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Letter to Editor Open Access

Alternatives to Animal Procedures in Drug Development

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Introduction

Drug discovery identifies new candidates for medications and drug development aims to deliver the efficient active pharmaceutical ingredient to the target side without causing adverse effects. In drug development animal studies usually represent an integrative part of the testing. In the past, animal procedures helped in salient discoveries of new drugs. Von Behring generated diphtheria and tetanus antitoxins in horses, Banting and Macleod identified the effect of insulin in dogs, Fleming tested penicillin in rats and Waksman verified the efficacy of streptomycin in chicken [1]. Nowadays, the use of animal species is more focused on specific research areas, e.g. rats and mice for cancer research, metabolic research, drug screening and genome research. Pigs are important in transplantation surgery, osteosynthesis and osteoporosis, emergency surgery, and diabetes research, while dogs are used preferentially for heart surgery, bone marrow transplantation, osteosynthesis and diabetes. Cats are models in heart surgery, neurophysiological studies, and development of hearing aids and rabbits are involved in vaccine development, arteriosclerosis research and drug activity testing [2].

Since several years, despite ongoing development of new drugs, the number of animal procedures has markedly decreased from about 1.5 millions interventions in 1972 to 834,000 in 2015 [3]. This trend was in part caused by the guiding principle of the 3 R's published by Russell and Burch in 1959 [4]. The 3 R's stand for replacement, reduction and refinement of animal studies and have become established as essential considerations when animals are used in research. Strategies aimed to replace animal experiments by using prokaryotes (*Escherichia coli*, *Bacillus subtilis*, *Caulobacter crescentus*), protists (*Dictyostelium discoideum*), fungi (*Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Apergillus nigrans*, *Neurospora crassa*), and invertebrates (*Amphimedon queenslandica*, *Aplysia sp.*, *Drosophila melanogaster*, *Hydra*, *Caenorhabditis elegans*) as model organisms to answer specific research questions [5]. The use of invertebrates is considered as suitable replacement for vertebrate studies by some but not all regulatory bodies. While Computer-Aided Drug Design and (Quantitative) Structure Activity Relationship software programs support the screening for promising drug candidates, the production of vaccines by bacteria and by animal cells instead of animals, replaces animal procedures to a large extent in the production of already approved medicines. In drug development cellular and tissue studies and *in silico* models represent the most promising tools to reduce or avoid the use of animal studies. *In silico* models are available to predict adsorption, distribution, metabolism, excretion and toxicity on the basis of input data describing physicochemical properties of the compound and of the formulation and on physiological properties of the exposed individual. Other programs are based on whole body model integrating compound distribution, metabolism and pharmacodynamics or focus mainly on metabolic pathways of the cytochrome P450 enzymes.

96% of all animals used in research are rats and mice despite the fact that they are not very representative for humans regarding the most common non-invasive application routes, e.g. dermal, oral and inhalation. Dogs, according to bile production and stomach capacity, are more similar to humans than small laboratory animals but still oral bioavailability is not very predictive for humans and even non-human primates can provide only qualitative not quantitative data [6,7]. Dogs are also better models for inhalation due to slower mucociliary clearance and larger alveolar macrophages compared to small laboratory animals [8].

Regarding the most common non-invasive routes dermal delivery is far ahead in the implementation of the 3 R's strategy and animal studies have almost completely been banned from the testing [9]. Permeability, corrosion and irritation can be assessed using excised and artificial skin samples. The respiratory barrier, on the other hand, is much less advanced in terms of *in vitro* models. Although reconstructed tissues are also available for inhalation and oral exposure the tissue composition is more complex than the skin and excised tissues maintain barrier properties and cellular composition only for very short times. In addition to that, physiologically relevant *in vitro* testing of inhalation also requires specific exposure systems (such as aerosol generators and flow chambers [10]. Due to these limitations, regulatory bodies have not approved any alternatives to inhalation or oral exposure of animals. Main challenges in the improvement of existing *in vitro* models are the inclusion of vasculature, immunocompetence, microbiota, and physiological mechanical forces with the final goal to have a human on a chip, where all organs are represented in a physiologically relevant way. Alternatively, combination of *in vitro* data and *in silico* modeling appears a promising strategy for a further reduction of animal studies. Not only physicochemical parameters of compound and formulation but also several important biological parameters (dissolution, permeability, metabolization by CYP enzymes, etc.) can be determined *in vitro* and been used as input parameters in the *in silico* programs. Validation of the alternative methods is not easy because comparison with results in animal models, due to their limited relevance for humans, is not the ideal way. Inclusion of reference substances, such products on the market with available data in humans, appears to be more suitable for validation.

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