Biochemical Pharmacology 87 (2014) 162–171

Contents lists available at ScienceDirect

Biochemical Pharmacology

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

Review – Part of the Special Issue – Pharmacology in 21st Century Biomedical Research

Animal models of human disease: Challenges in enabling translation

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ARTICLE INFO

Article history:
Received 2 August 2013
Accepted 5 August 2013
Available online 14 August 2013

Keywords:
Animal models
Translational models
Hierarchical data integration
Validation
Transgenic

ABSTRACT

Animal models have historically played a critical role in the exploration and characterization of disease pathophysiology, target identification, and in the in vivo evaluation of novel therapeutic agents and treatments. In the wake of numerous clinical trial failures of new chemical entities (NCEs) with promising preclinical profiles, animal models in all therapeutic areas have been increasingly criticized for their limited ability to predict NCE efficacy, safety and toxicity in humans. The present review discusses some of the challenges associated with the evaluation and predictive validation of animal models, as well as methodological flaws in both preclinical and clinical study designs that may contribute to the current translational failure rate. The testing of disease hypotheses and NCEs in multiple disease models necessitates evaluation of pharmacokinetic/pharmacodynamic (PK/PD) relationships and the earlier development of validated disease-associated biomarkers to assess target engagement and NCE efficacy. Additionally, the transparent integration of efficacy and safety data derived from animal models into the hierarchical data sets generated preclinically is essential in order to derive a level of predictive utility consistent with the degree of validation and inherent limitations of current animal models. The predictive value of an animal model is thus only as useful as the context in which it is interpreted. Finally, rather than dismissing animal models as not very useful in the drug discovery process, additional resources, like those successfully used in the preclinical PK assessment used for the selection of lead NCEs, must be focused on improving existing and developing new animal models.

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http://dx.doi.org/10.1016/j.bcp.2013.08.006

1. Introduction

As part of the current special issue of *Biochemical Pharmacology*, "*Pharmacology in 21st Century Biomedical Research*", the previous four articles reviewed the use of animal models in the representative areas of inflammation [1], asthma, [2], cancer [3] and CNS diseases [4] with an emphasis on their predictive value and inherent limitations. In these articles, the author(s) provided some practical insights as to the appropriate use of currently available models for each disease area. While the therapeutic areas reviewed differ with regard to the area-specific knowledge base of disease causality and the track record in the successful prediction of new chemical entity (NCE) efficacy, safety and toxicity in the clinic, the reviews also highlight common themes that reinforce the value of these assays in helping predict human dosing [5–7] and safety [8–10] for NCEs.

Historically, animal models have been used in the drug discovery and development process to characterize disease pathophysiology, evaluate the mechanism of action of existing drugs, discover new drug targets and biomarkers [11], establish pharmacodynamic/pharmacokinetic (PK/PD) relationships [6,7], and, as noted above, to estimate clinical dosing regimens and determine safety margins and toxicity. Perhaps their most significant application is in the assessment of the therapeutic utility of NCEs where they represent the pinnacle in the hierarchy of preclinical research to validate targets and compounds. As such, they can be of great value in the drug discovery and development process; but it is in this area that their perceived limitations are also the subject of the most vehement criticism. Inevitably, animal models represent imperfect facsimiles of human diseases and disorders often reflecting a functional phenotype of an approved drug or drug class, e.g., the forced swim test for antidepressants [12,13] or a genetically engineered model of a target or pathway thought to be causal in a given disease, such as amyloid overexpression as a model of Alzheimer's disease (AD) [14,15]. Consequently, discretion and seasoned judgment need to be exercised in the application of these models to drug discovery.

The present commentary is intended to highlight some of the universal issues and limitations common to animal models across all disease areas as well as unique aspects specific to individual diseases. It also asks the question "if the models have such serious limitations that they are not perceived as useful, why has so little effort been made to place these shortcomings in an appropriate context?" and "Why have consistent efforts not been made to address and resolve these limitations?".

2. A hypothetical ideal for an animal model of disease?

The ideal in an animal model is that it should replicate, to a major extent, both a human disease phenotype and its underlying causality, the latter in terms of a mechanism of action(s) that has a degree of fidelity with what is known about the human disease. Since, in many instances, the latter is not always clearly understood, the gap between the patient and the model of their disease state is often insurmountable, making the value of the animal model highly suspect and in need of appropriate context. Nonetheless, many putative animal models of human disease are routinely used in biomedical research to study pathology and to evaluate NCEs as potential drug candidates, even when attempts to demonstrate efficacy in humans have been uniformly futile, as in the case of stroke, where nothing that worked in animal models, e.g., MCAO (middle cerebral artery occlusion) in gerbil or rat, showed efficacy in human trials [16]. Unfortunately, this has not deterred the continued widespread use of the MCAO model.

A similar situation pertains to animal models of asthma [2], inflammation [1,17] and Alzheimer's Disease (AD) [4,18], raising obvious questions as to: (a) why such manifestly flawed models continue to dictate how so much of basic biomedical research is conducted; (b) how NCEs are eventually advanced to the clinic; (c) whether all animal models are equally flawed; (d) whether these models should just represent a minimum standard such that failure to demonstrate efficacy should terminate advancement of a new NCE; and perhaps most importantly; (e) what can be done to improve the situation?

These various issues can be viewed from several vantage points: (i) that some animal models are capable of predicting a particular human condition, e.g., animal models of hypertension, where all clinically effective antihypertensive agents demonstrate efficacy whereas those models that are not predictive, e.g., animal models of AD [18], have inherent flaws and require additional resolution and validation [19]; (ii) that genetically modified mice and rats involving single gene insertions or deletions are valid models of the targeted polygeneic human disease state despite mounting evidence to the contrary; (iii) that despite inherent limitations of a particular animal model, the major culprit is that the clinical trials were flawed in their design and that when the "right NCE" is "properly" evaluated in the clinic, the model will be validated and; (iv) that all animal models have useful phenotypes [20,21] and/or are equally flawed (including those yet to be developed), and thus cannot be viewed in isolation leading to the conclusion that there is only one model of human–the human; and (v) that advancing a safe, bioavailable NCE with some measurable effect in an animal model to experimental translational trials in the clinic is often a better use of resources than additional animal testing. In this setting, the primary goal of the animal model is to demonstrate target engagement with a view to extending that measure to the clinical state. This view requires, however, that such clinical trials are regarded as exploratory and not definitive and that appropriate consideration has been given to the therapeutic translatability of an NCE before it enters the process [22].

Given the last perspective and ethical issues with the use of animals in biomedical research [23,24], there has been considerable debate about whether in silico/systems biology approaches [25,26] to modeling human disease are no less useful and potentially superior to animal models, although there is as yet little to no evidence to support this view.

3. The validation challenge

A central issue common to all disease areas is the validity of any single model or collection of models [1–4]. For example, a set of criteria has been proposed to evaluate an animal model for CNS disorders [27] and includes: *face validity* – similar symptom manifestations to the clinical condition; *construct validity* – similar underlying biology; and *predictive validity* – similar response to clinically effective therapeutic agents. While these criteria are clearly sensible, broadly applicable to other disease areas and encourage a careful and systematic evaluation of individual disease and safety models, experience has indicated that they are much more difficult to satisfy than originally appreciated. For example, the underlying biology of the majority of human diseases is an ever changing landscape as technology and research tools continue to advance the understanding of the basis of most diseases. Moreover, there are several disorders, e.g., depression, anxiety, neurodegenerative (AD, Parkinson's disease) and autoimmune diseases (multiple sclerosis, type I diabetes, asthma, etc.) being chief among them, for which the causality and/or etiology of the disorder remains completely unknown, can change as a function of the latest technology applied to its study, or is so obscure that these criteria cannot be applied. The effort to establish predictive validity has resulted in the hunt for "gold standard" drugs that can be used in a reverse translational manner, like that