Comment

Launch of the Alliance for Human Relevant Science

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The Alliance is an exciting new collaboration, founded to address an urgent need to drive research and development, policymaking, awareness, outreach, and education into human-based methods of safety testing and biomedical research

The purpose of the Alliance for Human Relevant Science is to act as a centre of expertise, to progress improvement in the safety and efficacy testing of drugs, industrial chemicals and other everyday consumer products. Its innovative and forward thinking founder organisations are forming a knowledge cluster that will deliver tools and therapies focused on human biology, to help improve public health and safety. The Alliance, which initially is UK-centred, welcomes new organisations to join and expand — as well as benefit from — this ambitious new collegiate enterprise.

The Alliance was officially launched at a parliamentary event on 8 February 2017 in the House of Commons, which was attended by politicians and scientists from academia, industry and regulatory agencies. This paper summarises background information on the Alliance, its founder members, and its mission to drive an urgently needed paradigm shift toward more human relevant science and away from unreliable animal models, as well as detailing its hugely successful launch.

The Need for an Alliance

Drug safety and efficacy issues, from high profile drug withdrawals and clinical trial disasters[1,2] to less-publicised problems which occur routinely,[3] are symptomatic of the loss in translation from 'bench to bedside'. They are due to the failure of predominantly animal-based preclinical models to accurately predict human responses. The issue is now widely acknowledged and is gaining ongoing momentum.[4] This presents an ideal opportunity to divert resources to more clinically-relevant technologies that will better predict efficacy and safety for patients and consumers. *It is time to focus on the human.*

The US National Research Council's landmark 2007 publication, *Toxicity Testing in the 21st Century: A Vision and a Strategy*,[5] called for "*a paradigm shift from the use of experimental animals toward the use of more efficient* in vitro *tests and computational techniques… that will not only improve the current system but transform it into one capable of overcoming current limitations and meeting future challenges".* The report also envisioned that "*toxicity testing will be radically overhauled over the next 10 years, with the animal testing component virtually if not actually eliminated within the next 20 years*".

It is now a decade since the report was published. A new generation of more physiologically relevant and predictive toxicological tools, involving the use of human cells and tissues, is now available, with several UK companies offering them commercially. Uptake is increasing, but is far from universal. There is a critical need to accelerate the acceptance and use of human relevant technologies, which also presents an enormous commercial opportunity.

The UK is a world leader in biomedical research. But we must be proactive to avoid being left behind by others who are more enthusiastic about the current opportunity. For example, the Netherlands National Committee for the protection of animals used for scientific purposes (NCad) announced at the end of 2016 that: "*Legally prescribed animal testing for safety research on chemical substances, food ingredients, pesticides and medicines (including veterinary medicines) can be phased out by 2025".*[6] NCad's formal opinion, *Transition to non-animal research — on opportunities for the phasing out of animal procedures and the stimulation of innovation without laboratory animals,* was written at the request of the national Minister of Agriculture, who requested a roadmap for reducing animal experiments and becoming the "*world leader in innovation without the aid of laboratory animals by 2025*". To do this, NCad advises the need for a "*paradigm shift away from existing mindsets and practices*".[7]

Founder Members

The Alliance for Human Relevant Science aims to change mindsets and practices by:

— engaging in dialogue and building relationships in the experimental research, pharmaceutical, environmental and industrial chemicals sectors;

— communicating with funding agencies and regulators to gain more support for human relevant research;

— providing training and education in innovative new technologies for early-career researchers; and

— organising conferences, workshops and networking opportunities to bring interested partners together.

The launch of the Alliance follows many months of preparatory work by its founder members: Safer Medicines Trust, Dr Hadwen Trust, Kirkstall, Cyprotex, and CN Bio Innovations. Brief profiles of the co-founders are provided below.

Safer Medicines Trust (SMT)

The SMT[8] is an independent patient safety charity with extensive expertise in drug development and medical research. It aims to change the way medicines are tested to make them safer for patients, by encouraging a transition to a new drug safety testing system focused firmly on *human* biology. The Trust has initiated a number of highly supported parliamentary motions and a Safety of Medicines Bill, calling for independent scientific evaluation of the utility of preclinical animal tests as compared to human-based approaches. The SMT has held conferences on the subject at the Royal Society and the House of Lords.

Dr Hadwen Trust (DHT)

The DHT[9] is the UK's leading medical research charity that exclusively funds and promotes non-animal techniques to replace the use of animals in biomedical research. To date, the DHT has awarded grants to over 200 research projects in diverse areas of medical research, including cancer, Alzheimer's disease, asthma, diabetes, kidney, heart disease and liver disease, as well as many others. The DHT has recently created a new Animal Replacement Centre of Excellence, in conjunction with the Blizard Institute at Queen Mary University of London, which is already becoming a centre of expertise in head, skin and neck cancers, with strong links to breast cancer and prostate cancer as well. The DHT brings together scientists, campaigners and policymakers at its annual 'Animal Replacement Science' conference.

Kirkstall Ltd

Kirkstall Ltd[10] is a pioneering biotechnology company, whose mission statement — Saving Lives through Better Science — reflects its commitment to building more-accurate and more-reliable predictive models of human physiology without the use of animals.[10] The company has an exclusive worldwide licence to patented cell culture technology from the University of Pisa (Italy). Kirkstall has developed this research into a commercially available inter-connected cell culture system, which can be set up so that it mimics the human metabolism, resulting in high-quality screening, rather than just high-throughput screening. The system, now known as Quasi Vivo®, is commercially available, and is used by leading researchers in over 70 academic and industry laboratories worldwide. It has been proven to provide research data significantly closer to clinical data than the conventional static models, and, as its use continues to increase, it will reduce and eventually replace animal research.

Cyprotex

Cyprotex[11] is a contract research organisation, which offers a huge range of approaches to predict human clinical outcome following exposure to a drug or chemical, by using robust *in vitro* methods combined with *in silico* technology. Cyprotex is continually developing and improving an extensive range of patented technologies, which use physiologically-based pharmacokinetic modelling in conjunction with *in vitro* data to predict, for example, human intestinal absorption, drug–drug interactions, hepatotoxicity, skin sensitisation, endocrine disruption, and many other toxicities. Cyprotex serves more than 1500 organisations in the pharmaceutical and biotech, cosmetics/personal care and chemicals industries, as well as academia and not-for-profit organisations.

CN Bio Innovations

CN Bio Innovations[12] develops human organ-on-a-chip technologies: devices that enable the formation of miniature models of organs in the laboratory, by using living human cells, to more accurately aid clinical studies of disease and drug responses. Over the past three years, more than 25 pharmaceutical companies have used CN Bio's devices to study the effects of drugs and other

chemicals on organ function. CN Bio is also developing organ-on-a-chip models for specific diseases, including non-alcoholic steatohepatitis and hepatitis B. CN Bio is a co-recipient, with MIT, of a $26 million US Federal contract to develop a human body-on-a-chip incorporating 10 interconnected mini-organs, and has also received grant awards from Innovate UK. In 2016, CN Bio successfully showcased the world's first 7-organ-on-a-chip platform.

The Launch Event

The launch event was hosted by senior Conservative MP, Sir David Amess, in the House of Commons. The room was full to capacity, with senior scientists from 18 universities, 14 companies, eight charities and the MHRA (Medicines and Healthcare Products Regulatory Agency) in attendance. Some MPs also attended, although fewer than was hoped, as the timing unfortunately coincided with a Commons Brexit debate and vote!

There was great enthusiasm and support for the concept and formation of the Alliance, with a majority of the audience registering their interest in joining immediately after the event. During the discussions, there was overwhelming agreement on the need for changes to mindsets, and much shared frustration regarding continuing demands for 'validation' in animals, made by reviewers for grants and journals, among others.

Representatives from the founder organisations and other expert speakers provided insightful talks on their work, and how it reflects on the mission and aims of the Alliance. The introductory talks were filmed and can be viewed on the Alliance website at www.HumanRelevantScience.org, where a brief highlights video is also available.

Sir David Amess MP declared his wholehearted support for the Alliance and its aims. He said that we are at a historic moment in the history of science, and that *"we are already witnessing the start of a major transition from the dominant paradigm in the life sciences, which has been largely based on animal research, to a future based on human models for human diseases, thanks to the incredible advances made by the revolutions in science and technology in recent years"*. Sir David emphasised further how "*such a major change is going to need all stakeholders to work together towards the common goal. There are many different drivers towards the goal of human models for human disease; the most obvious one being that human relevant science will surely lead to more-effective and safer medicines and other chemicals. Not only can new technologies based on human biology be more predictive for humans, they are often much faster and cheaper, so there are huge economic advantages as well. And of course, greater use of human models means fewer animals will be used, which is a matter of great importance to many in society."* He wished the Alliance every success and offered to help in any way he can toward such an important initiative. We are very grateful to him for giving the Alliance such a positive and enthusiastic launch.

Kathy Archibald, Director of Safer Medicines Trust, explained the charity's mission in working to reduce the devastating impact of adverse drug reactions, which are now a leading cause of death, by making medicines safer by using more human relevant approaches. She explained the need to hasten the *recognition* of the best technologies, so that they will become used *routinely*. Safer Medicines Trust and the other founder members of the Alliance share the same vision to use more-accurate and more-reliable models of human physiology to improve public health and safety. Key to this is raising awareness of the impressive capabilities of techniques that are already available, to demonstrate that a human focus is a valuable asset, with great economic advantages, which will improve safety and accelerate medical progress.

Dr Brett Cochrane, Science Director of the Dr Hadwen Trust, summarised the work of the Trust over 47 years and its ethos in promoting *"human models for human disease*". In the last five years alone, the DHT has awarded more than £4 million in research grants for clinically relevant models of

Sir David Amess, MP.

human diseases. As he observed, the successes of the Alliance's commercial partners are *"a great testament to what can be done"*. Recent scientific and technical advances, coupled with increasing availability of human tissue, have enabled human relevant approaches to be developed where animal models have failed or where there is no model at all. Noting that human toxicity pathways are very complex and require multidisciplinary co-operation and engagement between biologists, immunologists, chemists, bioinformaticians and mathematicians, Dr Cochrane emphasised that the Alliance is keen to welcome new partners, to bring more insight and expertise and to help shape its future work.

Dr Malcolm Wilkinson, the founder and CEO of Kirkstall Ltd, explained the company's passion for using their science base to improve human health. He said: *"We are appalled really at how much science has been done previously using animal models, which are clearly not working. This represents a massive waste of resources — money and people's careers — on models which actually are not going to deliver solutions. So we have to find a way to do things better, and human focused research is the way to do it*." He acknowledged the scale of the challenge in conquering the inertia due to entrenched vested interests, but reiterated Kirkstall's desire to help and its belief in a multi-disciplinary Alliance as the way forward.

Dr Clive Dilworth, Chief Scientific Officer of Cyprotex, explained why he believes that "*the techniques we have currently can significantly reduce drug toxicity"*. He gave the example that *"twenty years ago, there were compounds failing in drug development due to poor PK (pharmacokinetics). So the industry changed and embraced human relevant* in vitro *techniques. Over the next ten years, that failure rate fell from over 40% to below 10%. I believe we can take those same approaches and techniques and apply them to the field of toxicity testing. Toxicity in human clinical trials and discovery is a big issue and it's increasing. The models we have don't currently work or predict humans very well."* He emphasised how much technology has moved on, and that predictive human 3-D micro-tissues are clearly the future of toxicity testing, and how we will be able to achieve so much by working together.

Dr Emma Sceats, CEO of CN Bio Innovations, outlined the company's development of pioneering human organ-on-a-chip technologies incorporating living cells to replicate the structure and function of human organs. She announced that "*this year, CN Bio and our partners at MIT in Boston will deliver a 10-organ so-called 'human body on a chip', to meet the final milestone of a $26 million contract from the US Department of Defence"*. She highlighted how the launch of the Alliance was a call to action. "*We call on the government, its funding agencies and the UK life sciences community, to grasp the enormous potential of non-animal technologies. By improving the evidence base and demand for these technologies, through collaboration and innovation in the UK, we can be confident of a bright future for our industry and the patients we serve."*

Professor Geoff Pilkington (Professor of Cellular and Molecular Neuro-oncology and Head of the University of Portsmouth's Brain Tumour Research Centre) spoke about their 3-D cell modelling of the blood–brain barrier to investigate mechanisms of cancer metastasis. He explained how the use of human relevant models, rather than animal models, can help to fast track promising compounds, particularly re-purposed or

Left to right: Dr Malcolm Wilkinson (Kirkstall); Dr Clive Dilworth (Cyprotex); Dr Gerry Kenna (Safer Medicines Trust); Sir David Amess, MP; Ms Kathy Archibald (Safer Medicines Trust); Dr Brett Cochrane (Dr Hadwen Trust); Dr Emma Sceats (CN Bio Innovations).

re-formulated drugs, into the clinic. He spoke of the difficulties in getting human *in vitro* work published, as the top journals almost invariably require 'validation' in animals. Funding also remains an issue, and Professor Pilkington thanked the Dr Hadwen Trust for funding the Centre's research over a number of years. He said that engaging politicians and decision makers is vital, and congratulated the Alliance on creating a fantastic opportunity to collaborate and exploit ideas to champion the study of human relevant models.

Dr Kelly BéruBé is Director of the Lung & Particle Research Group of the School of Biosciences at Cardiff University. She explained how major progress with her research on air pollution toxicology came with the advent of tissue engineering and being able to purchase human lung cells from healthy and diseased donors, instead of using lungs from laboratory animals. She emphasised how easy it is to become involved in tissue engineering research: the cells and off-the-shelf assay kits can be bought cheaply and published methods are available. She reiterated the difficulties in getting studies published and in gaining funding without the use of animals, despite the lack of relevance between human and rodent lungs, for example. Dr BéruBé is very enthusiastic for the Alliance to push progress forward, especially to raise awareness within undergraduate research, regarding the acceptance and use of new methods, and leaving the academic standard of animal models behind.

Dr Gerry Kenna, Pharmaceutical Director of Safer Medicines Trust, chaired the discussions and provided the closing address. He emphasised that the launch event should be seen as a starting point for dialogue between potential partners, and that the Alliance is very keen to include other members, who share the values and desire to drive change. It is expected that Alliance partners will work together to:

— promote improved awareness of existing human-based research methods and how they can be used;

— challenge and change flawed assumptions and perceptions of the inherent superiority of *in vivo* animal-based procedures; and

— promote faster and more focused development, validation and implementation of human-based methods in the future.

This will be achieved via meetings, education and training activities, and the writing of position papers. Interested scientists from academia, industry and regulatory agencies are strongly encouraged to join with us in this exciting venture.

Conclusions

Following its official launch, the Alliance is engaging with potential partners, reviewing expressions of interest, and will soon begin its work to accelerate positive change in promoting human relevant scientific research. Enquiries from organisations and individuals interested in joining are very welcome. Together, we will encourage and deliver better science, leading to improved health and safety, as well as greater efficiency in time, cost and scientific resources, by ensuring human relevant technologies gain their rightful status as the 'gold standard'.

For more information on the Alliance, or to register your interest, please visit www.HumanRelevantScience.org or email info@HumanRelevantScience.org.

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