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BIOMODELS AND ALTERNATIVE METHODS IN HEALTH LEARNING

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Résumé: L'utilisation d'animaux de laboratoire est un outil fondamental dans la recherche ainsi que dans l'enseignement. Cependant, l'utilisation de biomodèles est controversée en termes de questions éthiques et leur pouvoir prédictif dans la recherche peut être limité. La méthode la plus appliquée au niveau international en matière d'éthique animale est le concept des "3R" (raffinement, la réduction, et le remplacement). Afin d'optimiser le pouvoir prédictif des biomodèles, on commence à utiliser dans la recherche des outils alternatifs à l'utilisation d'animaux, comme la méthode *in silico*. Cette méthode est basée sur l'utilisation de modèles de calcul pour prédire le risque potentiel des nouvelles substances. Les biomodèles dans l'enseignement sont également remplacés par des logiciels qui permettent à l'étudiant de répéter tous les processus sans le stress des animaux. Les avantages de ces méthodes alternatives sont les suivants: faible coût par rapport à l'entretien des installations pour animaux, durée de vie indéfinie, optimisation de l'apprentissage et surtout, en rendant l'étudiant plus actif et engagé. En résumé, tant la nouvelle politique de réduction de l'utilisation des animaux de laboratoire que les nouvelles avancées en matière de technologie éducative favorisent les techniques d'enseignement qui augmentent les performances et le développement des élèves, permettant ainsi une éducation orientée vers l'avenir.

Abstract: The use of experimental animals represents a fundamental tool in academic and research. However, the use of biomodels raises controversy in terms of ethical issues, once their predictive power in research may be limited. The most internationally applied method for animal ethics is the "3 Rs" (Refinement, Reduction, Replacement) concept. Research begins to employ alternative tools to the use of animals, such as the in silico method, in order to optimize the predictive power of biomodels. This method is based on the use of computational models to predict the potential risk of new substances. Animals use is also being replaced by software that allows the student to repeat all the processes without animal stress. Some advantages in the use of these alternative methods are in: low cost compared to the maintenance of animal facilities, indefinite lifetime, optimization of learning and, above all, inciting the student to become more active and engaged. In summary, all of the new policy of reducing the use of animals and of the new advances in educational technology favor teaching techniques that increase the performance and the development of students, they are all allowing a futureoriented education.

1. HISTORICAL BACKGROUND

Animal research is essential for the advancement of new technologies and medicines, it is crucial to improving human and animal health. The use of animal models in the study of human anatomy and physiology dates back to the 6th century B.C.[1]. Aristotle (384–322 B.C.) who made detailed observations in human and animal experiments to explore the anatomy of the heart and vessels and thus provided the basis for modern CV medicine[2]. Claude Bernard (1813-1878), the father of modern experimental medicine, based his physiological experiments on the use of animals[3].

Animals were used in the development of novel surgical techniques such as the tracheostomy, initially performed on goats, and laparoscopy, using dogs in the 1900s[4,5]. Animal experiments have also contributed significantly to the development of vaccines, antibiotics, and our fundamental understanding of human disease processes. Albert Sabin used monkeys in the 1930s to develop the polio vaccine [6]. Insulin was discovered in the 1920s using canines, and the foundation of diabetes research relied on genetically modified mouse and rat models[7].

Animal testing grew popular and received government endorsement in the 1930s after the Lash Lure case, a toxic eyelash dye that caused injury and blindness[8]. The importance of pre-clinical studies was remarkable when catastrophic effects of thalidomide on the developing fetus were discovered. In 1957, the German pharmaceutical company launched a remedy that was used by pregnant mother for its anti-emetic effect. In 1960s, more than 10,000 babies had been born with severe malformations to mothers who had taken the drug during pregnancy. The tragedy had a dramatic effect on the development of new drugs. Since the disaster, drug screening policies have changed to incorporate several species as well as in vitro tests, and there has not been a repeat of the disaster[9].

1 Ericsson, A.C.; Crim, M.J.; Franklin, C.L. «A brief history of animal modeling» Mo. Med. 110, 201–205, 2013.

2 Shoja, M.M.; Tubbs, R.S.; Loukas, M.; Ardalan, M.R. «The Aristotelian account of "heart and veins"» Int J Cardiol. 25;125(3):304-10, 2008.

3 LaFollette, H.; Shanks N. «Animal Experimentation: the Legacy of Claude Bernard» International Studies in the Philosophy of Science. 195-210, 1994.

4 Haddad, F.S. «Ibn Zuhr and experimental tracheostomy and tracheotomy» J. Am. Coll. Surg. 2004.

5 Litynski, G.S. G.S. «Laparoscopy–the early attempts: spotlighting Georg Kelling and Hans Christian Jacobaeus» J. Soc. Laparoendosc. Surg. 1, 83–85, 1997.

6 Sabin, A.B. «Oral poliovirus vaccine. History of its development and prospects for eradication of poliomyelitis» J. Am. Med. Assoc. 194, 872–876, 1965.

7 King, A.J. «The use of animal models in diabetes research» Br. J. Pharmacol. 166, 877–894, 2012.

8 Sigmund, S.G «Dermatoconjunctivdiuteits o Lash-Lure,a n Eyelasha nd Eyebrow Dye » J . Amer.M ed.A ssoc. 101, 363-364, 1933.

9 Vargesson, N. «Thalidomide-induced teratogenesis: history and mechanisms» Birth Defects Res C Embryo Today. 105(2):140-56, 2015.

2. ANIMAL RESEARCH

In 1959, Russel and Burch introduced the Three R's of animal research: Replacement, Reduction, and Refinement. These three principles were designed to serve as a foundation for the development of future alternatives to the use of animals in research [10]. It was not until the 1980s, however, that legislative bodies across Europe and the United States began to develop committees and laws to govern the use of animals in research, many of which are largely based upon the three Rs.

In 1978, the concept of animal use began to change when UNESCO published the Universal Declaration of Animal Rights, where in other preambles it is considered: all animals have rights; disregard and contempt for the rights of animals have resulted and continue to result in crimes by man against nature and against animals; recognition by the human species of the right to existence of other animal species is the foundation of the co-existence of species throughout the animal world; from childhood man should be taught to observe, understand, respect and love animals.

In 1988 the American Medical Association (AMA) issued a White Paper defending biomedical experimentation on animals and promoting the appropriate use of research animals and explaining to the public and legislators the importance of research using animals to medical progress [11]. In 1992, the American Psychological Association (APA), have developed their own guidelines governing research with animals, "Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research" which reinforce and/or supplement all pertinent laws and other regulations. The APA produced one of the earliest and most complete sets of association guidelines pertaining to research on animals

In 2010, the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs), an independent organization based out of the United Kingdom, published the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines a checklist of recommendations to improve the reporting of research involving animals. In 2020 the guideline was Updated for reporting animal research in a 2.0 version [12]. The legislation and guidelines governing the ethics of animal use in experiments include the 3RS (Reduction, Refinement and Replacement) into experimental biology. Reduction concerns minimising the number

[10] Burden, N.; Chapman, K.; Sewell, F.; Robinson, V. «Pioneering better science through the 3Rs: an introduction to the national centre for the replacement, refinement, and reduction of animals in research (NC3Rs)» J. Am. Assoc. Lab. Anim. Sci. 54, 198–208, 2015.

[11] Smith, S.J.; Evans, R.M.; Sullivan-Fowler, M.; Hendee, W.R. «Use of Animals in Biomedical Research: Historical Role of the American Medical Association and the American Physician» Arch Intern Med. 148(8):1849–1853, 1988.

[12] Percie du Sert, N.; Hurst, V.; Ahluwalia, A.; et al. «The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research» PLoS Biol 18(7): e3000410, 2020.

of animals used to effectively achieve the goals of an experiment, just enough to obtained sufficiently informative results.

Refinement involves either reducing the invasiveness of a technique or improving animal welfare and health during scientific studies. Regardless of the species used, refining procedures to ensure the health and well-being of animals prior to and during experiments is crucial for the integrity of the results and legitimacy of the science. The refinement can be achieved through better assessment of the animal's state or improved husbandry and housing. A refinement procedure is environmental enrichment, that can involve physical objects that either make an environment more complex (e.g. plastic plants), apparatus to allow exercise (e.g. rodent running wheel) or even nutritional enrichment (e.g. diversity of feeding regimens).

Replacement involves the adoption of alternatives to protected animals – such alternatives may be immature forms; cell lines or cultured tissues; mathematical modelling of existing data sets or conceptual data; or the use of humans, their tissues or their cells (with permission). Despite, animals cannot be easily replaced, and reduction and refinement are more realistic ethical strategies. However, some alternative methods can provide valuable informations enabling scientifics and professors to embrace the replacement approach[13].

3. ALTHERNATIVE METHODS IN TEACHING

The society has achieved great successes and scientific advances in the area of health thanks to the use of animal models. On the other hand, their use raises controversy regarding ethical issues, in addition to the fact that their predictive power may be limited at a more translational level, since these models present a considerable phylogenetic distance from the human species. As a result of this genetic heterogeneity, the results of animal studies do not always carry over when trialed in human subjects. Another point to consider is the poor translation of the data and knowledge obtained from animal trials to subsequent human trials [14].

The conservation of physiological traits throughout the eukaryotes means that alternative non-vertebrate organisms can provide valuable information where processes are shared with model organisms, enabling experimental biologists to embrace the replacement approach. Most animal testing involves invertebrates, especially *Drosophila melanogaster*, a fruit fly, and *Caenorhabditis elegans (C.elegans)*, a nematode [15].

[13] Sneddon, L.U.; Halsey, L.G., Bury, N.R. «Considering aspects of the 3Rs principles within experimental animal biology» J Exp Biol. 1;220(Pt 17):3007-3016, 2017.

[14] Pound P, Ritskes-Hoitinga M. «Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail» J Transl Med. 7;16(1):304, 2018.

[15] Gois, A.M.; Mendonça, D.M.F., Freire, M.A.M.; Santos, J.R. «In vitro and in vivo models of amyotrophic lateral sclerosis: an updated overview» Brain Res Bull.159:32-43, 2020.

Cell cultures are important material of study for the variety of advantages that they offer. Culture systems have been developed that e.g. enable stem cells to grow and expand into fully functioning three-dimensional organ-specific tissue [16]. The long-term expansion capacity of organoids has opened possibilities for biobanking of disease-derived organoids. These biobanks represent valuable resources for clinical applications such as omics analysis for cancer stratification and drug screening for precision medicine. In the past few years, extensive efforts have been made to establish living organoid biobanks derived from many different tumor types. Additionally, biobanks generated from biopsy tissue have become instrumental to grow organoids that mirror molecular fingerprints of diseased patients [17].

In the last two decades, computational modeling has developed into a powerful technique to complement and reinforce traditional *in vitro* and *in vivo* experimentation. *In silico* methods or research using technology like computer modeling, in which biological experiments are carried out entirely in using computer models, as well as computational biomechanics have also become powerful and predictive tools to replace research animals.

Software known as Computer Aided Drug Design (CADD) is used to predict the receptor binding site of a potential drug molecule. CADD works to identify the likely binding site and thus avoids testing for unwanted chemicals with no biological activity [18]. Another *in silico* tool is the structure-activity relationship (SAR) computer programs. It predicts the biological activity of a drug candidate based on the presence of chemical moieties linked to the parent compound. Moreover, this method could theoretically help to modify the compounds to exhibit the most potency, most selectivity, best pharmacokinetics and least toxicity.

In addition to alternative research methods, the use of animals for academic activities has been an extremely complete and interesting methodology used in the training of professionals, especially in the biological and health sciences. However, its use in teaching is also being replaced by software, such as Sniffy the virtual rat, which allows the student to repeat all the processes and take their animal to the pendrive without involving the stress of handling and the suffering of water or food deprivation [19]. In addition, mobile applications such as 3D Brain, for the study of the central nervous system, and 3D Bones and Organs, for the study of anatomy, also innovate in teaching.

[16] Huch, M.; Dorrell, C.; Boj S.F.; van Es, J.H. et al. «In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration» Nature. 494:247–250, 2013.

[17] Van De Wetering, M., Francies, H.E., Francis, et al. «Prospective derivation of a living organoid biobank of colorectal cancer patients» Cell 161, 933–945, 2015.

[18] Kore, P.; Mutha, M.; Antre, R.; Oswal, R.; Kshirsagar, S. «Computer-Aided Drug Design: An Innovative Tool for Modeling» Open Journal of Medicinal Chemistry, 4, 39-148, 2012.

[19] Ficher, M. L. «Ética no uso de animais em atividades científicas e acadêmicas» (Coleção Ética em pesquisa Livro 3), Curitiba: PUCPRESS, 2017.

In silico studies allow us to improve our knowledge of small molecules that continue to attract the interest of pharmaceutical companies and academic research groups as drugs and drug candidates. It is evident that available information on small molecules with their properties and biological activities against of multiple biological targets is on the increase [20]. Some advantages in the use of alternative methods have already been demonstrated in the literature: low cost compared to the maintenance of the facilities and the preparation of the animals, indefinite useful life, better learning when using software and artificial models, and respect for evolution. academic, allowing repetition as many times as necessary [21].

Regarding the education scenario in the health sciences, we have the teaching tool called "problem-based learning" (PBL). PBL has been defined as “active learning stimulated by, and focused round a clinical, community or scientific problem” [22]. In the PBL, the learner is required to solve a specific problem whilst acquiring knowledge on how to solve similar problems. Within medical education a scenario is typically used to provide an example from which a trainee may learn. Much of an expert’s diagnostic and reasoning efforts are focused on the similarities and differences of a novel case with known cases. Thus PBL offers the opportunity to provide trainees with scenarios that will be of use throughout their professional life. The advantages in PBL methos are: Facilitating trainees becoming responsible for their own learning and Increased motivation of trainees to learn by focusing the learning on ‘real-life’ scenarios. On the other hand, the PBL not necessarily cover all areas within a medical topic teaching and the time required to fully engage in PBL, can be particularly problematic for time-poor students [23].

3. CONCLUSION

The contribution animal's models have had to human research is undeniable. Animal models allow understanding the pathophysiology of a number of disorders in humans, as well as developing treatments that are safe and effective. A deeper look at the current landscape, however, raises questions. Always seeking the relevance of the study and trying to involve the concept of the 3Rs when using experimental animals is extremely important. Therefore, especially in teaching focused on the area of biological sciences and health, the new policy of reducing the use of experimental animals, in addition to the new advances in technology and educational resources, results in an education that increases performance and development of los estudiantes.

[20] Zloh, M.; Kirton, S.B. «The benefits of in silico modeling to identify possible small-molecule drugs and their off-target interactions» Future Med Chem. 10(4):423-432, 2018.

[21] Greiff, S. «Alternativas ao uso de animais vivos na educação pela ciência responsável» São Paulo: Instituto Nina Rosa, 26p, 2003.

[22] Davis, M.H., Harden, R.M.; «AMEE medical education guide no. 15: problem-based learning: a practical guide» Medical Teacher 21:130-140, 1999.

[23] Jones, R.W. «Problem-based learning: description, advantages, disadvantages, scenarios and facilitation» Anaesth Intensive Care. 34(4):485-8, 2006.

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