



Keynote Lectures

Animals: biomechanisms or evolving organisms on the way to a reflexive thought?

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There are three approaches towards animals in a classical philosophy: (a) an animal as a mere thing or a kind of a biomechanism, (b) in the opposite extreme at least certain animals as equal to humans with no significant difference and (c) central position stating that an animal is occurring somewhere between a thing and human person. Modern evolutionary biology and especially the idea of a convergent evolution are shedding new light on this discussion. This new approach suggests that any general features of organisms that are of great adaptive value would have arisen in certain moment of evolution, and intelligence and reflexive thought are most probably not exceptions. From this perspective, animals, or at least some of them, can be viewed as organisms on the way to the reflexive thought. The philosophical consequences of this hypothesis are discussed in this text.

For further reading see Ayala, 2010; Morris 2003, 2008.

References

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The rational use of animals in drug development: contribution of the Innovative Medicines Initiative

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Animal models are widely used in research and development to assess the efficacy or safety of new pharmaceutical products. However, their limitations in predicting actions of drugs in humans is more and more apparent, therefore there is an urgent need to revisit the use of animals in pharmaceutical research. This presentation will focus on the review of how the Innovative Medicines Initiative (IMI), the largest public-private partnership in life sciences, is reducing, refining and replacing the use of animals in the context of its global mission, namely to boost research and development of new medicines across the European Union.

The Innovative Medicines Initiative is a public-private partnership between the European Commission and the pharmaceutical industries members of the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI's key mission is to enhance the competitiveness of the pharmaceutical sector in Europe for the benefit of patients and scientists by supporting open innovation and non-competitive research in the pharmaceutical research and development. IMI was launched in 2008 by the European Union and the EFPIA, with a total budget of 2 billion euro to be spent over a 7-year period, making the IMI the largest PPP in life sciences. EFPIA pharmaceutical companies invest in the IMI in the form of in-kind contributions by committing internal human resources or providing access to data sets and infrastructure and sometimes in the form of direct monetary contributions. This industry investment is matched by funds from the European Union to support the other consortium members, including academic teams, small and medium-sized enterprises (SMEs), patients' organizations, regulatory agencies, and relevant not-for-profit institutions. IMI fosters open innovation in pharmaceutical R&D and biomedicine via public private collaboration by addressing industrial and societal challenges and by setting a neutral platform for aligning healthcare, research and regulatory priorities.

Use of animals in research and testing is a highly sensitive, yet vital part of the long and complex process of creating new medicines. However, the insoluble problems of species differences and animal to human extrapolation inevitably limit the value of animal studies for the prediction of the action of drugs in humans. A number of major technological developments have recently opened up possibilities for more directly human-based approaches with the further added value of a dynamic two-way interaction between what takes place in the laboratory and in the clinic. This progress is leading to a fundamental re-thinking of the role and use of experimental animals in pharmacological research and biomedicine.

In an era of increasing economic pressure on the healthcare systems and the pharmaceutical industry, public-private partnerships (PPPs) offer unique opportunities to overcome the hurdles which prevent efficient and safe medicines to reach patients suffering from debilitating diseases. With increased attention paid to investigations centred on human beings, human materials or based on in silico models, PPP like IMI contributes to rationalise the use of animals in biomedical research by focusing on validated models directly pertinent to drug action in patients.

European strategy for 3Rs and replacement of animal experiments (example of cosmetics sector)

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In 2010 the European Union adopted Directive 2010/63/EU on the protection of animals used for scientific purposes. The aim of the Directive is to strengthen legislation, and improve the welfare of those animals still needed for research and safety testing, as well as to firmly

anchor the principle of the Three Rs, to Replace, Reduce and Refine the use of animals, in EU legislation. Directive 2010/63/EU took full effect on 1 January 2013. The European Commission strongly supports efforts to find alternative methods to testing on animals. Where this is not possible the number of animals used must be reduced or the testing methods refined so as to cause the least harm to the animals.

In the field of cosmetics, provisions in relation to animal testing were introduced into the Cosmetic Directive 76/768/EEC in 2003. Accordingly, animal testing in the Union was prohibited since 2004 for cosmetic products and since 2009 for cosmetic ingredients (“testing ban”). As from March 2009, it is also prohibited to market in the Union cosmetic products containing ingredients which have been tested on animals (“partial marketing ban”). On 11 March 2013 the European Union put in place a complete ban on the marketing of the remaining cosmetic substances tested on animals. This was the final step in a 10 years process to totally ban animal testing for cosmetic purposes.

The EU has set a good example in demonstrating the safety of cosmetics without new animal tests. This example is one which many other countries are now starting to follow. From China and India to the countries of South East Asia we see encouraging steps towards the banning of animal testing for cosmetics. The European Commission is willing to work with all stakeholders in any country which wishes to follow the European Union’s lead and embrace alternative methods to test the safety of cosmetics.

Human-on-a-chip – a paradigm shift from animal testing

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The keynote lecture provides a historical sketch of my efforts since 1990 to replace laboratory animals by emulating systemic human biology. It started with a multi-cartridge hollow fibre bioreactor in the early 1990s combining five human organ equivalents failing to operate, but perfectly replacing ascites mice. Scientific and commercial implementation of a miniaturized artificial human lymph node in 2004 (Giese et al., 2006) reinvigorated my enthusiasm to design a human-on-a-chip platform with a team of equally enthusiastic scientists. The ten-organ-chip visualized by 2009 was too radical to get full funding. Instead, the platform development of an integrated two-organ-chip operated by an on-chip-pump was funded in 2010. Proof of concept combining human liver and skin equivalents at steady culture conditions over 28 days was achieved in 2012 with repeated dose troglitazone testing (Wagner et al., 2013; Schimek et al., 2013). Subsequently, industry interest is resulting in diverse feasibilities, varying organ arrangement and substance exposure on the platform. 2012 also marked the launch of an amazing top-down US initiative on that topic. Highlights of this programme are given. Hot spots for human-on-a-chip development in other parts of the world are summarized. The keynote finally emphasise scientific aspects of further development (Marx et al., 2012; Giese C., Marx U., 2014), ethical repercussions and economic feasibility of the human-on-a-chip.

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Industrial perspectives on the 3Rs and animal welfare

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Contract Research Organizations (CRO) can creatively partner with their pharmaceutical, biotech, and chemical customers to implement and devise new applications of the 3Rs in research and in animal welfare. CROs run many discovery and safety studies, including *in vitro* technologies and a wide range of animal based models, so they are in a unique position to accelerate innovation and develop new approaches to the assessment of new drugs, devices, and chemicals. This presentation will cover the progress across all aspects of animal use in applying the principles of 3Rs and improved animal welfare. We will focus on the pharmaceutical industry and the trend towards integrated toxicology testing strategies to maximize the information obtained using different platforms, including *in vitro* technologies. In addition, progress on the use of 3Rs in animal production will be discussed. Finally, the challenge of validating and applying viable *in vitro* alternatives and identification of current gaps for other alternatives to animal use will be addressed.

How long must they suffer? Success and failure of our efforts to end the animal tragedy in laboratories

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This World Congress is the first outside of the “old” Western hemisphere and thus can be regarded a historical milestone. It reflects the evolution and outreach of scientific and ethical principles regarding animal experiments. In the last decades, many initiatives to advance the 3Rs have come into existence. Even the idea to replace animals as a whole is no longer seen as the unrealistic vision of sentimental animal-lovers but has become an official doctrine of the European Union as well as – for toxicology – of the US government.

However, too many intentions and conventions have proved to be no more than lip services. Most major political initiatives to avoid or reduce animal experiments have either failed dramatically, like the EU-REACH regulation; or they have been watered down in the political decision-making process, losing much of their potential effectiveness, like the revised EU Directive on animal experimentation.

The core ethical problem persists: The question how to decide for which purposes it could be regarded ethically acceptable to deliberately inflict pain, suffering or distress on sentient beings has been extensively investigated, and solutions have been proposed by academia, authorities and different stakeholders. However, the reality in the laboratories reveals that almost always the decision at the end of an ethical review process still is at the cost of the animals.

The presentation gives a closer look at these inconsistencies, puts them into the context of our society’s general views on animals, and highlights the most urgent needs for action.



Future perspectives for alternatives to animal testing in China

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The alternatives to animal testing (AAT) is a concrete manifestation of the principle of 3Rs in scientific research and product safety evaluation, and also, is a scientific problems of great concern for us in the field of life science and biological technology. With the rapid development of AAT technology and acceptance of animal welfare concept internationally, it is a driver for alternative approaches to animal testing research in China.

In 1997, 3Rs principle was firstly written into government documents-Several opinions about the development of laboratory animal science- which was issued by Ministry of Science and Technology, the research on alternative methods was started in a lot of institutes. In 2002, the project on research of laboratory animal welfare guideline and technical specifications in accordance with global standard, was supported by Ministry of Science and Technology. In 2006, the Ministry of Science and Technology published the "Guidance suggestions for the care and use of laboratory animal". It is emphasized in Chinese Pharmacopoeia (2010 Edition) that the chemical methods, physical methods or cytological methods should be used, instead of animal test, for biological product quality verification to minimize animal use. In 2012, "To encourage the development of AAT, and Ensuring animal welfare" was written in "Twelfth Five-Year Plan" (2010-2015) developed by Ministry of Science and Technology.

In China, approach to AAT mainly conducted in regulatory testing for cosmetics and pharmaceuticals in the past three years, for example, research on the methodology of AAT (such as alternative methods to pyrogen test); to organize academic and activities training courses by cooperation with scientific groups worldwide, to enable technical personnel to understand and master the AAT methods approved by OECD (BOCP, HET-CAM, 3T3 NRU phototoxicity test, EPISKIN®, etc.); to compile academic books (e.g., Laboratory Animal and Animal Experimentation, Alternative Laboratory Animal Methods Principles and Application, Toxicology Alternatives). The all mentioned above showed that the importance and position of AAT in the test technology has been received and approved by government and scientists. There are signs that some significant changes in attitude to AAT in regulatory testing are taking place. At present, the preliminary results obtained by scientific groups play an important role in promoting the development of AAT in China.

However, compared with the rapid development of AAT methodology in other countries, the research on AAT started later in China, and is still in early days for us. The AAT method is at the stage in laboratory research level, and have not be validated by formal procedures. Now, the research on AAT is mainly conducted in the field of cosmetics toxicology testing in China, others rarely involved. The research and validation system for AAT has not been established, and the relevant laws and regulations beneficial to promote the development of AAT still need to strengthen and improve.

Looking to the future, the Chinese government is trying to establish guideline and technical standards for AAT according to OECD guideline, hoping to promote the research on AAT in cosmetics toxicology and drug testing, and also to promote the validation, regulatory acceptance and application of AAT for cosmetic safety assessment and drug safety evaluation in China. Therefore, the academic activities for AAT need to be strengthened to make technical staff to know the latest research progress of alternative methods. The training course should be performed regularly to make technical staff to master the AAT which has been approved by OECD, and latest technology in this field. In the meanwhile, we also hope to strengthen the close collaboration with international organizations and scientific groups, and promote the development of AAT in China.

Lessons learned from ToxCast and prospects for the future

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More than a decade ago, the US Environmental Protection Agency began exploring how the field of computational toxicology, which blends advances in modern molecular biology and chemistry with information sciences, could help improve the fundamental manner in which the safety of chemicals could be evaluated. In 2007 it launched the ToxCast program to rigorously evaluate the use of high throughput screening assays to elucidate the range of biological activities that large numbers of chemicals could interact with to cause disease. Since that time it has screened nearly 2000 chemicals across hundreds of biological pathways and developed a number of approaches to characterize the potential hazards, and indeed risks of chemicals. This presentation will cover some of the lessons learned in that program, including the critical need to build supporting infrastructure (tools and databases), the need to build robust data workflows, the value of building large scale collaborations, of factoring in exposure aspects as well as potency in assessing priorities, to be transparent in data collection, processing and release, of working closely with scientists in the regulatory arena to facilitate translation of the effort into practical applications, and lastly, that as in any research program, unexpected findings happen and you need to be prepared to critically assess all aspects of the outputs. The last few years has witnessed an evolution in viewpoints of this transformative approach, with much attention now focused on how and when the approach can be utilized in the chemical safety arena. Current examples include the USEPAs endocrine screening program and OECDs efforts in codifying adverse outcome pathways. But clearly much more work needs to be done, and additional challenges lie ahead, such as more robust incorporation of metabolic competency in *in vitro* assays, accounting for the complexity of emergent properties of tissues and organs, and considering how the effects of cumulative exposures can be evaluated. However, we have made great strides in the last decade at transforming toxicology. This is an abstract of a proposed presentation and does not necessarily represent EPA policy.