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Contribution of experimental animals in biomedical research

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Abstract
Experimental animal models are mostly vertebrate animals used as living simulations to study human and animal diseases to learn host-pathogen interaction, underlying mechanisms of biological systems for its functioning, understand pathogenesis and finally find appropriate remedies for human and animal sufferings. These experimental animals in biomedical research is immense for helping in the creation of the world's first vaccine, which in turn helped in the eradication of smallpox. Thereafter number of studies with monkeys, dogs, and mice led to the development of polio vaccines and drugs used to combat cancer, HIV/AIDS, Alzheimer's, hepatitis, malaria, etc. would not have been possible without using these animals in research. The selection of an animal as a model for research is critical for the reliability of the outcomes and must have a high contract validity referring to the ability required to mimic the mechanism of the target species under investigation. In this context, Rat and mice are the most widely animal species used as animal models globally owing to their ease in handling, and housing, as well as their high homologous to humans. Furthermore, the right choice of an animal model to target species is very important to avoid tragedies in human populations.

Keywords: Experimental animals, biomedical research, human and animal diseases

Introduction
Why animals are being used in biomedical research?
Animals kept in captivity as per prescribed norms and guidelines for experimental purpose is commonly known as laboratory animals. However, in a normal sense laboratory animal species covers a wide range of animals from sea to wild habitat. In the beginning drug is to be studied first by examining *in vitro* using methods like ex vivo tissue and isolated organs, thereafter it must be studied in a suitable animal models system to meet out legal and ethical concerns before clinical trials in humans. Animal studies provide information on efficacy and safety in a more précised manner.
Latest advances in genetic engineering have helped to create several transgenic and humanized mice models for the better construct validity of an animal model to replicate the disease as in the target species. Approximately 95% of all warm-blooded laboratory animals used for biomedical research are rodents. At present rodents are mainly used to perform basic research to understand the disease mechanism and evaluate the preclinical therapeutics of new drug molecules for proof of concept, which is later tested on large animal models. Most importantly among large animal models, Beagle dogs are used for regulatory studies and pharmacokinetics studies, Pigs, sheep, and goats have been used to perform various cardiovascular surgeries in medical device testing while NHPs are invaluable animal models for studying human brain function and neurological diseases owing great similarity to humans.

History of experimental animal research
Alcmaeon of Croton (6th-5th century BCE) greek medical writer, Aristotle, Diocles, Praxagoras (4th century BCE), Erasistratus, and Herophilus (4th-3rd century BCE) were well-known legendary figures. They conducted "vivisections" (Stricto sensu and lato sensu) (Maehle and

Tröhler, 1987) [1]. Galen (130–201 AD) conducted physiological studies on pigs, monkeys, and dogs. Their studies served as the foundation for medical procedures for decades. Following Galen, Vesalius began his empirical research with anatomical examinations.

Rene' Descartes (1596-1650), a French philosopher, claimed that Animals are more like machines. The distinction between humans and animals is that humans have a mind, heavily criticized by many of his contemporaries. William Harvey (1578-1657), one of the founders of modern science, and in 1628, "An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings" was published, which is the most accurate description of heart anatomy and circulation of the blood system. Charles Darwin's (1809–1882) On the Origin of Species was published in 1859, and it provided a promising scientific foundation for advancing our knowledge about genetic relationship with the rest of the animal species in the animal kingdom

Edward Jenner produced the smallpox vaccine using the cowpox virus in the late (1796) 18th century. Accordingly, cows were frequently employed as experimental animals in vaccine development until the illness was eradicated in the late 20th century. Fluid from cowpox pustules is extracted, purified, and injected into humans. Louis Pasteur (1822–1895) and his German equivalent, Robert Koch (1843–1910), often used animal experimentation in their microbiology and pathology-associated studies. After that germ theory was reconsidered and microbes were known as the reason for disease, not miasma. Robert Koch theory of "Koch postulates" was a milestone development that was established through the use of animals. (McMullen, 1995) [2]. Behring and Ehrlich (1854–1915) in the field of microbiology contributed for the development of the first diphtheria antitoxin from horses. Shibasaburo Kitasato (1853–1931) also developed tetanus antitoxin with his coworker Behring (Arthur M Silverstein, 2001) [4] experimenting on horses.

Paul Ehrlich utilized thousands of mice to develop Salvasaran an arsenicals, the anti-syphilis medication (Bosch and Rosich, 2008) [5]. Since the turn of the century, biomedical research has contributed to human health, through animal research which played a key role in several significant breakthroughs by using animals in research and development of preventive and therapeutic candidates. Another indirect measure of the impact of biomedical advances on the twentieth century was the increase in life expectancy. Of the 103 Nobel Prizes in Physiology or Medicine awarded since 1901, work undertaken on vertebrate species (Other than humans) was rewarded on 83 occasions (Oeppen and Vaupel, 2002; Henig, 2000) [6, 7]. Gregor Mendel began the early study on mice in the 1850s, but due to religious taboos, he turned to peas. Lucien Cuenot (1866), who came after him, proved that mammals have Mendelian genes and inheritance laws (Gordon and Ruddle, 1981) [8]. In the 1980s, John Gordon and Franck Ruddle developed the first transgenic mouse, and in 1988, Capecchi, Evans, and Smithies produced the first gene knockout model. European Commission, 2012). After humans, the mouse was the second mammal to have its entire genome sequenced in 2002.

Nobel Prize in Lab animal research

The Swedish chemist Alfred Bernhard Nobel (1833–1896) founded the Nobel Prizes in 1895, and the first physics, chemistry, peace, and literature prizes were given out in 1901. Animal research frequently results in Nobel Prizes. In fact, 188 of the 225 prize winners in the Physiology or Medicine category conducted their study using animal models. A German scientist who worked with horses to produce the diphtheria vaccine got the first prize in 1901. After that, the Nobel Prizes were given out annually for significant discoveries, usually for work involving animals (Baptista *et al*., 2021) [10]. Recently, David Julius and Ardem Patapoutian, for instance, won in 2021 for their work with mice. The discovery of temperature and touch receptors was made possible by their ground-breaking research in mice (Zhang *et al*., 2021) [11] (Fig No: 1).

Classification of experimental animals

Experimental animals are broadly classified as rodents and non-rodents, large and small animals, as well as vertebrate and non-vertebrate animals. Small animals include Mice, Rats, Guinea pigs, and Hamsters. Other small animals like-Rabbits come under lagomorphs. Under large animals - Sheep, goats, pigs, and Equines such as horses, mules and donkeys played a role in immunological and behavioural research. At the next step of preclinical studies in non-human primates such as Monkeys, Langurs, and Loris were used to confirm the reliability of results obtained from the lower vertebrate animals and avian species. Invertebrate models – the fruit fly, nematodes, and wax moth. Also, amphibians like frogs, toads and lizzards contributed significantly. In advanced lab animal science, animals are grouped as Specific pathogen-free animals, Gnotobiotic animals, and transgenic animals are also classified as of defined environment, microbiota, and growing conditions. The usage of individual species is described briefly under separate subsections.

Mice: Mice's genome was published in 2002 and 85% of protein-coding sequences were identical to the human genome. Thus, every human gene has a counterpart in the mice model. The variability is present in the noncoding part of DNA or junk DNA. As compared to other mammals, mice is a well-established model to replicate human in biomedical research. With this, 60.9% of the laboratory animals used in the research are mice (Luechtefeld *et al*., 2018) [12]. Among inbred and outbred animals, except for toxicological studies, all sophisticated experimental research involved inbred strains of mice to overcome variability. Outbred stocks are used in toxicological studies and primary screening of drugs. BALB/c, C57BL/6, CD-1, SCID, Swiss albino, and A/J are the commonly used mice strains for experimental purposes. Among that only CD1 and Swiss albino are outbred animals (Zott *et al*., 2019) [13] and are used in many toxicological testing studies (Irena Živković *et al*., 2016) [18], vaccine development, and basic pharmacological research (Zhao *et al*., 2020) [19]. C57BL/6 strain serve as *in vivo* model for many physiological and pathological diseases and in Alzheimer's and Parkinson's disease model (Kam T *et al*., 2018; Nordmann *et al*., 2020) [14, 15]. BALB/c is an immunodeficient mice model, which is also being used in oncological studies and is involved in hybridoma and monoclonal antibody productions (Besse *et al*., 2019; Luther A, 2019) [16, 17]. CB17 SCID mouse is an albino strain with a spontaneous SCID mutation and a valuable immunodeficient animal model for testing cancer treatments (Richter CP, 1959) [20].

Rats: Norway rats were the first domesticated rats for research purposes 170 years ago (EC, 2012). Rats are the second choice (13.9% of all animals) in overall biomedical research while the first choice in studying cardiovascular and neurobehavioral research (Jacob HJ, 1999) [22]. Wistar rats and Sprague-Dawley rats were the most widely used strains of lab rats worldwide. These two strains of rats with albino coats and of outbred stocks. In addition, rats are excellent models to study diabetes, obesity, and cardiovascular studies (van der Spek *et al*., 2012) [23]. The rat brain looks like a primitive structure of the human brain as well as occurring similar kinds of behavioral disorders. Therefore, rats are one of the best rodent models to study in the neuro-psychology field. Outbred stocks like Wistar, Wistar han, wister Kyoto, Sprague Dawley, Long Evans, and Zuker fatty rats as well as inbred strains like Lewis, Brown Norway, and nude rats were also used for research purpose in the field of pharmacology and toxicology studies.

Wister rat models are used for general-purpose, infectious, and surgical or oncological studies. Wister Kyoto for hypertensive and autism model. Sprague Dawley was established to do behavioural-related research, obesity models, and oncological research. Long Evans was used for behavioural studies because of its docile nature. Zuker fatty rats were models for genetic obesity and showed resistance to leptin (Kava *et al*., 1990) [24]. Brown Norway is a pigmented model used for transplantation and immunological studies (Zhang, 2010) [26]. Lewis strain is used for autoimmune models such as thyroiditis, arthritis, encephalitis, and enterocolitis (Hanes MA, 2006) [27]. Nude rats are widely used for dermatological procedures and can develop tumour masses without showing any distress (Yarto-Jaramillo, 2011) [28].

Guinea pigs: Guinea pigs originated from South America and are caviomorph rodents (McMurray, 1994) [29], phylogenetically distant from humans as compared to mice/rats. These are preferred models for studying infectious disease, pathogenesis, and vaccine safety testing and toxicological studies. Less than 1% of Guinea pigs are used for research in the UK. Guinea pig shows similarity with regards to the hormonal and immunological system (Complement and Delayed type hypersensitivity) to humans (Seya *et al*. 1991; García-Carrillo, 1990) [30, 31]. Outbred strains of Guinea pigs include Hartley Guinea pig, Duncan-Hartley, and English short hair, while Strain 2 or 13 Guinea pig is the only inbred strain. Among this, Duncan Hartley is widely used for multiple research purposes (Hensel and Arenas-Gamboa, 2018) [32]. Many bacterial (Tuberculosis, Diptheria, Brucellosis, Chlamydia, Legionnaire, etc.) and viral diseases (Zika, Ebola, Lasa, and Influenza) were studied systematically using this animal as a model (McMurray *et al*., 1996; Padilla-Carlin *et al*., 2008) [33, 34]. Most of the sexually transmitted diseases and reproductive disorders scan very well in Guinea pigs as compared to the mice. More than 20 Nobel Prizes were awarded for the research, involving the use of Guinea pigs (Pasteur L, 1885) [35].

Rabbits: Rabbits are lagomorphs and much closer to primates as compared to rodents. It is the first animal model used for immunological studies by Louis Pasteur for the rabies vaccine (Neves *et al*., 2015) [36]. Immunity-associated genes present in rabbits are similar to humans. Laboratory rabbits are derived from the European rabbit. New Zealand White (NZW), New Zealand Red (NZR), Californian White (CW), Dutch belted rabbits, and Polish rabbits are used for laboratory purposes. Rabbits are generally used for bone and periodontal research (Aline Schafrum Macedo *et al*., 2019) [37]. NZW are widely used for monoclonal and polyclonal serum raising, cancer, studies dealing with atherosclerosis and lupus (Mage and Rai, 2012) [38], and other complex disease models (Kónya *et al*., 2008) [39]. NZR/NZW rabbit is used to study TB, leprosy, and other infectious diseases (Dharmadhikari and Nardell, 2008; Esteves *et al*., 2018) [40, 41]. Dutchbelted and Polish rabbits are used in pharmacological/toxicology studies and for eye-related research (Gwon A, 2008) [42].

Non-Human Primates (NHPs): Non-Human Primates have a close phylogenetic relationship to humans Further NHPs and humans share a common ancestor. The development of vaccines, therapeutic molecules, and implant devices need to be translated into NHPs after completing experiments in rodents. Primates are arboreal and plantigrade animals. Classified into two suborders Prosimii and Anthropoidea include animals such as lemurs, lorises, bush babies, tree shrews and monkeys (Old World and New World), gibbons, and apes, respectively. Macaques, Bonnet, Rhesus, Lion-tailed, Assamese, Pig-tailed, and Stump-tailed macaques were used in various kinds of biomedical research. Every year, 65000 NHPs in the USA and 5000 in the European Union were used (EC, 2013; US, 2012). NHPs were used in infectious (HIV, Smallpox, Polio, and Hepatitis), non-infectious diseases (Nervous and reproductive model), and xenotransplantation research. In 1940, Salk and Sabin developed the Polio vaccine by passaging the virus in a Rhesus monkey model to create a live attenuated vaccine (Spice B, 2005) [42], (americanhistory.si.edu). Vaccines, therapeutic studies, and pathogenesis of AIDS, Zika, Ebola, Yellow fever, and Hepatitis virus also studied preclinical as definitive models (Friedman *et al*., 2017) [46]. Medical breakthroughs in drug delivery and treatment for brain cancer were studied critically using NHPs (Staprans *et al*., 2004; Lesniak, 2014) [47, 48]. Rhesus monkey was used for the malarial vaccine and atherosclerosis-associated research. Bonnet and Langur monkey was used for studying the pathogenesis of Kyasanur Forest Disease (KFD), Japanese Encephalitis (JE), and Dengue virus (Holbrook, 2012) [49]. Physical, chemical, and immune contraceptive methods were tested in the NHPs before applying to humans (Liechty *et al*., 2015) [50]. Monkeys were used in space research to know the physiological changes because of space travel (Sharp, 2021) [51].

Canines: Dogs are the ideal model to study metabolism and physiological associated studies. Diabetes, Cardiovascular, Muscular dystrophy, Epilepsy, and Cancer occurring in dogs are similar to human conditions which make dogs compatible with biomedical research. Beagle dogs are most preferred because of their known biological and genetic status as well as docile and friendly behaviour. Therefore, accepted for biomedical research. However, Mongrels and Hounds are also used because of their medium size. In 1920, Banting received the Nobel Prize for the use of pancreatic insulin from cows that controlled diabetes in dogs. Also in the year 1904, Pavlov was awarded the Nobel for finding the control of the digestive system by the reflex from the central nervous system (Gerard P. Smith, 2000) [52]. Nutritional research associated with Vitamin D supplementation through cod liver oil reduced rickets incidence in dogs (Mellanby, 1976) [53]. Dog is the better model to study multiple sclerosis and age-related problems because of their food habits like humans. As dogs can also be affected by Granulomatous meningo encephalomyelitis and chemical damage of DNA methylation leading to aging problems, hence, they are the best-suited model for these studies. Antiaging procedures and technology tested in dogs can be translated into humans (Abdallah, 2019) [54]. Louis Pasteur used dogs as experimental animals for rabies vaccine development and successfully applied vaccines to control rabies in humans. The electrocardiogram (ECG) was invented by Einthoven with the use of dogs as laboratory animal models. Different cardiac problems were identified using the ECG pattern in dogs, which can be applied in humans C.F. Beck., *et al*. (1947) [55]. Cardiac valve xenograft was performed on rabbits, G. pigs, sheep, and subsequently pigs to dogs finally leading to identify biologically inert bio-prosthetic valves in pigs. Dogs are often used in oncology and toxicity studies. Since dogs and humans reported high homology for cancer-related illnesses, drugs developed for the cancer were tested in dog models (Lucroy and Suckow, 2020) [57].

Equines: Equines are monogastric of lesser comparative intestine length and much more sensitive to allergens. Commonly used to raise the hyperimmune plasma against snake venom (Guidlolin *et al*., 2010) [58]. From 1890, horses were used to produce antitoxin for diphtheria. This research was awarded a Nobel Prize for Emil von Behring's work. Horses were also utilized to study the autonomic nervous system and cartilage repair research (McIlwraith *et al*., 2011) [59]. However much is involved in orthopedic-related research.

Other experimental models in biomedical research

Hamsters comprise 25 species but only Syrian/Golden hamsters are used in biomedical research. Potency testing of the leptospira vaccine was carried out in the hamster model as well as pathogenesis and therapeutic candidate investigations (Samrot AV *et al*., 2021) [60]. Mongolian gerbil models were used in biomedical research for gastrointestinal tumours, stroke, and inflammatory bowel diseases (Small and Buchman, 2000) [61]. The effect of drug molecules on steroid hormone and cholesterol level were analyzed in this model (Rybakova, A. and Makarova M, 2017) [62]. Chinchilla (long-tailed) is broadly investigated for auditory-related studies such as otitis media (Shofner W.P and Chaney M, 2013) [63]. The nine-banded armadillo is the only ideal model to study the infectious organism, *Mycobacterium leprae* (Balamayooran *et al*., 2015) [64]. Alternative model organisms such as the zebrafish, silkworm, tobacco hornworm, fruit fly, and nematodes don't come under the ethical considerations as in the case of higher vertebrates (Peterson *et al*., 2008) [65]. The Greater Wax moth (*Galleria mellonella*) has emerged as an infection model to demonstrate bacterial virulence factors. The fruit fly *Drosophila melanogaster* and the minuscule nematode *Caenorhabditis elegans* were commonly used invertebrate models, as these are used for Parkinson's, Alzheimer's, Huntington's disease, diabetes, cancer, immune disorders, as well as the development and testing of therapeutic agents for these diseases (Wilson-Sanders S E, 2011) [66]. In addition, these models were used for molecular mechanism and genetics-associated studies. The wax moth model is used to screen a variety of antimicrobial molecules such as antibiotics, peptides, and phages against potential bacterial pathogens for their efficacy (Tsai *et al*., 2016) [67].

Conclusion

Animal studies are critical to advance our understanding of complex disease pathogenesis, genetics, risk factors, safety of drugs, and vaccines for several life-threatening health diseases. Every Nobel Prize awarded in medicine in the last three decades has depended on data from animal experimentation. Testing on animals are very important to ensure the safety and efficacy of various drugs, vaccines, and devices before they are used in humans. Several animals ranging from small animals like mice to large animals including non-human primates are available to unravel the fundamental questions of many diseases, which are yet to be conquered by finding their diagnosis, understanding the host-pathogen interaction, and finally addressing upon cure.

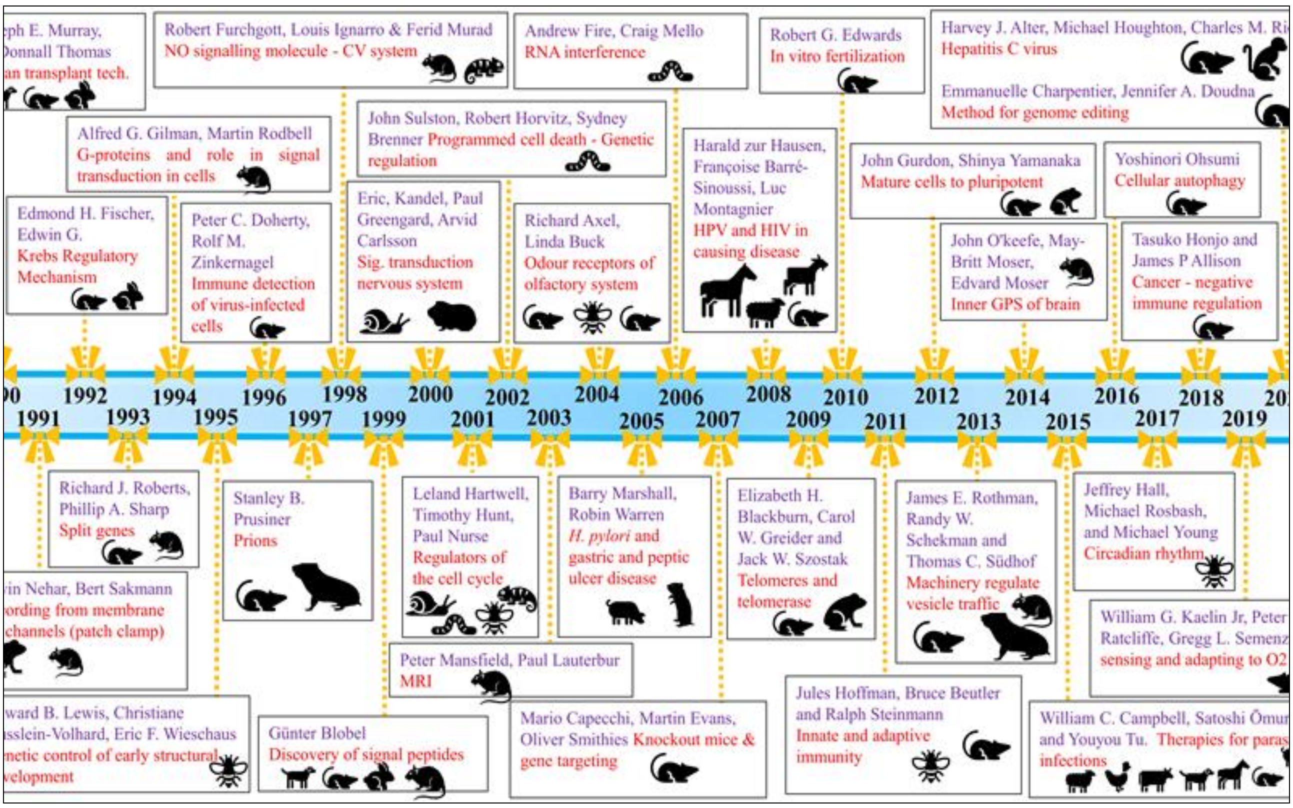

Fig 1: Graphical representation of lab animals utilized in the Nobel Prize research

Conflict of Interest: None.

References

1. Maehle AH, Tröhler U. Animal experimentation from antiquity to the end of the eighteenth century: Attitudes and arguments. In: Rupke NA, editor. Vivisection in Historical Perspective. London, UK: Croom Helm; 1987.
2. McMullen ET. Anatomy of a physiological discovery: William Harvey and the circulation of the blood. J R Soc Med. 1995;88(9):491.
3. Bazin H. Vaccination: a history from Lady Montagu to genetic engineering. John Libbey Eurotext; c2011.
4. Silverstein AM. Paul Ehrlich's receptor immunology: the magnificent obsession. Elsevier; c2001.
5. Bosch F, Rosich L. The contributions of Paul Ehrlich to pharmacology: a tribute on the occasion of the centenary of his Nobel Prize. Pharmacology. 2008;82(3):171-179.
6. Oeppen J, Vaupel JW. Broken limits to life expectancy. Science. 2002;296(5570):1029-1031.
7. Henig RM. The monk in the garden: the lost and found genius of Gregor Mendel, the father of genetics. Houghton Mifflin Harcourt; c2000.
8. Gordon JW, Ruddle FH. Integration and stable germ line transmission of genes injected into mouse pronuclei. Science. 1981;214(4526):1244-1246.
9. European Commission. Seventh report on the statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union. Accompanying document to the Report from the Commission to the Council and the European Parliament, Brussels, 5.12. 2013, COM (2013) 859 final; c2013.
10. Jota Baptista CV, Faustino-Rocha AI, Oliveira PA. Animal models in pharmacology: A brief history awarding the Nobel Prizes for Physiology or Medicine. Pharmacology. 2021;106(7-8):356-368.
11. Zhang Y, Zhang D, Qin C. Animal models and experimental medicine and the Nobel Prize in Physiology or Medicine 2021-TRPV and PIEZO receptors for temperature and touch sensation. Animal Models and Experimental Medicine. 2021;4(4):297.
12. Luechtefeld T, Marsh D, Rowlands C, Hartung T. Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility. Toxicological Sciences. 2018;165(1):198-212.
13. Zott B, Simon MM, Hong W, Unger F, Chen-Engerer HJ, Frosch MP, *et al.* A vicious cycle of β amyloid–dependent neuronal hyperactivation. Science. 2019;365(6453):559-565.
14. Kam TI, Mao X, Park H, Chou SC, Karuppagounder SS, Umanah GE, *et al.* Poly (ADP-ribose) drives pathologic α-synuclein neurodegeneration in Parkinson's disease. Science. 2018;362(6414):eaat8407.
15. Nordmann GC, Malkemper EP, Landler L, Ushakova L, Nimpf S, Heinen R, *et al.* A high sensitivity ZENK monoclonal antibody to map neuronal activity in Aves. Scientific Reports. 2020;10(1):915.
16. Besse A, Besse L, Kraus M, Mendez-Lopez M, Bader J, Xin BT, *et al.* Proteasome inhibition in multiple myeloma: head-to-head comparison of currently available proteasome inhibitors. Cell Chem Biol. 2019;26(3):340-351.
17. Luther A, Urfer M, Zahn M, Müller M, Wang SY, Mondal M, *et al.* Chimeric peptidomimetic antibiotics against Gram-negative bacteria. Nature. 2019;576(7787):452-458.
18. Živković I, Rajnpreht I, Minić R, Mitić K, Aleksić I, Kadrić J, *et al.* Characterization of Intor: Swiss albino mice adopted in the Institute of Virology, Vaccines and Sera–Torlak, Belgrade in the early twentieth century. Acta Veterinaria. 2016;66(3):279-293.
19. Zhao L, Han X, Lu J, McEachern D, Wang S. A highly potent PROTAC androgen receptor (AR) degrader ARD-61 effectively inhibits AR-positive breast cancer cell growth *in vitro* and tumor growth in vivo. Neoplasia. 2020;22(10):522-532.
20. Richter CP. Rats, man, and the welfare state. Am Psychol. 1959;14(1):18.
21. European Commission. Seventh report on the statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union. Accompanying document to the Report from the Commission to the Council and the European Parliament, Brussels, 5.12. 2013, COM (2013) 859 final; c2013.
22. Jacob HJ. Functional genomics and rat models. Genome Res. 1999;9(11):1013-1016.
23. Van der Spek R, Kreier F, Fliers E, Kalsbeek A. Circadian rhythms in white adipose tissue. Prog Brain Res. 2012;199:183-201.
24. Kava R, Greenwood MRC, Johnson PR. Zucker (fa/fa) Rat. ILAR J. 1990;32:4–8.
25. University of Utah Weiss RB, Dunn DM, NISC Comparative Sequencing Program, NHGRI Green ED, Blakesley RW, Bouffard GG, *et al.* Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature. 2004;428(6982):493-521.
26. Zhang L. Glycosaminoglycans in development, health and disease. Academic Press; c2010.
27. Hanes MA. The nude rat. In: The Laboratory Rat. Academic Press; c2006. p. 733-759.
28. Yarto-Jaramillo E. Respiratory system anatomy, physiology, and disease: Guinea pigs and chinchillas. Vet Clin Exot Anim. 2011;14(2):339-355.
29. McMurray DN. Guinea pig model of tuberculosis. In: Tuberculosis: pathogenesis, protection, and control; c1994. p. 135-147.
30. Seya T, Okada M, Hazeki K, Nagasawa S. Regulatory system of guinea-pig complement C3b: tests for compatibility of guinea-pig factors H and I with human factors. Mol Immunol. 1991;28(4-5):375-382.
31. García-Carrillo C. Laboratory animal models for brucellosis studies. Animal Brucellosis. 1990;423:442.
32. Hensel ME, Arenas-Gamboa AM. A neglected animal model for a neglected disease: guinea pigs and the search for an improved animal model for human brucellosis. Front Microbiol. 2018;9:2593.
33. McMurray DN, Collins FM, Dannenberg AM, Smith DW. Pathogenesis of experimental tuberculosis in animal models. Tuberculosis. 1996;157-179.
34. Padilla-Carlin DJ, McMurray DN, Hickey AJ. The guinea pig as a model of infectious diseases. Comp Med. 2008;58(4):324-340.
35. Pasteur L. Méthode pour prévenir la rage après morsur; c1885.
36. Neves F, Abrantes J, Almeida T, de Matos AL, Costa PP, Esteves PJ. Genetic characterization of interleukins (IL-1α, IL-1β, IL-2, IL-4, IL-8, IL-10, IL-12A, IL-12B, IL-15 and IL-18) with relevant biological roles in lagomorphs. Innate Immun. 2015;21(8):787-801.
37. Schafrum Macedo A, Cezaretti Feitosa C, Yoiti Kitamura

Kawamoto F, Vinicius Tertuliano Marinho P, dos Santos Dal-Bó I, Fiuza Monteiro B, *et al*. Animal modeling in bone research-Should we follow the White Rabbit? Animal models exp med. 2019;2(3):162-168.
38. Mage RG, Rai G. A rabbit model of systemic lupus erythematosus, useful for studies of neuropsychiatric SLE. Systemic lupus erythematosus. 2012;201-217.
39. Kónya A, Wright KC, Gounis M, Kandarpa K. Animal models for atherosclerosis, restenosis, and endovascular aneurysm repair. In: Sourcebook of models for biomedical research. 2008;369-384.
40. Dharmadhikari AS, Nardell EA. What animal models teach humans about tuberculosis. Am J Respir Cell Mol Biol. 2008;39(5):503-508.
41. Esteves PJ, Abrantes J, Baldauf HM, BenMohamed L, Chen Y, Christensen N, *et al*. The wide utility of rabbits as models of human diseases. Exp Mol Med. 2018;50(5):1-10.
42. Gwon A. The rabbit in cataract/IOL surgery. In: Animal models in eye research. 2008;184-204. Academic Press.
43. European Commission. Seventh report on the statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union. Accompanying document to the Report from the Commission to the Council and the European Parliament, Brussels, 5.12. 2013, COM (2013) 859 final. 2013.
44. US 2012 Statistics" Archived 2014-08-06 at the Wayback Machine, Speaking of Research.
45. Spice B. Tireless polio research effort bears fruit and indignation. The Salk vaccine: 50 years later. 2005.
46. Friedman H, Ator N, Haigwood N, Newsome W, Allan JS, Golos TG, *et al*. The critical role of nonhuman primates in medical research. Pathogens Immunity. 2017;2(3):352.
47. Staprans S, Feinberg MB. The roles of nonhuman primates in the preclinical evaluation of candidate AIDS vaccines. Expert Rev Vaccines. 2004;3(1):S5-S32.
48. Lesniak MS. Development of preclinical models for immunogene therapy of brain cancer: it's not monkey business! Mol Ther. 2014;22(2):247-249.
49. Holbrook MR. Kyasanur forest disease. Antiviral Res. 2012;96(3):353-362.
50. Liechty ER, Bergin IL, Bell JD. Animal models of contraception: utility and limitations. Open Access J Contracept. 2015;27-35.
51. Sharp LA. Primate Nation: The (after) lives of iconic creatures in American space science. Bio Societies. 2021;1-25.
52. Smith GP. Pavlov and integrative physiology. Am J Physiol-Regul Integr Comp Physiol. 2000;279(3):R743-R755.
53. Mellanby E. An experimental investigation on rickets. Nutr Rev. 1976;34(11):338-340.
54. Abdallah AN, Shamaa AA, El-Tookhy OS. Evaluation of treatment of experimentally induced canine model of multiple sclerosis using laser activated non-expanded adipose derived stem cells. Res Vet Sci. 2019;125:71-81.
55. Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. JAMA. 1947;135(15):985-986.
56. Ionescu MI, Ross DN, Wooler GH. Biological tissue in heart valve replacement. (No Title).
57. Lucroy MD, Suckow MA. Predictive modeling for cancer drug discovery using canine models. Expert Opin Drug Discov. 2020;15(6):731-738.
58. Guidlolin RG, Marcelino RM, Gondo HH, Morais JF, Ferreira RA, Silva CL, *et al*. Polyvalent horse F (Ab) 2 snake antivenom: Development of process to produce polyvalent horse F (Ab) 2 antibodies anti-african snake venom. Afr J Biotechnol. 2010;9(16):2446-2455.
59. McIlwraith CW, Fortier LA, Frisbie DD, Nixon AJ. Equine models of articular cartilage repair. Cartilage. 2011;2(4):317-326.
60. Samrot AV, Sean TC, Bhavya KS, Sahithya CS, Chan-Drasekaran S, Palanisamy R, *et al*. Leptospiral infection, pathogenesis and its diagnosis-A review. Pathogens. 2021;10(2):145.
61. Small DL, Buchan AM. Animal models. Br Med Bull. 2000;56(2):307-317.
62. Rybakova A, Makarova M. Using Mongolian gerbils for biomedical research. Mezhdunarodnyy vestnik veterinarii. 2017;(2):117-124.
63. Shofner WP, Chaney M. Processing pitch in a nonhuman mammal (*Chinchilla laniger*). Journal of Comparative Psychology. 2013;127(2):142.
64. Balamayooran G, Pena M, Sharma R, Truman RW. The armadillo as an animal model and reservoir host for Mycobacterium leprae. Clinics in dermatology. 2015;33(1):108-115.
65. Peterson RT, Nass R, Boyd WA, Freedman JH, Dong K, Narahashi T. Use of non-mammalian alternative models for neurotoxicological study. Neurotoxicology. 2008;29(3):546-555.
66. Wilson-Sanders SE. Invertebrate models for biomedical research, testing, and education. ILAR journal. 2011;52(2):126-152.
67. Tsai CJY, Loh JMS, Proft T. Galleria mellonella infection models for the study of bacterial diseases and for antimicrobial drug testing. Virulence. 2016;7(3):214-229.