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 |
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

| 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 Helicobacter pylori and its role in gastritis and peptic ulcer disease |
| 2004 | Richard Axel | Mouse, Drosophila (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]).
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.

Author details

Ibeh Bartholomew Okechukwu

Address all correspondence to: barthokeyibeh@yahoo.com

Laboratory of Animal Models for Human Diseases (LAMHD), Medical Biotechnology Department, National Biotechnology Development Agency, Abuja, Nigeria

References

[1] Rand MS. Selection of Biomedical Animal Models. In: Conn PM, editor. Source Book of Models of Biomedical Research. Totowas, NJ: Humana Press Inc.; 2008. p. 9-15

[2] Charles Singer Galen as a modern. Section of the history of medicine. Proceedings of the Royal Society of Medicine. 1949;XLII:563-570

[3] Bernard C. An Introduction to the Study of Experimental Medicine. 1st ed. USA: Henry Schuman Inc.; 1865 Transl. Henry Co–pley Greene, AM. 1929. p. 4-250

[4] Foundation for Biomedical Research. Animal Testing and Nobel Prize. https://fbresearch.org/medical-advances/nobel-prizes [Accessed: 14th May, 2017]

[5] Haigwood NL. Update on animal models for HIV research. European Journal of Immunology. 2009;39:1994-1999

[6] Bartholomew I, Yasuhide F, Lucy O, Josiah H. Humanized mouse as an appropriate model for accelerated global HIV research and vaccine development: Current trend. Immunopharmacology and Immunotoxicology. 2016;38(6):395-407

[7] Snoy PJ. Establishing efficacy of human products using animals: The US food and drug administration’s ‘animal rule’. Veterinary Pathology. 2010;47(5):774-778
[8] Gerdts V, Wilson HL, Meurens F, van Drunen L, van den Hurk S, Wilson D, Walker S, et al. Large animal models for vaccine development and testing. ILAR Journal. Oxford University Press. 2015;56:53-62

[9] Product Development Under the Animal Rule Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). https://www.fda.gov/downloads/drugs/guidances/ucm399217.pdf October 2015 Accessed: 12 June 2017

[10] Hessell AJ, Haigwood NL. Animal models in HIV-1 protection and therapy. Current Opinion in HIV and AIDS. NIH Public Access. 2015;10:170

[11] Hamburg MA. Advancing regulatory science. Science. 2011;331(6020):987
