SAFER MEDICINES
Putting patient safety first

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Newsletter 2017

Alliance for Human Relevant Science

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 away from animal testing, towards more efficient and predictive models based on human biology. Many breakthroughs are lost in translation from animals to humans. 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, including cutting-edge models of the liver, 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."

The brief introductory talks can be viewed on the Alliance website at www.HumanRelevantScience.org, as well as via www.SaferMedicines.org. The 3-minute highlights video is highly recommended. A report was published in the journal ATLA: Alternatives To Laboratory Animals, who have kindly allowed us to make it available on our website.

Sir David Amess MP

Scientists from academia, industry and regulatory agencies are strongly encouraged to join this exciting venture. Together, we will encourage and deliver better science, leading to improved health and safety, by ensuring human relevant technologies gain their rightful status as the 'gold standard'.

Safer Medicines Campaign is an independent group of scientists and doctors with extensive expertise in drug development. Our aim is to change the way medicines are tested, to a system based on *human* biology: the *only* way to ensure safety for patients. A million people are hospitalised by their medicines every year in the UK, costing the NHS £2 billion*. Many thousands are killed. This cannot be allowed to continue: the time for action is NOW!

*Sarah Boseley, The Guardian, 3 April 2008

Safer Medicines Trust is a registered charity. Our international conferences at the Royal Society and the House of Lords showed the benefits to drug safety and medical progress offered by a focus on human, rather than animal biology. Our system of 'pragmatic validation' offers a way to speed the use of superior methods.

Help us put patient safety first

> *"We don't have to look for model organisms any more because we are the model organism"*
>
> **Nobel Laureate Sydney Brenner CH FRS**

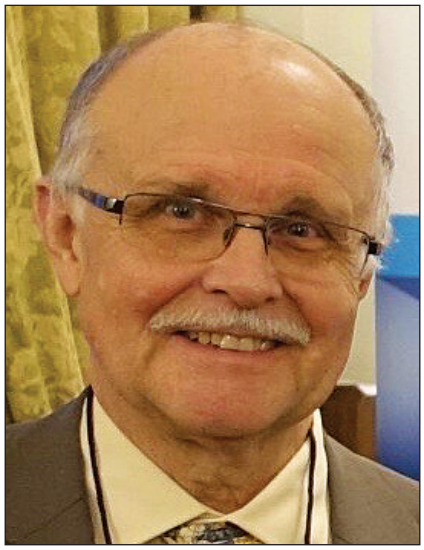
OUR PATRONS

Sir David Amess MP
Caroline Lucas MP
Paul Flynn MP
Mat Fraser
Carol Royle
Dr James Le Fanu

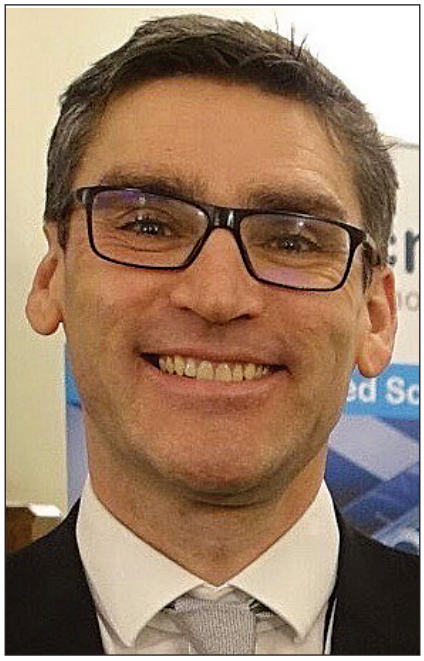
Highlights from the launch

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 Malcolm Wilkinson, the founder and CEO of Kirkstall (watch the 1 minute video at www.Kirkstall.com), explained the company's passion for using their science base to improve human health. He said: "We are appalled 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 their belief in a multi- disciplinary Alliance as the way forward.



Dr Malcolm Wilkinson



Dr Clive Dilworth

Dr Clive Dilworth, Chief Scientific Officer of Cyprotex, explained why he believes that "the techniques we have currently can significantly reduce drug toxicity", if they are embraced by industry. He emphasised how much technology has moved on, and that predictive human 3D 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 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."

Dr Emma Sceats

Professor Geoff Pilkington, Head of the University of Portsmouth's Brain Tumour Research Centre, spoke about their 3D cell models of the blood–brain barrier to investigate mechanisms of cancer metastasis. He explained how the use of human relevant models can help to fast track promising compounds into the clinic. He spoke of the difficulty in getting studies published and in gaining funding without the use of animals, and of the importance of engaging politicians and decision makers.

Professor Geoff Pilkington

Dr Kelly BéruBé, Director of the Lung & Particle Research Group at Cardiff University, explained how her research was boosted by the availability of human lung cells from healthy and diseased donors, in place of lungs from laboratory animals. She hopes the Alliance will help to raise awareness within undergraduate research, regarding the acceptance and use of new methods, and leaving the academic standard of animal models behind.

Dr Kelly BéruBé

Welcome to our Pharmaceutical Director

Dr Gerry Kenna

Safer Medicines Trust is delighted that Dr Gerry Kenna joined us last year as Pharmaceutical Director. Dr Kenna is an independent Drug Safety Consultant and a leading figure in the field of human drug-induced liver injury. From 2014-2016, he was the Scientific Director of FRAME. Previously, he was a senior toxicologist in the pharmaceutical and agrochemical industries (at AstraZeneca, Syngenta and Zeneca). Before that, he led academic research teams exploring mechanisms underlying human adverse drug reactions, at Imperial College School of Medicine, the National Institutes of Health, USA, King's College Hospital Medical School, and the National Institute for Medical Research, London. He has authored or co-authored over 100 peer reviewed scientific publications, and is a member of the International Society for the Study of Xenobiotics and a Fellow of the British Toxicology Society. We are very happy that Dr Kenna has offered to lead the Alliance for Human Relevant Science.

… and to our Scientific Consultant

Rebecca Ram

We are also delighted that Rebecca Ram has joined our team. Rebecca is also a Scientific Consultant to the Lush Prize team at the Ethical Consumer Research Association. She holds an MSc in Toxicology with Bioinformatics and has worked as a Clinical Data Manager at University College London Hospital, and in pharmaceutical clinical trials for GlaxoSmithKline. She was a Project Manager of cancer clinical trials and whole genome sequencing for Genomics England, as part of the 100,000 Genomes Project. In addition to her role with Safer Medicines Trust, she has volunteered to be the Communications Officer for the Alliance for Human Relevant Science.

Latest publications

Expert Opinion on Drug Metabolism & Toxicology published a paper by Dr Kenna, entitled: "Human biology-based drug safety evaluation: scientific rationale, current status and future challenges". The paper (available on our website) explains that the animal toxicity studies used to assess the safety of new medicines prior to their progression into human clinical trials are unable to detect numerous clinically serious side effects. In contrast, many of these side effects can be identified using human-based in vitro assays.

Ref: *Expert Opinion on Drug Metabolism & Toxicology* Vol. 13, Issue 5, 567-574, 2017

Alternatives to Laboratory Animals published our Comment on the "Launch of the Alliance for Human Relevant Science", written by Rebecca Ram.

Ref: *ATLA* Vol. 45, Issue 1, 49-53, 2017

Alternatives to Animal Experimentation also published a news item on the launch of the Alliance.

Ref: *ALTEX* Vol. 34, Issue 2, 2017

What Doctors Don't Tell You magazine published an article by Kathy Archibald, entitled: "Of mice, but not men". It argued that: "the regulatory guidelines that govern how drugs are developed must be updated and improved to encourage adoption of the best new approaches. The current regulations are stifling innovation by failing to keep pace with scientific progress."

Ref: *What Doctors Don't Tell You* Vol. 27, Issue 5, 2016

New Scientist published our letter entitled: "Brain models could replace primates", which can be viewed via our website. It concluded: "Models using human tissues, reproducing key features of biochemistry and physiology, have enormous potential in brain research. A 2016 paper in *Alternatives to Laboratory Animals* concludes: "neuroscience would be more relevant and successful for humans if it were conducted with a direct human focus". As scientists dedicated to ensuring the best outcomes for patients, we concur."

Ref: *New Scientist* Vol. 231, Issue 3083, 2016

We have also written a number of book chapters, which will be reported in the next newsletter and on our website, as soon as they are published.

Tackling drug-induced liver injury (DILI)

DILI is a leading cause of drug failure in clinical trials, of withdrawals of licensed drugs and of iatrogenic harm to patients. Human DILI is poorly predicted by preclinical animal tests.

Dr Kenna has been instrumental in devising and promoting the adoption of a superior approach to human DILI prediction, in the form of a "Hazard Matrix" produced from a multi-assay in vitro test cascade. The assays detect key mechanisms by which drugs can cause DILI. These are cell cytotoxicity, formation of reactive metabolites, mitochondrial inhibition and inhibition of a liver cell membrane transporter called the bile salt export pump (BSEP).

A study published with colleagues during his time at AstraZeneca showed that the Hazard Matrix demonstrated excellent discrimination between 27 toxic drugs and 9 non-toxic drugs, with 100% sensitivity and 78% specificity.

Ref: *Chem Res Toxicol* Vol. 25, 1616, 2012

An even greater challenge than devising an appropriate in vitro test cascade, is persuading pharmaceutical companies to implement it routinely. Together with scientists from Pfizer, Dr Kenna has written a chapter for a forthcoming book, which reviews the success of the strategies used at AstraZeneca and at Pfizer, and offers valuable advice to others, distilled from their respective experiences.

Dr Kenna presented a webinar series on the BSEP, organised by the US Critical Path Institute, and is leading an international team to write a White Paper which will make recommendations to the regulatory agencies concerning BSEP screening in drug discovery and development. He spoke at the 2016 World Preclinical Congress in Lisbon on the use of in vitro test cascades, and again on DILI at the 2016 Meeting in South Korea of the Society for the Study of Xenobiotics (the leading global ADME/toxicity scientific society). He also gave a presentation at the 2016 Lush Prize Conference in London: "How understanding drug toxicities can aid human chemical safety assessment without using animals."

Another exciting new collaborative effort to improve drug safety and reduce DILI, using biomarkers and imaging techniques, is the IB4SD-TRISTAN (Translational Imaging Methods in Drug Safety Assessment) Consortium, funded by the European Commission's Innovative Medicines Initiative. Dr Kenna is co-leading the DILI area of the Consortium.

Moving from animal-based to human-based research

The Netherlands is now leading the world, with its announcement that it intends to phase out all legally prescribed animal-based safety testing by 2025. A report by the Netherlands National Committee for the protection of animals used for scientific purposes (NCad) was presented to the Dutch Minister of Agriculture, who commissioned it, in December 2016. The Committee recognises that the transition will not happen of its own accord, and will require a clear strategic direction, to change attitudes and practices. They make recommendations in three areas: 'Clear transition goals'; 'Transition strategy', and 'Management of the transition'. Coordination and collaboration between all interested parties will be essential to accelerate the transition to animal-free research.

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Also in December 2016, the European Commission hosted a conference in Brussels: "Non-Animal Approaches – The Way Forward", which was organised in response to a European Citizens' Initiative petition, with more than a million signatures, calling for an end to animal experiments. Again, the key message from the conference was that all stakeholders must work together to drive change. This was echoed by a consensus report published following an international workshop attended by experts from academia, government institutions, research funding bodies, and the corporate and non-governmental organisation sectors, entitled: "Towards a 21st-century roadmap for biomedical research and drug discovery: consensus report and recommendations". Using expert analysis of five human disease areas, the report showed that animal models have failed to provide answers or treatments for any of them. The authors concluded that – as with safety testing – "advanced human biology-based models and tools hold the key to progress". Human-based approaches to developing medicines for human disease must become the central thread of 21st century research.

Ref: *Drug Discovery Today* Vol. 22, Issue 2, 327-339, 2016

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There is also some cause for optimism from the USA. The Director of the National Institutes of Health, Dr Francis Collins, predicted in a hearing before a US Senate Committee in April 2016 that within 10 years, human biochips "will mostly replace animal testing for drug toxicity and environmental sensing, giving results that are more accurate, at lower cost and with higher throughput".

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More tangibly, the US FDA (Food and Drug Administration) has announced a one-year partnership with Emulate (a spin-out company from the Wyss Institute for Biologically Inspired Engineering at Harvard University), to evaluate whether their 'Human Emulation System' (watch the 5 minute video about this "awesome" system at www.emulatebio.com) can reliably model human reactions to food and food-borne illnesses. It is the first time that a regulatory agency anywhere in the world has pursued organs-on-chips as a replacement for animal testing. FDA food-safety scientists will first evaluate the human liver chip, before moving on to kidney, lung and intestine models. We hope this collaboration will expand to include pharmaceuticals.

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The US Interagency Coordinating Committee on the Validation of Alternative Methods is producing a Strategic Roadmap for incorporating new approaches into safety testing of chemicals and medical products. The draft document is currently open for public comments, with the final Roadmap due to be published in December. The plan was discussed at a Public Forum in May 2017, to which Safer Medicines Trust once again submitted comments jointly with the Center for Responsible Science (CRS).

The thrust of our comments was that: "Major limiting factors for implementing 21st century approaches to toxicity testing include policy and regulation… Minor amendments to outdated existing regulations would have great impact on the use and development of better tools for drug and device development, which could save lives."

Dr Warren Casey, Director of the NTP (National Toxicology Program) Interagency Center for the Evaluation of Alternative Toxicological Methods, gave an excellent presentation, acknowledging institutional resistance and the fact that: "It is

Study to compare safety prediction of animal versus non-animal tests

We are delighted that Dr Katya Tsaioun, Director of the Evidence-based Toxicology Collaboration (EBTC) at the Johns Hopkins Bloomberg School of Public Health, USA, is leading an important new study, which she had previously helped to devise for Safer Medicines Trust. The EBTC project will use, for the first time, evidence-based methods to compare drug-induced liver toxicity in humans to preclinical animal data, and to US EPA ToxCast in vitro data.

An EBTC workgroup, including stakeholders from academia and industry, has already begun the evidence-gathering process to perform a systematic review of the literature on ten marketed drugs, some of which caused adverse reactions in humans. The results will provide an objective comparison of the relative predictive abilities of the animal vs. non-animal methods, and should help to inform regulatory agencies as to which tests are better able to protect human health.

Dr Kenna is a member of the EBTC Board of Trustees, and Rebecca Ram is a member of the Tox21 workgroup who are screening the scientific literature in preparation for the performance of the systematic review. We look forward to reporting on the progress of the project in our next newsletter.

difficult for evolving institutional practices to keep pace with revolutionary advances in science and technology". He explained that the new Roadmap is designed to overcome roadblocks through its "top down" approach (driven by Federal agencies) and its implementation plans, which will be tracked and publically reported. It is an ambitious and well-crafted proposal, which we hope will succeed in its vision to improve the relevance to human health of the approaches used to evaluate the safety of chemicals and medical products in the United States.

A disturbing number of deaths in recent clinical trials emphasise that the stakes could not be higher. In January 2016, one man died and four more suffered serious neurological damage in a Phase 1 study of the drug BIA 10-2474 in Rennes, France. Experts convened by the French National Agency for Medicines and Health Products concluded that the compound being tested had caused an "astonishing and unprecedented" reaction in the brain. Why this wasn't clear in early trials on animals is "inexplicable", according to the expert panel's report. The drug had been tested in mice, rats, dogs and monkeys, with few ill effects, despite doses up to 650 times higher than those given to the volunteers.

A new study published in June 2017 by an international group of researchers investigating BIA 10-2474 found that the drug is far more promiscuous in its 'off-target' effects in humans than in animals.

Professor Steven Kushner, Chair of Neurobiological Psychiatry at the Erasmus University Medical Center and co-leader of the study, said:

"The safety testing in animals of BIA 10-2474 was not successful in predicting the side effects in humans. This underscores the importance of expanding drug testing to include new human cellular models that are better able to determine the safety profile of experimental drugs."

Furthermore, he said that such tests should be mandated as part of preclinical safety testing. This is precisely what our petition to the UK government is calling for.

Some regulatory agencies have made statements in support of these models, though their use remains optional. Professor Kushner says: "The support is there. The question is at what level of urgency." We believe that the urgency could not be greater: the lives of clinical trial participants are at stake.

Safer Medicines Trust is proud to join CRS in presenting their Citizen Petition to the FDA (see www.crs501.org), requesting changes to the wording of the regulations, to encourage drug developers to use the most predictive preclinical tests available. The Petition has been updated to reflect at least 42 further treatment-related deaths in clinical trials since it was first filed in 2015, including the death in the Bial trial in France, which could have been prevented if human-relevant test methods had been used.

Refs: *Science* Vol. 356, 1084–1087, 2017

ScienceDaily.com, 9 June 2017

OutsourcingPharma.com, 19 June 2017

Holding back progress

Despite the multitude of positive developments to accelerate the transition to a new human-centric paradigm for biomedical research, there are still major obstacles holding back the transition and consequently holding back medical progress.

There is an ongoing exponential increase in new human relevant technologies and improvements in existing technologies, with superior capabilities that enable scientific inquiry that simply has never been possible before. Yet these astonishing opportunities are being largely ignored by an establishment so wedded to animal models that it cannot see the holy grail that is already within our grasp.

For example, a new comparison of insulin-producing pancreatic beta cells has revealed major differences between mice and humans. This helps to explain why positive results in mice rarely translate into successful diabetes treatments for humans. One of the scientists involved, Associate Professor Albert Salehi, said: "This is well known, and a source of great frustration for researchers and the pharmaceutical industry. Is it then right to continue to develop drugs based on research conducted on mice, when these drugs cannot be used on humans?" The team catalogued differences and similarities in gene expression, which they say will "provide an essential resource for the translation of mouse islet functional data to the human islet context."

Refs: *Scientific Reports Vol. 7*, Article number: 46600, 2017

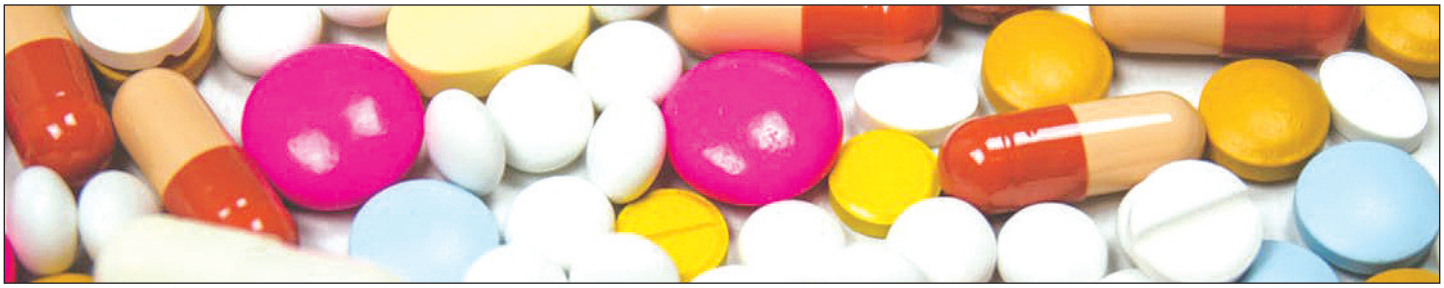
ScienceAlert.com, 4 July 2017

Yet more than 10 years ago, a team from the Diabetes Research Institute at the University of Miami published an important comparative study of human versus rodent pancreatic islet cells, which, according to their press release, showed that the composition of a human islet is so different from that of the rodent model, it is no longer relevant for human studies. "Our major finding is that human pancreatic islets have a unique architecture, and work differently than rodent islets," said Per-Olof Berggren, adjunct professor at the Diabetes Research Institute and professor at the Rolf Luft Center for Diabetes Research at the Karolinska Institute in Sweden. "We can no longer rely on studies in mice and rats. It is now imperative that we focus on human islets. At the end of the day, it is the only way to understand how they function."

Refs: Diabetes Research Institute Foundation, Miami, Florida, press release, February 2006

PNAS Vol. 103, Number 7, 2334–2339, 2006

Professor Michael Balls and Dr Robert Combes observe in their editorial comment in ATLA that "there continues to be a great desire to maintain established practices and to avoid the evidence which strongly indicates the need for changes in attitudes and activities." They highlight the need for



greater "recognition of the inadequacy of animal models, and investment in the clinical research and non-animal approaches that should replace them." But they conclude, with regret, "many members of the biomedical research community in the UK prefer to use laboratory animal procedures, rather than face up to the difficult challenge of finding human-focused, relevant and reliable replacement procedures."

Ref: *ATLA* Vol. 45, Issue 1, 1-3, 2017

ATLA has also published a very important paper by Anne Beuter, professor emeritus in neuroscience at the National Polytechnic Institute (University of Bordeaux) in France. She has devised a new method of electrical stimulation of the brain for patients with Parkinson's Disease who are not suited to deep brain stimulation (DBS), for example due to age limit criteria. Despite the proven benefits of DBS, it has limitations, including side effects that can greatly reduce quality of life. The new 'closed loop' technique stimulates nerve tissue only as and when needed, and avoids deep structures within the brain; obtaining a good therapeutic effect simply by stimulating the cortex (the outermost layer of the brain), which is less invasive for patients.

However, this new approach is still awaiting support for a proof-of-concept study. This situation is another example – analogous to the situation with new methods of safety testing – of 'technological lock-in' (as described by the economist Joshua Frank), where an established technology benefits from a 'selectional advantage' that prevents the development of other technologies.

Professor Beuter explains how computational neuroscience offers many advantages over the current use of brain research in primates, saying: "from a mechanistic perspective, too much reliance on animal models in the field of brain stimulation can no longer be justified… Neuro-computational models are getting increasingly close to representing the underlying computation of the neural processing that is taking place in the human brain, in general – and in the brain of a specific patient, in particular. These models are being developed in human subjects, because there is no alternative that can adapt to the fluctuating state of each patient's brain over time, as well as to the evolution of the disease. This situation is in contrast with animal models, which generate data that are species dependent and static."

Yet, despite major advances over 25 years and the advantages they offer, practical use of these models has disappointingly lagged behind. Professor Beuter lists the major obstacles blocking their implementation, which stem from entrenched behaviours that favour the 'traditional' model (primates) and resist the challenge and disruption of new approaches. These obstacles arise from behavioural, financial, institutional and technological lock-in, mediated through regulatory and political constraints. We could not agree more with her conclusions:

"To overcome these obstacles, concrete actions must be initiated, such as the development of more-effective communication and collaboration between modelling experts and clinical experts, and the unlocking of resources from the current animal-based research path to the proposed non-animal alternative approach. Acting without delay to address the various aspects of 'lock-in' will contribute to the promotion of more-personalised and human-relevant medicines for the future."

Ref: *ATLA* Vol. 45, Issue 2, 91-99, 2017

We hope that the Alliance for Human Relevant Science will help to achieve some of these goals, and look forward to helping it grow and flourish.

We are extremely grateful to all of our supporters for helping to spread the word and for your generous donations: we couldn't do what we do without you!

We are also deeply grateful for and humbled by the generous legacies bequeathed to us by Margaret Davey, Judith Goodsell, Edith Harrison and Marjorie Pooley.

How to help

If you would like to fundraise for us in any way, we would be extremely grateful, and more than happy to provide collecting tins and literature for the event.

One of the best ways to reach people with our message is through our new leaflet. If you can help by distributing leaflets to friends and family, in the street, or at an event, we would be delighted. Just let us know how much literature you would like (please see back page) – thank you!

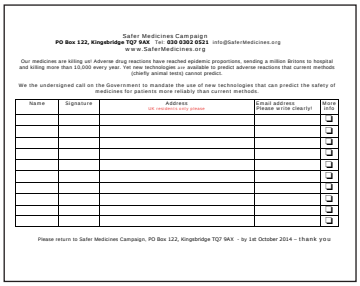
ACTION

Leaflets

If you can help by distributing our leaflets we will be delighted. Donations to help with postage and printing costs will be greatly appreciated.

Petition

Sign our petition calling for the use of more reliable safety tests. You can sign on our website or on paper: download a form from our website or order by email, phone or post.



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Please help us to modernise and humanise the safety testing of medicines, and to distribute our resources to teachers, students and MPs.

You can donate on our website or by post – please see below.

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We rely completely on your generosity. We receive no corporate or government funding and have no expensive overheads: all of our office space is donated without charge.

If you want to see real progress towards a future where medical research is based on studying humans rather than animals, please give generously today.

Booklets

A Critical Look at Animal Experimentation:
Free booklet examining the impact of animal research on medical progress and outlining more valid human-focused methods of research.

Please copy this section or cut it off and return to us – thank you

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