Alliance for Human Relevant Science

The UK is a world leader in life science research. Yet many breakthroughs are lost in translation from preclinical animal models to humans. There is now a tremendous opportunity to bridge the translational gap with human relevant technologies.

**It is time to focus on the human.**

# OUR LAUNCH EVENT

Newsletter Winter 2017

On 8th February 2017, Safer Medicines Trust, Dr Hadwen Trust (now Animal Free Research UK), Kirkstall, Cyprotex and CN Bio Innovations launched the Alliance for Human Relevant Science in the House of Commons.

Sir David Amess MP hosted the event, which was full to capacity with senior scientists and MPs whose enthusiasm and support were palpable.

Working together, the Alliance will help to speed the transition towards more efficient and predictive models of toxicity and human diseases, based on human biology. Currently, many breakthroughs are "lost in translation" from animals to humans. Hence there is now a tremendous opportunity to make drug development faster and safer, using human relevant technologies.

Some exciting technologies were highlighted at the meeting. These include cutting-edge models of liver and cardiac biology, in which relevant human cells are maintained under physiologically relevant conditions and can be linked together with other organs to realistically mimic the human body.

Sir David said: "Britain is a world leader in life science research. But we had better look to our laurels if we do not want to be left behind, while others take the lead in embracing more predictive tools based on human biology. I wish the new Alliance every success with this hugely important initiative."


Malcolm Wilkinson, Clive Dilworth, Gerry Kenna, Sir David Amess, Kathy Archibald, Brett Cochrane, Emma Sceats

## WHO WE ARE

**The Alliance for Human Relevant Science** is an inclusive collaboration of like-minded companies, organisations and individuals. Working together, we will accelerate innovation and create positive change.

**Find out more about our founder members:**

## AND A WARM WELCOME TO NEW MEMBERS:

- Apollo Technology Partners Ltd
- Symcyp Ltd (a Certara company)
- Institute of Bio-Sensing Technology, University of West of England
- Brain Tumour Research Centre, University of Portsmouth
- Cell and Tissue Engineering Group, Department of Pharmacy, University of Hertfordshire
- Lord Dowding Fund for Humane Research
- Dermal Technology Laboratory Ltd

Organisations and individuals who support human relevant science can join the Alliance by signing our Memorandum of Understanding (MoU). Contact Rebecca Ram to register your interest and receive a draft copy of the MoU, at: humanrelevantscience.org/interested

## AIMS OF THE ALLIANCE

- Support better science for better health
- Save lives – human and animal – through improved safety and efficacy testing of medicines and other chemicals
- Save money by promoting more scientifically relevant research

## ALLIANCE MEETINGS HELD DURING 2017

Several members of the Alliance met at the Alderley Park BioHub on 4th May and 17th October 2017. Meeting minutes will shortly be available on the members' section of the Alliance website.

## NEW LOOK FOR ALLIANCE WEBSITE

The Alliance website is undergoing change and will have a fresh, new look from early 2018 onwards. Its content will continue to include details of the parliamentary launch event (plus videos). New features will include future activities and events, opportunities to subscribe to the newsletter, a scientists' and members' area and more. Visit: HumanRelevantScience.org

## PLANNED 2018 ACTIVITIES

The Alliance intends to publish a White Paper by the end of Q1 2018 with a proposed theme of 'In place of strife: A roadmap for human based safety testing of new medicines'.

The paper will focus on the urgent need to improve prediction of drug safety for humans, by examining challenges in current methods and the way forward by wholesale investment in human relevant testing methods and mechanistic assays.

The paper is one of a series of position papers intended for publication by the Alliance.


Alliance founder member Kirkstall Ltd will hold another of its hugely successful annual Advances in Cell and Tissue Culture (ACTC) conferences, at Cardiff University School of Bioscience from 21 – 23 May 2018. ACTC 2018 already has a great scientific programme taking shape, with the aim to create an interdisciplinary forum in which over 100 industry and academic researchers, working in cell culture can exchange knowledge, promote their activities and set up new collaborative projects. Research areas to be addressed include Advanced Cell Culture, Creating More Realistic Gut Models, Disease Modelling, DMPK, Animal Replacement, In Vitro Models for the Study of Neurological Diseases, Microphysiological Systems and Stem Cells. The 2018 conference also marks its 10th anniversary and full details including the scientific programme are available at (http://actc2018.com/Programme).

Thanks to Kirkstall, the next meeting of the Alliance will take place at ACTC in Cardiff. Further details to follow in the next newsletter.

## FDA SIGNS COLLABORATIVE AGREEMENT WITH CN BIO INNOVATIONS TO USE ORGANS-ON-CHIPS TECHNOLOGY

In October 2017, Alliance founder member CN Bio Innovations announced a landmark deal signed with the US Food and Drug Administration (FDA) who will assess its Organ-on-a-Chip devices for potential use in future drug development and clinical trials. The collaboration marks a major step forward in assessment and use of human relevant technologies in safety assessment of new medicines.

In the past four years, CN Bio has worked on more than 25 projects with pharmaceutical partners, using Organs-on-Chips and related microfluidic devices to gather precise, human-relevant data. CN Bio is backed by prestigious grant awards from sponsors including the US Department of Defense and Innovate UK. Spun out from the University of Oxford, the company is developing intellectual property licensed from the Massachusetts Institute of Technology and Vanderbilt University.

For full details of the agreement, read the press release on the CN Bio website.

# AN UPDATE FROM ALLIANCE FOUNDER MEMBER, CYPROTEX

## USE OF HUMAN FOCUSED IN VITRO MODELS FOR TOXICITY PREDICTION

### PREDICTION OF CARDIOTOXICITY

The story of BMS-986094 is a classic tale of clinical stage failure, with cardiotoxicity being missed in preclinical testing. Tragically, failure to pick up this liability led to one death and eight patients being hospitalised with significantly reduced left ventricular ejection fraction (LVEF) during phase 3 clinical trials, and the drug was subsequently discontinued. Retrospective analysis of the clinical data showed that 40% of patients dosed with BMS-986094 had some evidence of cardiac dysfunction.

In recent years, more sophisticated in vitro techniques have been developed including the use of functional human iPSC-derived cardiomyocytes in combination with microelectrode array; an approach currently being evaluated within CiPA (Comprehensive In Vitro Proarrhythmia Assay) for understanding proarrhythmic risk during preclinical testing. Using this combined approach, repeat dosing of BMS-986094 could be assessed over an extended time period, and the technique was found to be extremely sensitive with the detection of significant electrophysiological functional effects observed at low concentrations of BMS-986094.

We presented these findings at the Safety Pharmacology Society Annual Meeting in Berlin recently.

### 2D VS 3D IN VITRO CELL MODELS – AN OPINION

2D vs 3D is still a hot topic for debate, and the case is not clear-cut. Indeed, 2D models are still very strong due to throughput, industry acceptance and the question being asked. Some applications may not yet be amenable to 3D, furthermore, 2D models may be sufficient in addressing the industry requirement in terms of speed and quality of data. This is evident in the case of electrophysiology studies where sensitive techniques such as patch clamp and microelectrode array are being used to monitor electrical activity, with 2D models currently the in vitro system of choice for these studies.

The argument for 3D models in other areas appears to be growing as their value becomes demonstrated through enhanced research and validation, leading to a dramatic surge in publications over the past 10 years. It makes sense that the environment of the 3D model should be more organotypic and representative of the in vivo situation due to the cell-cell interaction and communication. These features improve the longevity of the models allowing for long term repeat dose testing. With time and as the technology has advanced, the models have become more complex with co-culture models being developed and iPSC-derived cells incorporated. Features such as bile canaliculi, active transporter processes and drug metabolising capabilities have all been characterised in 3D cellular models, and enhanced predictivity has been touted for many studies.

Our experience, particularly in the field of predictive in vitro human toxicity testing, has shown that what's key is not only whether the model is 2D or 3D but how amenable that model is for multi-parametric mechanistic measurements of cell health. For example complex co-culture 3D models have been developed for the prediction of liver injury which only utilise a single biochemical endpoint for prediction of toxicity. This type of approach, whilst having a more organotypic cellular model, does not give any mechanistic insight into cell death and as such does not utilise the full value and potential of 3D approaches. The combined use of 3D cellular models with multiple, predictive and mechanistic endpoint analyses

is, we believe, one of the most powerful and predictive approaches for human toxicity testing.

In terms of further development of 3D models we still are very much at the tip of the iceberg. Organ-on-a-chip and 3D bioprinting models are even more complex technologies that offer future promise. The holy grail will be a fully functional human relevant multi-tissue model which can be linked to other organs for full body simulation, leading to the accurate prediction of human efficacy, pharmacokinetics and toxicity.

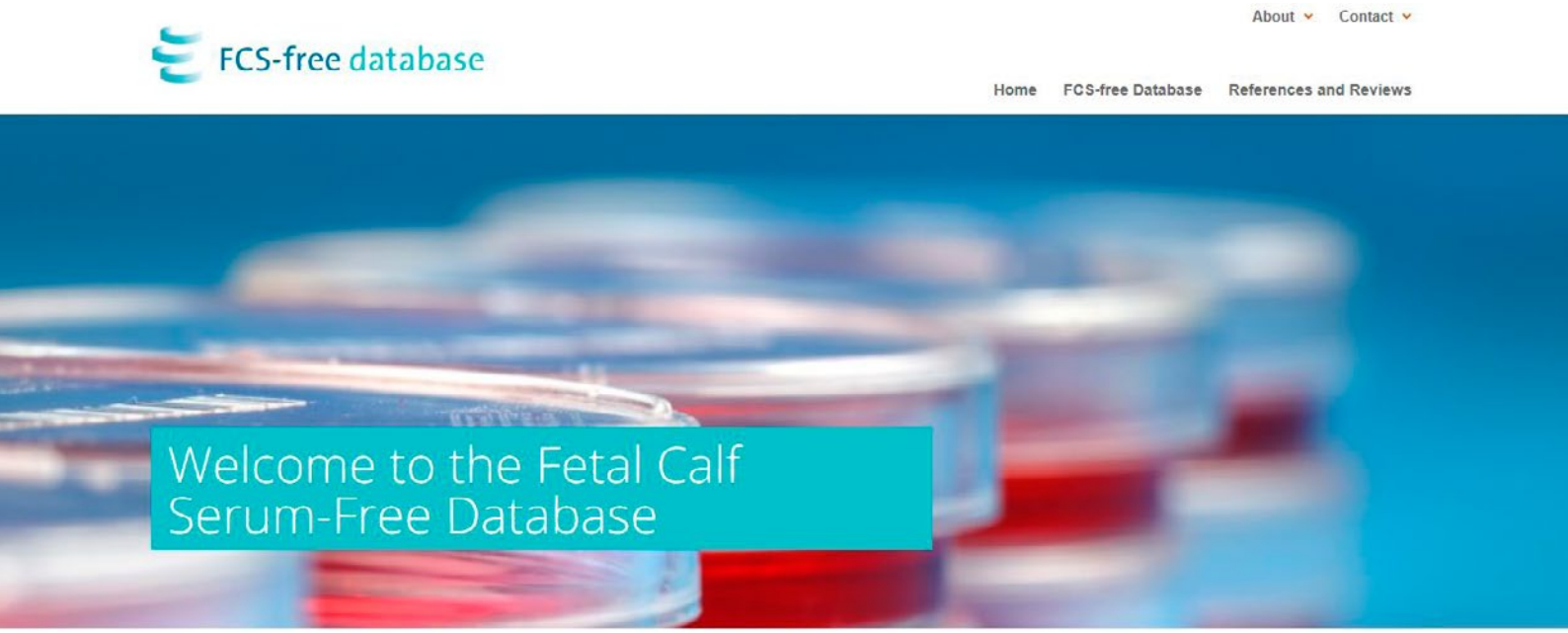
However, some may argue that the complexity and cost may limit widespread access and success. From a more optimistic view, imagine how this could revolutionise pre-clinical testing – precluding the need for animal testing and drastically reducing drug failure during clinical trials. Based on the vast expense of bringing a drug through the discovery and development process, the development of such a system may become a reality. www.cyprotex.com

## FCS-FREE.ORG – NEW SERUM-FREE DATABASE

This year, Animal Free Research UK ,and the 3Rs-Centre Utrecht Life Sciences launched a new website dedicated to promoting the use of serum-free media in biomedical research. The website, www.fcs-free.org, will allow scientists to identify foetal calf serum free (FCS-free) media for use in all types of cell culture and for specific cell types. The website will also allow scientists to exchange information on the use and applicability of all FCS-free media. This website and database further allows AFR UK to develop methods and promote the replacement of animals used for research to the scientific community.

More info - www.animalfreeresearchuk.org/fcs-free-org/


Ted van den Bergh, director of Triodos Foundation and one of the partners of the 3Rs Database programme, together with Dr. Alpesh Patel, pushing the red button that officially launched www.fcs-free.org



# INTERNATIONAL PBPK MODELLING SURVEY

A survey conducted by the EU Joint Research Centre (JRC) and the US EPA investigated the extent to which physiologically based pharmacokinetic (PBPK) models are used in toxicity testing. Simcyp Ltd (a Certara Company), leading experts in PBPK modelling and member of the Alliance provided contributions to the survey, which also included feedback from 93 representatives and 19 countries across the industrial chemicals, pesticides and personal care product sectors and aimed to assess the current level of use of PBPK models, as well as challenges associated with their regulatory acceptance and uptake. The survey found that while such models are widely used in industry and academia, key barriers to regulatory buy-in include a lack of appropriate guidance. More projects are planned to address this. Further information including the survey results can be seen at

https://ec.europa.eu/jrc/en/science-update/biologically-based-mathematical-models-toxicology

Paina, A. et al. (2017). Investigating the state of physiologically based kinetic modelling practices and challenges associated with gaining regulatory acceptance of model applications. Regulatory Toxicology and Pharmacology. 90: pp104-115.

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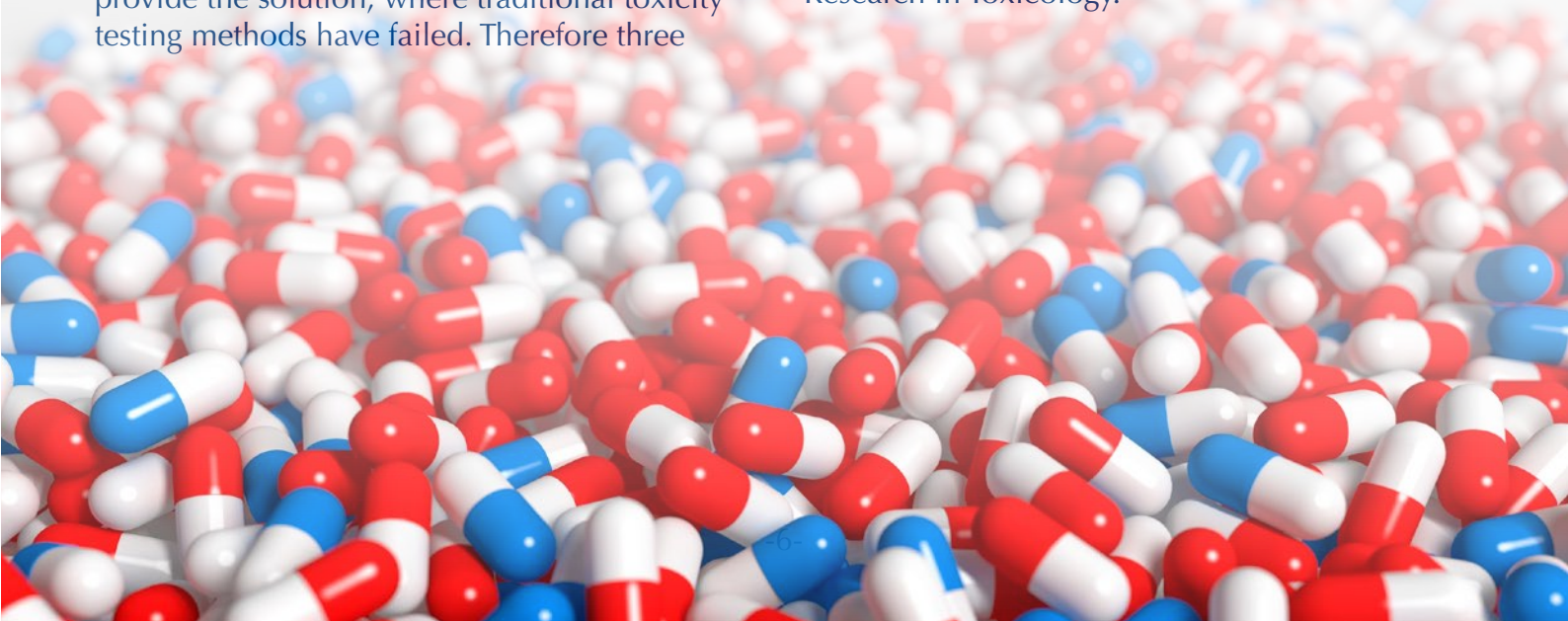
A recently published perspective paper, co-authored by Alliance member organisation Simcyp Limited (a Certara company) in collaboration with CAAT USA and Europe and other key stakeholders in industry and academia highlights key developments which are enabling the progress of systems toxicology towards a more pathways-based and 'real world data' approach. The publication follows the International Systems Toxicology 2016 conference in Switzerland, aimed at initiating further progress in quantitative systems toxicology.

Although development of pathway-based approaches requires ongoing long-term commitment, there is strong evidence from extensive foundational work over recent years that this paradigm shift in toxicology will provide the solution, where traditional toxicity testing methods have failed. Therefore three main themes agreed from the conference and publication are (1) reliable and relevant in vitro test systems, (2) high-throughput and high-content methods generating large-scale data streams, and (3) in silico model systems.

A combination of these approaches is considered as the way forward, to ensure data reliability and human relevance.

Hartung, T. et al. (2017) Systems Toxicology: Real World Applications and Opportunities. Chemical Research in Toxicology.



## LORD DOWDING FUND FOR HUMANE RESEARCH

The Alliance is delighted to welcome new member, The Lord Dowding Fund for Humane Research (LDF). The LDF awards grants to scientists for advanced medical and scientific research that does not use animals. Projects have included breast cancer and brain tumour research, the development and improvement of neuroimaging techniques and programmes to replace the use of animals in teaching. www.ldf.org.uk

## DERMAL TECHNOLOGY LABORATORY (DTL)

Dermal Technology Laboratory Ltd (DTL) was founded in 2007 by Professor Jon Heylings.

DTL is an exclusively in-vitro CRO (Contract Research Organisation) offering services to the pharma, cosmetic, agrochemical and industrial chemicals sectors.

The focus of the organisation is the use of donated human skin for dermal absorption research and regulatory projects under test guideline OECD 428. The guideline itself was written by Prof. Heylings in the 1990s. The human skin method is now widely used instead of rat skin and rats in vivo, a poor model of human predictivity.

The photo shows Prime Minister Theresa May visiting DTL's facility at Keele University Science Park during her time as Home Secretary when responsible for the licencing of animal experiments and implementation of the 3Rs, to hear how DTL had set up its organisational facilities to maximise use of human tissue for dermal absorption studies. DTL has also offered several successful studentships with Keele University at both MSc and PhD level. (L to R: Dave Fox, Theresa May,Councillor Tony Cox and Jon Heylings).

For more information on DTL, visit www.dermaltechnology.com

# OTHER NEWS IN BRIEF

## LAUNCH OF THE CANADIAN CENTRE FOR ALTERNATIVES TO ANIMAL METHODS

October 2017 marked the launch of the Canadian Centre for Alternatives to Animal Methods/ Validation of Alternative Methods (CCAAM/CaCVAM) in collaboration with the University of Windsor, Ontario. As part of the launch, a Strategic Visioning Workshop was held at UW over two days, to celebrate the start of Canada's first centre dedicated to human-relevant research. Headed by Dr. Charu Chandrasekera and Dr. Andrew Hubberstey, CCAAM and its subsidiary, CaCVAM, aim to develop, validate, and promote human relevant methodologies, with a vision to replace animals in Canadian biomedical research, education, and regulatory testing.

Alliance members Dr Malcolm Wilkinson and Dr Gerry Kenna were delighted to attend the launch and offer their insights during the workshop. Although the Alliance is initially UK-focused, we hope that once fully established here, it will broaden its horizons internationally, and partner with organisations such as CCAAM/CaCVAM.

Dr Charu Chandrasekera


Gerry Kenna, Nicole Kleinstreuer, Charu Chandrasekera, Malcolm Wilkinson, Ingrid Newkirk.

## FDA LAUNCHES PREDICTIVE TOXICOLOGY ROADMAP

At the time of preparation of this newsletter, the US FDA's Toxicology Working Group announced its Predictive Toxicology Roadmap; a six-part framework for integrating predictive toxicology methods into safety and risk assessments.

In developing the roadmap, the Working Group relied heavily on the recommendations in the NRC's two reports, "Toxicity Testing in the 21st Century: A Vision and a Strategy" and the 2017 follow-on report "Using 21st Century Science to Improve Risk-Related Evaluations".

The report includes a promising proposal to rely on "qualification" rather than on "formal validation". It states: "Rather than validation, an approach we frequently take for biological (and toxicological) models and assays is qualification." In essence, the FDA is suggesting that within the stated context of use, qualification is a conclusion that the results of an assessment using the model or assay can be relied on to have a specific interpretation and application in product development and regulatory decision-making.

The report concludes: "Although the challenges to achieving the visions of the earlier reports often seem daunting, 21st century science holds great promise for advancing risk assessment and ultimately for improving public health and the environment."

Meanwhile, ICCVAM is coordinating the development of a strategic roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States: https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html.

## ECHA REPORT ON CURRENT STATUS OF NON-ANIMAL APPROACHES

ECHA's latest report, published in November 2017 on "Non-Animal Approaches: Current status of regulatory applicability under the REACH, CLP and Biocidal Products regulations" states that whilst non-animal approaches are the focus of 'very active ongoing research', solutions for the more complex endpoints (e.g reproductive or repeat dose toxicity) remain unavailable and 'the nature of such future approaches cannot be established yet'. However, the report has drawn criticism for its comparison throughout to animal studies as the gold standard, rather than focusing on human relevance.

The report emphasises that an inventory of non-animal approaches at different stages of development and regulatory applicability would help to identify current gaps and determine future steps to enhance their use.

## EVIDENCE BASED TOXICOLOGY COLLABORATION (EBTC)

US-based EBTC's Tox 21 Working Group has completed its first level literature review of a study to compare drug induced liver injury (DILI) in humans and animals.

The EBTC Tox 21 WG, comprises a number of stakeholders from academia and industry and Safer Medicines Trust, who devised the original study. The first stage, involving the literature review of over 5,800 abstracts based on availability of primary DILI data for 10 selected drugs in humans and in several animal species (rat, mouse, dog, non-human primate) is now complete. Stage 2 is now commencing and will involve review of the full text for those studies selected as relevant in stage 1. The study will progress through further streams to compare the data from human and animal studies with US EPA ToxCast data. More info at: http://www.ebtox.org/work-groups/Tox21/index.html

**More reviewers very welcome!** Please contact Rebecca@SaferMedicines.org

## EURL ECVAM STATUS REPORT 2017 ON ALTERNATIVE METHODS

The EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) has published its Status Report 2017 presenting an update on the development, validation and regulatory acceptance of alternative methods to animal testing. It appears to present a much more optimistic view of progress than the ECHA Report.