

# It is about time to change research strategy in the 21<sup>st</sup> century

## Accelerating the Growth of Human Based and human Relevant Life Sciences in Italy

At present, research carried out simplistic *in vitro* models or animals has been questioned by large part of the scientific community (1-12). 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 (13-25). 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 (26-32).

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 21<sup>st</sup> Century: A vision and a Strategy (33), which together with the European Directive 2010/63/EU on the protection of animals used for scientific purposes (34) foster the use of alternatives to animal methods to enable mechanistic understanding.

The Organisation for Economic Cooperation and Development (OECD) launched a programme on the development of **Adverse Outcome Pathways (AOPs)** in 2012. AOPs give 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.) (35, 36). 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 (14, 37).

There are several examples\* of international scientific organizations that support the need for a paradigm change in traditional animal-based research strategy. These scientists believe that the traditional animal-based approaches must be surpassed, since have been proven inadequate and generally not predictive of human biology.

A substantial international effort over the last decade has produced many different experimental models that use human cells and reproduce key features of human biology. These new approach methodologies (NAMs) do not use animals, thus circumventing the problem of animal-

human species differences that can confound data interpretation (38, 39). 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).

**Government and regulatory support are crucial to drive progress in harnessing the business and public health potential of NAMs in Italy.** A government-backed body is needed to support early career researchers and institutions in order to accelerate the growth of NAMs. To achieve this, OSA\*\* “Oltre la Sperimentazione Animale” (Beyond Animal Experimentation) and the Scientific Community represented by the signatories of this Manifesto call for supportive infrastructure, strategic funding, education, collaboration between industries, and regulatory engagement.

This is even more important in view of COVID-19 research, where NAMs are already providing promising results (40-46). **The need for a vaccine to prevent SARS-CoV-2 and treatments for the COVID-19 illness require technologies that can be used quickly and that won't lead scientists astray with information that isn't relevant to humans (47).** The greater the support will be, the faster the collective benefit for the human health problems will ensue.

\* Some examples of international organizations supporting a human-focused paradigm in health research: (<https://biomed21.org/>), Alliance for human-relevant Science (<https://www.humanrelevantscience.org/>), Canadian Centre for Alternatives to Animal Methods (<http://www.uwindsor.ca/ccaam/>), Animal free Safety Assesment (<https://www.afsacollaboration.org/>), Center for Contemporary Sciences (<https://www.contemporarysciences.org/>)

\*\*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.*

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