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Comment from the New Editor-in-Chief: A Journey to Replacement and the Inevitable Question

Judith Madden

Keywords

AOP, alternatives to animals, integrated frameworks, replacement, Three Rs

In this, my first issue of *ATLA* as Editor-in-Chief, I would like to introduce myself and to share with you my vision for the evolution of the journal in the months ahead. Since its inception, *ATLA* has played a key role in identifying, collating and disseminating the latest ideas and innovations in the area of alternatives. Truly multidisciplinary in its scope, *ATLA* has provided the waymarkers for the journey towards replacing the use of animals in experiments. In terms of moving towards *replacement*, I view this very much as a journey, from past practice where animal testing was undertaken with scant consideration of alternatives, to a future where such testing has been consigned to history, as science evolves to provide the requisite answers through the integration of alternative methods, relevant to the species of interest, that are fully acceptable to all stakeholders — industry, consumers and regulators.

“*Are we nearly there yet?*” You will no doubt recognise that this is the inevitable question, but how can we gain the most insightful response to it? In the context of both long journeys with restless passengers and moving towards *replacement*, the question itself is not particularly constructive. One problem is that it invites a simple ‘Yes/No’ response. But would a binary response be appropriate for this complex situation? I suspect that, if we were very close to this particular journey’s end, then we would already know the answer, all systems would be in place for relying on alternatives and the question would then be redundant. If the answer were ‘No’, then we have not learned very much from posing the question.

Two, more pertinent, questions may help to elicit a more appropriate response: Firstly, “*How far away are we?*”; and secondly, “*What is the most efficient route forward?*” I do not claim to have the answer to those two questions either! However, we now have opened up an essential debate, enabling those interested to express an opinion on how much further there is to go and what we can do to get there faster. Through well-informed scientific debate and exchange of ideas and innovations, we can move forward

more efficiently; this is the *raison d’être* for a scientific journal.

There is an ever-increasing number of journals, testament to the astounding pace of scientific developments in our time and the need to make this new information available to others. However, no one person can be an expert across multiple disciplines, and science advances so rapidly that it is impossible to maintain a breadth of knowledge in numerous diverse subjects. The unfortunate consequence of this is that scientists may be unaware of ideas, new practices or innovations in one area that could be used to advantage across a range of other areas. It is generally accepted that, for the majority of scenarios, no single alternative solution (such as an *in vitro* assay or an *in silico* model) can be used alone as a one-for-one replacement of existing animal tests. The replacement of animals is more likely to be achieved through the application of a wide range of alternative methods, each supplying a piece of information that can be used to complete the picture.

What we are trying to accomplish through the use of alternative methods is highly complex. We want to know how different organisms (environmental species, farm/companion animals, humans, etc.) will respond to the presence of a chemical, or mixture of chemicals, to which it is exposed. The chemical may be a pharmaceutical, food ingredient, cosmetic or environmental pollutant. The organism may be exposed at a low level on a daily basis for many years or exposed to a single high dose on one occasion. It could be at any stage of its life cycle — newly developing or aged — it may be healthy, diseased or particularly susceptible for a number of reasons. How can we

Alternatives to Laboratory Animals
1–2

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predict the potential responses, across all relevant species, for all chemicals of interest under different exposure scenarios? In order to solve such enormously complicated problems, we need to be aware of all of the tools at our disposal, to understand the potential that each tool has to offer and look beyond our own area of expertise to embrace all that is available. A hammer is a very useful tool, but you cannot build a house with it. To build something complex, imaginative and forward-looking, you need to appreciate the full array of existing tools; what they are capable of, their individual potential and limitations, and how they can be used in combination to solve more intricate problems. Importantly, this also helps to identify the gaps in what is currently achievable with alternative methods and, therefore, where future efforts should be directed.

There have been tremendous advances in the complementary fields of *in vitro*, *in silico* and *in chemico* techniques as well as mathematical biology and -omics. These can provide a wealth of diverse information that can be used to inform (quantitative) adverse outcome pathway ((q)AOP) development and systems biology approaches. Systems biology and qAOPs provide frameworks for a more mechanistic understanding of how chemicals can interact with biological macromolecules to elicit an effect; this fundamental research aids our understanding of activity, toxicity and internal distribution of chemicals. These approaches can be used synergistically to fill gaps in knowledge and build a complete picture of chemical–biological interactions that in future will obviate the reliance on animal use in product development and safety assessment across all sectors.

The focus of the Fund for the Replacement of Animals in Medical Experiments (FRAME) reflects this philosophy: that new methods for the replacement of animals in experiments must be based upon the principles of best scientific practice. Therefore, the vision for *ATLA* (FRAME's scientific journal) is for it to build upon its strong history as a resource where the latest innovations, ideas and methods, based on the Three Rs principles are collated, promoted and disseminated as widely as possible.

ATLA is a unique journal that brings together the many facets of the underlying research and how it can be applied. While broadly encompassing topics such as *in vitro* testing,

in silico modelling, mathematical biology, -omics, data mining, and systematic reviews, it is recognised that within these areas is a multitude of sub-disciplines to be investigated. In the forthcoming issues, a series of special collections is planned for *ATLA*, each presenting a state-of-the-art review of a key subject area, with accompanying articles exemplifying how the research is applied within academia, industry and/or the regulatory sector. These reviews will include the potential uses and limitations of the techniques, current barriers to uptake, how these may be overcome and how the area is likely to develop in the next few years. Unarguably, the most important resource in every discipline is the people involved: researchers, developers, promoters and decision makers. New initiatives planned for *ATLA* will also involve supporting the education and fostering the enthusiasm, of those new to the area, reporting ongoing activities and opportunities for development.

As the overriding purpose is to expedite progress towards the replacement of animals, it remains essential that the journal continues to provide scrutiny of the extent and nature of animal use, the uptake of alternatives (or lack thereof) across different sectors and the implications of international legislation from the perspective of animal welfare. There is still some way to go on the journey to *replacement*: I hope that you enjoy the quest and discover new ideas to capture your interest and imagination along the way.

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