It is about time to change research strategy in the 21st century

At present, research carried out simplistic *in vitro* models or animals has been questioned by large part of the scientific community (1-8). New progress in the fields of biotechnology and biomedical science aimed at understanding human biology underlines the importance of renewing current research strategies, especially when the goal is the development of new drugs (9-20). The immediate necessity to change traditional research approaches is even more evident if we consider the availability of new methods, which in some cases have been shown to be more efficacious in predicting human physiological and biological responses (21-26). Let us take the example of modern toxicology, where progressively the standards have changed: in the past 20 years, research has progressively shifted from studying animals towards animal-free methods, such as *in vitro* and *in silico* systems that, when integrated, are considered to be more predictive to study the physiological and toxicological responses occurring in humans.

In 2007, the U.S. National Academy of Sciences released the article "Toxicity Testing in the 21st Century: A vision and a Strategy (27), which together with the European Directive 2010/63/EU on the protection of animals used for scientific purposes (28) foster the use of alternatives to animal methods to enable mechanistic understanding, underlining the importance of the "Adverse Outcome Pathway" (AOP) concept. An AOP gives an overview on the effects of environmental chemicals or other chemical substances at multiple levels of biological complexity (i.e. population, individual, organ, tissue, cells, molecule, etc.) (29,30).

This new conceptual approach is easily applicable to biomedical research – e.g. the identification of molecular signals altered during the onset and the consolidation of a pathological process (10,31).

Here are some examples of international scientific organizations that support the need for a paradigm change in traditional animal-based research strategy: Biomed 21 (https://biomed21.org), Alliance for human relevant Science (https://humanrelevantscience.org), Canadian Centre for Alternatives to Animal Methods (http://www.uwindsor.ca/ccaam/) and Human Toxicology Project Consortium (https://humantoxicologyproject.org). These scientists believe that the traditional animal-based approaches must be surpassed, since have been proven inadequate and generally not predictive of human biology. In Europe, new alternative methods are emerging (New Approach Methodologies – NAMs). The European Commission within the framework Horizon 2020 has designated more than 100 million euros for research programs aimed at developing new methods that exclude the utilization of animals. Unfortunately, Italy is not among the leading countries in such research endeavour due to lack of researchers, specific expertise and infrastructures, although there are many Italian scientists who are participating. On the other hand, many scientists in The Netherland are leading such research activities, and the Dutch

government aims at becoming world leader in devising new scientific methods that do not encompass the use of animals with the aim to phase out animal testing by 2025. They have invested a considerable amount of money in this project with avant-garde laboratories, which enable these ambitious research programs. In the United States of America the Environmental Protection Agency (EPA) has declared that by 2035 they will stop using animals for toxicological purposes. To this aim, they have invested more than 4 million dollars to create new toxicological procedures based on human cell cultures (projects ToxCast and Tox21).

O.S.A.: "Oltre la Sperimentazione Animale" (Beyond Animal Experimentation) favours this concept and promotes a petition addressed to Italian biomedical Scientists: **It is about time to change research strategy in the 21st century.** Why? Because it is important to foster innovation, moving beyond outdated concepts, in order to become part of the new progress and new conceptual thinking that promotes human biology as the gold standard in biomedical research. It is about time to create and teach the future scientists who will be involved in working with the new models. What is needed? Political and economical support. The greater the support will be, the faster the collective benefit for the human health problems will ensue.

° *O.S.A: oltre la sperimentazione animale (Beyond Animal Experimentation) is an association formed by biomedical experts. This association promotes and supports human relevant and ethically sustainable biomedical research.*

https://oltrelasperimentazioneanimale.eu

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