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Introductory Chapter: Animal Models for Human Diseases, a Major Contributor to Modern Medicine

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1. Defining animal models

The use of animals as experimental models for human diseases is currently seen as an imperative in understanding the causes, biology, and prevention of diseases. Animal models over the years have been used extensively in biomedical field since the early 1980s [1]. Current understanding of these models tends to be a specific combination of an animal species, cell, tissue, organ, gene, or a challenge agent, and its directed route of exposure to produce and/or mimic a disease process or pathological condition in multiple important aspects approximating or corresponding to the human disease scenario or condition of interest. An important fact is that the models have to be reproducible.

It is obvious that laboratory animals play a crucial role in scientific research, discovery, and technological advances and in a substantive manner improve the lives of people and other useful animals. It may suffice to say that animals are used as models to study human biology and diseases and as test subjects for the development and testing of drugs, vaccines, and other biologicals (i.e., antibodies, hormones, etc.) to enhance and promote human health. This book, therefore, was written for medical practitioners, drug/therapeutic agent developers, biomedical scientists/bioengineers research students, bioethicists, behavioral scientists, and the general public who aspire to enrich their understanding of human diseases and development of effective therapeutics using animal models as clearly defined herein. Over the last century, almost all medical knowledge, treatment regimes, and medical device development have involved research using animals. Disease experimentation using animal models may be a deliberate design or an inevitable choice which possible due to the common descent of all organisms which even in the face of evolution many of them conserve their metabolic, developmental, and genetic material.

2. Trendy outlook

Animals were used to study human physiology and anatomy in the second century AD as documented by a Greek physician and philosopher, Galen, using mainly apes and pigs [2]. Galen applied his findings directly to humans without considering taxonomic relatedness. It was until the late sixteenth century that this error began to be recognized. Previously in 1865, a French physiologist by name Claude Bernard published the first book, *An Introduction to the Study of Experimental Medicine* [3], advocating the use of chemical and physical induction of disease in animals for biomedical research. Around that same time, Louis Pasteur in France and Robert Koch in Germany introduced the concept of specificity into medicine and the “germ theory of disease.”

It is noted that from 1901, two-thirds of the Nobel Prizes in medicine have relied majorly on animal models for their research, more recently seven (7) of the last ten (10) were animal model-based breakthroughs (**Table 1**) [4]. Researchers now rely heavily on development of animal models to explore all areas of medical science specifically in the assessment of pathogenic mechanisms, diagnostic and therapeutic procedures, vaccine development, nutrition, metabolic diseases, and the efficacy of novel drug development as captured in this book.

A typical instance in the trending use of animals as disease model is the transition from nonhuman primates such as chimpanzee to mouse/rat models in diabetic retinopathy (Chapter 2/3) and in HIV research (chapter 9) [5]. Larger animals are deemed relatively closest to humans (e.g., chimpanzee). However, these animals have become increasingly difficult to maintain and to handle; besides their costly nature. A more disturbing fact is that most human diseases could not be replicated in them, and the causative human agent hardly infects these nonhuman primates as well as difficulty in development of human symptoms and therapeutic responses. Scientists, therefore, resulted to started developing simpler and effective models most especially transgenic (humanized) mouse models [6] that mimic human responses to study and understand various aspects of infectious agents, pathogenesis, disease progression, nature of protective immunity and vaccine development. An ideal animal model for human disease research should possess certain characteristics as a prerequisite for a standard model. The chapters presented in this book elucidate the following notable characteristics of a chosen animal model:

- (i) A close relative or closely associated with the host tissue distribution, disease progression, and similar route of infection, if not identical.
- (ii) Disease course should be relatively shorter in the animal model, to allow for completion of the efficacy test in reasonable time, permitting rapid transition to human clinical testing.
- (iii) Despite the differences in genetic makeup of humans and animals, there should be sufficient disease correlation and pathological equivalence.
- (iv) The model should be easy to maintain, work with, easily available in adequate number, relatively inexpensive, and free of regulatory constraints.

Year	Nobel Laureate	Animal model	Contribution to modern medicine
2015	William C. Campbell and Satoshi Ōmura and Youyou Tu	Mice, dogs, sheep, cattle, chickens, monkeys	Campell and Omura for discoveries concerning a novel therapy against infections caused by roundworm parasites and Youyou Tu for her discoveries concerning a novel therapy against malaria
2014	John O'Keefe and May-Britt and Edvard I. Moser	Rats	Discoveries of cells that constitute a positioning system in the brain (an inner GPS)
2013	James E. Rothman	Hamsters	Discoveries of machinery regulating vesicle traffic, a major transport system in our cells
2013	Thomas C. Südhof	Mice	Discoveries of machinery regulating vesicle traffic, a major transport system in our cells
2012	Sir John B. Gurdon	Frogs, mice	For the discovery that mature cells can be reprogrammed to become pluripotent
2012	Shinya Yamanaka	Frogs, mice	For the discovery that mature cells can be reprogrammed to become pluripotent
2011	Bruce A. Beutler	Mice	Discoveries concerning the activation of innate immunity
2011	Jules A. Hoffmann	Flies	Discoveries concerning the activation of innate immunity
2011	Ralph M. Steinman	Mice	For his discovery of the dendritic cell and its role in adaptive immunity
2010	Robert G. Edwards	Rabbits	The development of in vitro fertilization
2009	Carol W. Greider	Protozoan, mouse, frog	Discovery of how chromosomes are protected by telomeres and the enzyme telomerase
2009	Elizabeth H. Blackburn	Protozoan, mouse	Discovery of how chromosomes are protected by telomeres and the enzyme telomerase
2009	Jack W. Szostak	Protozoan	Discovery of how chromosomes are protected by telomeres and the enzyme telomerase
2008	Harald zur Hausen	Hamster, mouse, cow	Discovery of human papilloma viruses causing cervical cancer
2008	Françoise Barré-Sinoussi	Monkey, chimpanzee, mouse	Discovery of human immunodeficiency virus
2008	Luc Montagnier	Monkey, chimpanzee, mouse	Discovery of human immunodeficiency virus
2007	Mario R. Capecchi	Mouse	Discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells
2007	Sir Martin J. Evans	Mouse, chick	Discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells
2007	Oliver Smithies	Mouse	Discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells

Year	Nobel Laureate	Animal model	Contribution to modern medicine
2006	Andrew Z. Fire	Nematode roundworm	Discovery of RNA interference—gene silencing by double-stranded RNA
2006	Craig C. Mello	Nematode roundworm	Discovery of RNA interference—gene silencing by double-stranded RNA
2005	Barry J. Marshall	Piglet	Discovery of the bacterium <i>Helicobacter pylori</i> and its role in gastritis and peptic ulcer disease
2004	Richard Axel	Mouse, <i>Drosophila</i> (fruit flies)	Discoveries of odorant receptors and the organization of the olfactory system
2004	Linda B. Buck	Mouse	Discoveries of odorant receptors and the organization of the olfactory system”
2003	Paul C. Lauterbur	Clam, mouse, dog, rat, chimpanzee, pig, rabbit, frog	Discoveries concerning magnetic resonance imaging (MRI)

Table 1. Contributions of lab animals to biomedical research (adapted from Foundation for Biomedical Research [4]).

3. Expert view vs. common sense

Many scientific articles and books written in recent times have attempted to bridge the gap between effective animal model and the equivalent human pathological replication. It may seem controvertible on the acceptance of animal models as equivalent to human testing. As this may not apply in all cases, however, there are notifiable instances where animal models may substantially suffix. This is exemplified by the US FDA Animal Efficacy Rule (also known as Animal Rule) which applies to development and testing of drugs and biologicals in animal models to reduce or prevent serious/life-threatening conditions caused by exposure to lethal or permanently disabling toxic agents (chemical, biological, radiological, or nuclear substances) and in instances where human efficacy trials are not feasible or ethical [7].

In this book, animal models of global disease of interest were extensively discussed. The seventeen (17) chapters presented by experienced experts in the field detailed the practical and theoretical steps in animal model development and various approaches to achieve and/or develop specific models X-raying their limitations, interspecies variations, and comparison of different models (chemically induced, biological, xenograft, syngeneic, and genetically modified) which best suited for good experimental results. The book is designed to assist researchers make a beneficial choice of experimental animal relevant to their research design, hypothesis, and expected results. The chapters as much as intriguing presents scientific bases for choice of experimental animals on notable and widely researched global disease of interest ranging from central diabetes insipidus, diabetic retinopathy, hair research and regeneration, skeletal remodeling, ductular reaction in chronic human liver diseases, induced oxidative stress, inflammatory bowel diseases, and double incontinence HIV/AIDS to neuroinflammatory disease.

One of the factors impeding the translation of knowledge from preclinical to clinical studies has been the limitations of in vivo disease models in which specific animal models discussed

in the chapters tend to address. Regulatory authorities, however, require vaccine candidates to undergo preclinical evaluation in animal models before they enter the clinical trials in humans [8]. The overarching goal of a new vaccine is to stimulate the immune system to elicit an effective response against the pathogen it is being designed for; currently, experts have noted that no alternatives to the use of live animals exist for evaluation of the vaccine response despite advances in computational sciences for the search of an *in silico* model. One of the issues bordering scientific expediency in the development and use of animal models is on bioethics and animal rights. Thus, qualification and ethical consideration need appropriate clarification.

4. Need for standardization of model

There is a need to qualify and/or standardize animal models. Qualification of an animal model implies that a specific animal species given a specific challenge agent by a specific route produces a disease process or condition that in multiple important aspects corresponds to the human disease or condition of interest [9]. The experts' discussion (chapters) presents the need for standardization or qualification of models. The question of whether or not there should be a standardized or qualified model is the basis of one of the main current controversies in developing animal models for human diseases. Having a standardized animal model relates to the appropriate research use and may be regarded as a complete and precise description of intended use and application of the qualified animal model in drug development and regulatory processes. The process must specify the details necessary to replicate the model. Other criteria may be summarized as follows:

- (a) Known and identified animal thus proposed for use
- (b) Known and characterized challenge agent
- (c) Procedural information for the challenge agent exposure
- (d) Identification of the primary and secondary endpoints
- (e) Potential triggers for intervention

5. Next-generation models

An interesting aspect of the book is the respective discussion in each chapter of next-generation models and how perceived limitations of current animal models could be obviated. Recent animal model research has focused on the (i) refinement of existing models and the development of new ones, (ii) use of these models to research key questions about the disease pathology, and (iii) key findings with these models testing therapeutic and vaccine concepts [10]. Margaret Hamburg wrote "We must bring 21st century approaches to 21st century products and problems" [11]. This scientific era entails rapid and unprecedented development of enabling biotechnologies with great promise for the future.

6. What this book argues

As implied above, the concept of animal models dealt with in this book discusses appropriate mechanistic models for selected prevalent human diseases. An animal model is imperative for preclinical trials, disease pathway and pathological elucidation, new drug development, and vaccine construction. Against any odd, the use of animals especially rat and mouse seems indispensable in today's scientific world. The book presents reproducible experimental approach using animal models for human diseases with measurable equivalence to that of humans. It also presents models of high human predictive value. Despite the current insights and promising technologies, no scientific method can at this time fully address the limitation(s) of using animal models as complete surrogates for humans.

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