

Executive Summary

Model organisms have long been a mainstay of basic and applied research in the life sciences. Among model organisms, it is model animals that have had a central place in medical research and in pharmaceutical and biotechnology company research, including drug discovery, preclinical studies, and toxicology. Although pharmaceutical companies have long employed animal models based on such mammalian species as mice and rats, dogs, cats, pigs, and primates, more recently the pharmaceutical/biotechnology industry has also adopted several invertebrate and lower vertebrate animal models that have emerged from academic laboratories. These animal models include the nematode *Caenorhabditis elegans*, the fruit fly *Drosophila*, and the zebrafish. The adoption of invertebrate and zebrafish animal models by industry has been driven by the advent of genomics, especially the finding that not only genes, but also pathways, tend to be conserved during evolution.

Researchers use animal models in basic research, in developing new therapeutic strategies for treating human diseases, and in drug discovery research (including target identification and validation, drug screening and lead optimization, and toxicity and safety screening), as well as in preclinical studies of drug safety and efficacy. The use of animal models in developing novel therapeutic strategies for human diseases overlaps with basic research that uses animal models to understand physiological and disease pathways. But its aim is to achieve knowledge of pathways and targets in a disease that leads to the development of new paradigms for discovery and development of drugs or other therapeutics. It thus also overlaps with use of animal models in drug discovery. The use of animal models in development of novel therapeutic strategies is the main emphasis of this report.

The creation of new animal models is an important part of animal-based therapeutic strategy research. A major reason why the pharmaceutical/biotechnology industry needs new animal models is because poorly predictive animal models are a major cause of drug attrition during development. This is especially true in therapeutic areas (e.g., oncology and central nervous system [CNS] disease) in which animal models are the most unpredictable. Due to the poor predictivity of many animal models, some researchers would like to work with “human models” based on induced pluripotent stem (iPS) cells. This early stage technology may allow researchers to develop disease models based on cells from people with such genetically determined diseases as spinal muscular atrophy (SMA), Parkinson’s disease, Huntington’s disease, Duchenne and Becker muscular dystrophy, amyotrophic lateral sclerosis (ALS),

etc., which more faithfully model the cellular basis of these diseases than animal models. However, most human diseases involve interactions between multiple organs and tissues. Researchers therefore need to continue to use animal models, which are whole, living systems that model physiology—not just cell and molecular biology. Cellular models based on iPS will be used in screening (which may in some cases reduce the numbers of animals needed in a drug discovery program) and to provide information on human disease pathways to supplement information derived from studies with animal models. Information derived from cellular models, and in some cases the cells themselves, may also be used to design new animal models to more faithfully model human diseases.

The final section of Chapter 1 discusses the issue of animal welfare, which is an important consideration in research involving animals. The United States and various European countries, as well as other jurisdictions (national and local), have sets of animal welfare regulations. Central to these regulations is implementation of the 3Rs (Reduction, Refinement, and Replacement.) Academic and corporate research organizations have been incorporating these regulations into their research practices.

However, some types of animal research, especially research involving nonhuman primates, are particularly controversial. Moreover, animal rights activists have had their impact on the practice of animal research, especially in Europe.

The absolutely essential need for animal research for progress in medical science and healthcare is well proven, and researchers and the general public generally support animal research. However, there is an increasing concern for animal welfare, including pressure for research organizations to find ways to reduce the numbers of vertebrate animals used in research. There is also the increasing need for researchers and their organizations to foster open engagement with the public and policy-makers to promote the value of animal research and discuss animal welfare issues.

Chapters 2 through 7 each focus on a particular type of animal model. Chapters 2, 3, 4, and 6 focus on *C. elegans*, *Drosophila*, the zebrafish, and the mouse, respectively. Each chapter includes case studies of the use of each of these established animal models in developing novel therapeutic strategies for human disease. Chapters 5 and 7 focus on emerging animal models for use in drug discovery and development of new therapeutic strategies, the African clawed toad *Xenopus tropicalis* (Chapter 5) and emerging mammalian animal models (Chapter 7). Each of these two chapters focuses on technological developments now in progress to develop tractable animal models based on these organisms for use in drug discovery research. Chapter 7, in addition to the development of model systems based on non-rodent mammals (mainly pigs, ferrets, and marmosets), includes a discussion of the reemergence of the laboratory rat as an animal model. The rat, despite its important uses in physiological research, in studies involving surgery, and in other types of studies, has been eclipsed by the mouse in the post-genomic era. However, it is now “reemerging” as the result of new technologies (*e.g.*, the sequencing of the rat genome and the construction of knockout rats via various novel gene-targeting technologies) and collaborations. Some

of these technologies are also being applied to the development of nonrodent mammalian models.

Chapter 8 discusses the use of computer models and translational biomarkers in helping researchers to more effectively move from preclinical animal studies to human clinical trials. Pharmaceutical and biotechnology company researchers have been increasingly applying pharmacokinetic/pharmacodynamic (PK/PD) modeling to all stages of drug development. This especially includes moving from preclinical animal studies to human clinical trials. These models, as well as biophysical models such as those developed by Novartis and physiological models such as those developed by Entelos, can help researchers more effectively use animal model data in the design of clinical trials. In particular, they can help researchers reduce drug attrition in clinical trials due to suboptimal dosing.

Entelos' virtual NOD mouse model for type 1 diabetes can be described as a "virtual animal model." This mathematical model is made possible by the extensive studies that have been carried out over 30 years with the living NOD mouse, and the acceptance by the diabetes research community of the usefulness of this mouse model and its relatively faithful modeling of human disease. The virtual NOD mouse is designed to help researchers design more effective animal studies using fewer animals, and hopefully to design more effective and successful clinical trials of agents designed to prevent progression to type 1 diabetes. Nevertheless, the usefulness of the virtual NOD mouse in enabling researchers to discover innovative drugs that achieve proof of concept in clinical trials, let alone reach the market, remains to be confirmed.

Chapter 6, which focuses on the mouse, concludes with a discussion of the issue of developing more predictive animal models of drug efficacy, specifically more predictive mammalian models. The two main reasons for researchers' difficulties in producing predictive mouse models are 1) differences between the mouse and humans, and 2) major unknown factors in disease biology. These unknown factors have been revealed, for example, by studies in human genetics showing that common variants do not account for most of the heritability of disease, the discovery of the role of copy number variation and of non-coding DNA sequences in human disease determination, and the discovery in recent years of new layers of cellular regulation based on small regulatory RNAs and epigenetics. Although these factors make developing predictive animal models difficult, researchers can use animal models to learn about unknown or poorly understood areas of disease biology. This is expected to lead to the development of improved animal models and the development of new therapeutic strategies and drugs. Researchers can also bridge some of the differences between the mouse and humans by creating humanized mouse models. In some cases, other mammalian species may be better models for certain diseases (*e.g.*, rats for cardiovascular diseases, pigs and ferrets for cystic fibrosis) than the mouse. As discussed in Chapter 7, there are new technologies for producing gene-modified disease models based on these mammalian species.

Developing animal models that are more predictive of efficacy is an iterative process. But progress is being made, as researchers apply new knowledge and experimental approaches

in elucidating the biology of particular diseases to creation of animal models. Researchers developing new drugs for complex diseases are well advised to test drugs in more than one animal model and in mouse strains of different genetic backgrounds. They should also, if possible, employ translational efficacy and/or pharmacodynamic biomarkers to link the efficacy seen in preclinical studies with clinical results.