Is there a future for scientific animal research?

Vitor F. Ferreira[1], Cristina M. Hüter[2], Wilson C. Santos[3, 4]

[1] Universidade Federal Fluminense, Faculdade de Farmácia, Departamento de Tecnologia farmacêutica, Programa de Pós-Graduação em Ciências Aplicadas a Produtos para a Saúde.

[2] Universidade Federal Fluminense, Escola de Engenharia, Departamento de Engenharia Agrícola e Meio Ambiente.

[3] Universidade Federal Fluminense, Faculdade de Farmácia, Programa de Pós-Graduação em Ciências Aplicadas a Produtos para a Saúde.

[4] Instituto Teófilo Hernando, Departamento de Farmacología, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain.

Contact:

Vitor F. Ferreira

https://orcid.org/0000-0002-2166-766X

vitorferreira@id.uff.br

Cristina M. Hünter

https://orcid.org/0000-0003-0655-5966

cristinahuther@gmail.com

Wilson C. Santos

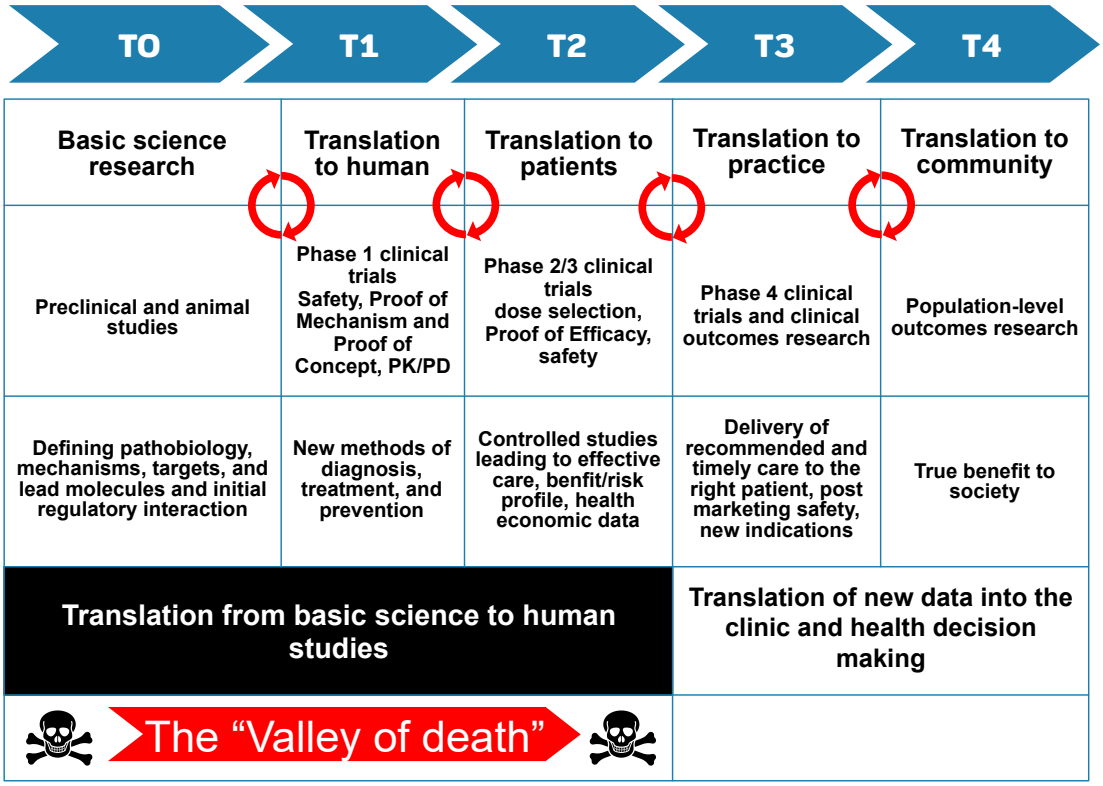
https://orcid.org/0000-0001-9971-094X

wsantos@id.uff.br

The use of animals in scientific research has been a topic of debate for many years. However, a recent decision from the US Food and Drug Administration (FDA) agency on experimental animal use (Lanese, 2023) has caught the biomedical research community and laboratories all over the world as a big surprise. In fact, the decision was made on an approved law by US Congress in 2022 (https://www.congress.gov/bill/117th-congress/senate-bill/5002, accessed on March 9, 2023). For it, the agency no longer requires new drugs to be tested in animals before being approved. The agency now has the option to approve drugs that are tested in non-animal studies only, including those that use lab-grown tissues or computer models, before being tested in clinical trials with humans.

On one side, although it seems to be a major decision that attends to many claims from animal's protection societies, on the other way around however researchers criticized that the technologies for non-animals experimentation procedures are still so far away to be willing to replace the animal experiments. Animal experimentation helps to comprehend how the drugs act and perform during their time course in a living organism, how they interact to the tissues and possible the targets they have to reach to exert their pharmacological effects – and also their putative toxicity. Usually, international agencies require drugs to be tested in one rodent and one non-rodent species, before they were moved into human trials. Therefore, animal experimentation intends to support the safety and efficacy of potential treatments.

However, what is taken as a very serious dilemma on the pre-clinic phase of a drug discovery project is exactly the strong difficult to translate the knowledge from basic scientific research into clinical research to create novel treatments, treatment options devices, medical procedures, preventions, and diagnostics. Actually, a recent review from Seyhan (2019) has shown that more than 90% of drugs that pass initial animal tests end up being unsafe or ineffective in humans. A speech from the Author has really caught us to consideration: "There is a consensus both in academia and industry that there is a crisis involving the translatability of preclinical science to human applications and that most research findings are irreproducible or false". The figure bellow, quoted from the article, brings some light to the discussion:



Operational phases and associated challenges for translational research. Translational research has many layers (T0-T4) and associated operational obstacles that must be overcome. T0, basic science research that define cellular mechanisms, their relationship to disease and, consequently, the identification of therapeutic targets and development of methods of treatment (new molecular entities). T1, is the proof of concept studies conducted in volunteer human subjects as phase 1 clinical trials that aim to define proof of safety, mechanism, and concept. T2, phase 2 and 3 clinical (ideally randomized) trials that are necessary to test the proof of efficacy of the therapeutic agent in cohorts of patients representing the relevant disease that may include control groups. T3, phase 4 clinical trials that are associated with optimizing the therapeutic use of a therapeutic agent in clinical practice. T4, Population-level outcomes research or comparative effectiveness research aims to determine the ultimate utility and cost effectiveness of a therapeutic agent relative to others currently in use. Translation from basic science to human studies form the critical path, as defined by the FDA, or the "valley of death", as defined by the pharmaceutical industry. This "valley of death" encompasses T0-T2 phases of research. However, each of these phases have overlapping sets of challenges as discussed in the text.

Extracted from Seyhan, 2019 (https://doi.org/10.1186/s41231-019-0050-7)

Seyhan also presented some credible data for the process of getting a new drug: for example, from first testing to final FDA approval and ultimately to market is a long (from discovery to approval of a new drug takes more than 13 years), costly, and risky and almost 95% of the drugs entering human trials fail. Still, almost 50% of all experimental drugs fail in Phase III trials. Hence, moving new drug candidates from preclinical research into human studies and the approved drug is only approximately 0.1%. Despite efforts to improve the predictability of animal testing, the failure rate has actually increased, and the major causes of failure are lack of effectiveness and poor safety profiles that were not predicted in preclinical and animal studies. Additionally, Akhtar (2015) has presented some other conditions that may undermine the reliability on animal experimentation conclusions: the effects of the laboratory environment and other variables on study outcomes; disparities between animal models of disease and human diseases; species differences in physiology and genetics. The combination of those conditions may mislead the results obtained in animals experiments use. Furthermore, there is greater emphasis of animal wellbeing issues in

the scientific literature and new lines of research that address issues of animal welfare (Lohse, 2021).

On the other hand, the *Americans for Medical Progress* has commented on the **FDA Modernization Act** and has pointed out that computer models, organs-on-a-chip and organoids are not able to replace animal studies in most cases because these technologies are still in their infancy; thus, as a result, they only provide a limited amount of information required in the drug safety testing process and also in other health research areas. Still, they also mean that alternative models (such as computer models) can only mimic what is already understood about the human body. As a result, there are many areas where we have a tremendous amount to learn (Newman, 2023).

Another worrying point is that the FDA's decision only has the force of law in the USA. It is possible that other countries will try to follow FDA guidelines, but this is not automatic. In order to not fulfill with FDA regulations, pharmaceutical companies can transfer their clinical tests on laboratory animals to other countries that are more flexible and/or without legislation on the theme. However, in the human testing phase the same can happen. In the past, there have been documented cases of clinical trials on prisoners without their consent, and there are also reports of abuses by pharmaceutical companies when carrying out clinical trials in the human phase in developing countries and that after trials they did not have access to adequate medical care after the end of the study (https://ors.umkc.edu/services/compliance/irb/history-of-research-ethics.html# , accessed on March 16, 2023).

Actually, the recent decision from FDA was not an isolated action. We feel that a strong believe that the practice of animal use on experimental procedures is unethical and does not produce results that can be reliably translated to people there really exists. We also notice that the overall public is generally in favor of efforts to replace animals, in order to benefit animal welfare, public health and even the economy. To our own, we really believe that there is an urgent require to revise biomedical and translational researches following ethical guidelines; it's urgent to search for proven techniques and technologies that have direct relevance to human patients and thus replace animal experiments.

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PÍLDORA DE INFORMACIÓN

CEGAR UN ENSAYO CLÍNICO

Si conoce el tratamiento que está recibiendo, el paciente que participa en un ensayo clínico podría reaccionar subjetivamente al relatar los efectos del mismo. Lo mismo acontece con el investigador médico; si conoce el tratamiento asignado al paciente podría cometer sesgos en la interpretación de los resultados. Por ello, el paciente o el médico deben ignorar el tratamiento asignado (simple ciego); en el caso de que ambos, paciente y médico ignoren el tratamiento, el ensayo clínico se tilda como doblemente ciego.