In other words, every individual case with a result outside the 95% confidence interval (or similar interval) is considered non-informative and hence excluded from data analysis. Since outliers may occur for various reasons, they may well inform about the intrinsic characteristics of the model, or the intrinsic characteristic of the medicine under study. Hence, much may be gained by paying more attention to the occurrence of outliers, rather than neglecting these as being defiant and non-informative. To conclude, outliers in animal studies are essentially informative and should get proper attention.

Finally, a number of manuscripts address reverse translation, in simple terms the feedback from clinical experience to the preclinical field. If new medicines fail in clinical trials, most often clinical development is put on hold. This leaves the question why the clinical trial failed unanswered, unless this is taken up by research institutions interested in developing alternatives. Alternatively, at the positive side, there are now examples in which new medicines have been successfully developed—partly based on the outcome of studies in animals—which proved beneficial for most, but not all patients. Based on these clinical observations, animal studies have been initiated, which address the difference between responders and non-responders in the clinical situation. Thus, it is of utmost importance to analyze failures of medicines in clinical trials in detail, so that lessons can be concluded regarding the value of animal models and need to adapt or develop models with higher translational value.

In conclusion, there are clear examples that animal models have translational value and have contributed to the development of many medicinal products over the years. But, progress in the field has made it increasingly clear that animal models have their limitations regarding translational value, and this issue of Eur J Pharmacol illustrates the increased awareness for this topic. Some general principles and points of attention can be put forward to explain the difference between successes and failures, as indicated above. Obviously, it is justified and necessary for scientists to discuss the translational value of animal models, in a general sense and in relation to design and performance of studies. We hope that the content of this special issue will contribute to this discussion, and are most grateful to all authors who spend time and efforts in preparing their manuscript of highest scientific quality.

Guest Editor
Lucianne Groenink
Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

Guest Editor
Gert Folkerts
Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

Guest Editor
Henk-Jan Schuurman*
SchuBiomed Consultancy BV, Frederik Hendrikstraat 81, 3583 VH Utrecht, The Netherlands
E-mail address: SchuBiomed@gmail.com

Received 12 March 2015; accepted 12 March 2015

Available online 27 March 2015

* Corresponding author. Tel.: +31 6 3195 3962.