

Safer Medicines

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Newsletter Summer 2014

Safer Medicines Trust making waves in the toxicology world

We are very fortunate to be represented by scientists as eminent as Dr Katya Tsaïoun (our Science Director, US) and Dr Robert Coleman (our Science Director, UK). Dr Coleman co-founded Pharmagene (now Asterand), the first drug discovery and development company to work exclusively on human biology. He holds a DSc in recognition of his scientific achievements and his contributions to the use of donated human tissues in drug research.

Dr Tsaïoun is a highly-regarded expert on *in vitro* metabolism and toxicity assays and is the founder of Apredica, a pioneering company offering a range of *in vitro* tools for faster and safer drug development. She serves as a member of the Center for Scientific Review for the US National Institutes of Health and is also an advisor for Tufts University, the Alzheimer's Drug Discovery Foundation and a number of pharmaceutical companies.

Drs Coleman and Tsaïoun have been meeting with scientists from industry, academia and regulatory agencies around the world, explaining our proposal to humanise drug safety testing through a comparison of the relative capabilities of animal tests and human-based *in vitro* tests to predict the safety of medicines. We are hugely encouraged by the level of support for this groundbreaking approach, and delighted that so many organisations and individuals are keen to work with us in making our vision a reality. With so much expert input, we



Dr Bob Coleman



Dr Katya Tsaïoun

have refined our proposed studies considerably, which has inspired the US Government ToxCast programme to incorporate our pilot study within their current programme. We look forward to the results being released for analysis later this year.

Drs Coleman and Tsaïoun have spoken* at many meetings and conferences on both sides of the Atlantic, where they have been able to engage with and influence some of the world's leading toxicologists. Recognition of the need for a much greater human focus in medicines research is unanimous, but awareness of the availability and capability of human-based methods is not so universal. We hope all the discussions and ongoing dialogue will lead to the initiation of real changes to the mindset and practice of toxicology worldwide.

*Some recordings can be heard on our website

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, so they are safer for patients: moving from a system based mainly on animal tests to one focused firmly on *human* biology. 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. We have hosted international conferences at the Royal Society and the House of Lords, showing the benefits to drug safety and medical progress offered by a focus on human, rather than animal biology.

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

Dr Caroline Lucas MP

Mat Fraser

Carol Royle

Our publications



We are delighted to have been invited to write an article on "The Way Forward", which was published on the *AltTox* website, March 27 2014. Our article explains the real opportunity that our unique approach presents for a powerful 21st Century approach to developing safer medicines. The article can be viewed from our website or directly at www.AltTox.org

EXPERT OPINION

on Drug Metabolism & Toxicology

Expert Opinion on Drug Metabolism & Toxicology published a review article (September 2013, Vol. 9, No. 9, pp 1155-1169) by Dr Margaret Clotworthy, director of Human Focused Testing and Kathy Archibald, director of Safer Medicines Trust. The article: "Advances in the development and use of human tissue-based techniques for drug toxicity testing" explains that human tissues have a vital role to play in drug toxicity evaluation and that, for many toxicity issues, the reliability of animal models is so poor that the greater relevance of human tissues offers invaluable advantages.

NewScientist

New Scientist printed our Opinion article: "How human biology can prevent drug deaths" on 15 December 2012. It said: "It is a tragedy that so many suffer or die through the use of inadequately tested drugs when tests based on human biology are readily available. Yet governments

continue to mandate animal tests, despite the lack of a formal demonstration of fitness for purpose, and a growing global realisation among scientists that animal toxicity tests are inadequate and must be replaced." The full article is available via our website.



Pharmacology Matters, the newsletter of the British Pharmacological Society, published an article by Dr Coleman (independently of Safer Medicines Trust), entitled: "How good are animals in predicting safety and efficacy of new medicines for man?" in April 2012 (Vol. 5, Issue 1, pp13-14). The article made a powerful appeal to researchers to "[move on from surrogate biology to the real thing](#)."

NewStatesman

New Statesman printed a letter by Kathy Archibald as their Letter of the Week on 4 January 2013. The letter concluded: "The "traditional" scientific perspective is that animals predict safety for human beings, and that criticism is based on sentimentality rather than reason. However, this is one controversy where established opinion needs fresh scrutiny in the light of new evidence. Several studies have calculated the ability of animal tests to predict adverse drug reactions. Estimates are often below 50 per cent. A recent study shows that animal tests missed 81 per cent of the serious side effects of 43 drugs that went on to harm patients. Surely this is sufficient evidence to rethink our reliance on animal testing?"



**WE HAVE
MOVED**

Please note our new address. Our new contact details mean that all of our old leaflets are now out of date, so please do not give out any old leaflets. If you would like to distribute copies of our new leaflet (enclosed), just let us know how many you would like – *thank you!*

Introducing our newest Science Advisers

We are delighted to welcome and introduce our newest Science Advisers, who bring a wealth of expertise from academia and industry:



Professor Barbara Pierscionek is Associate Dean of Research and Enterprise at Kingston University's Faculty of Science, Engineering and Computing. She qualified with clinical and scientific degrees in Australia and obtained an MBA and legal qualifications in the UK, including a Masters degree in Law (LLM). Her scientific expertise is in the area of eye and vision research. She is a pioneer of multidisciplinary approaches, leading to new insights into the lens, with the potential to improve outcomes for cataract patients. Her research has been supported by the Royal Society, the British Council, the Institute of International Education and charities including Fight for Sight and the RNIB. Based on her experience as an experimental scientist, Barbara has long advocated alternatives to animal models in research.



Dr Frank Rinaldi is a director and co-founder of Evolution Bioscience Ltd. He holds a PhD in breast cancer research and an executive MBA sponsored by one of the world's largest bioscience players. Frank specialises in commercial strategy formulation of innovative bioscience technologies for revenue generation. He is well known and respected in the industry and has a wide global client network including university bioscience establishments, start ups/SMEs, large blue chip organisations, as well as the venture capital community. In the area of *in vitro* and *ex vivo* toxicology and disease models, he has worked with a number of promising alternatives to traditional animal model approaches. This experience has made him a passionate advocate of consideration of these technologies.

Tony Benn 1925-2014



We are deeply honoured and proud that Tony Benn was our Patron for 9 years. He was a passionate advocate for Safer Medicines' belief that human medicine should focus on humans rather than animals. His support for us included hosting the launch of our film in the House of Commons in 2007 and presenting our petition to 10 Downing Street in 2011. He leaves an enduring legacy of inspiration and encouragement to change the world for the better, the aim to which he devoted his life.

Farewell to Tessa, our Office Manager

After 6 years with Safer Medicines, Tessa has left to resume her singing career and other creative pursuits. We thank Tessa for 6 great years and wish her every success for the future.

Thanks to all our wonderful supporters

We are deeply 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!

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 (enclosed). If you can help by distributing leaflets door-to-door, 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!*



Medical Research in the News

As the following news stories show, the safety of medicines is of very serious concern and the number of victims of side effects continues to grow. At the same time, a new generation of predictive human biology-based tests, which could improve the safety of new medicines, continues to expand in both variety and sophistication. Furthermore, evidence of the inability of government-required animal tests to predict safety (or other properties, such as effectiveness) in humans continues to mount.

This is a public health emergency. The time for governments to act is now.

Adverse drug reactions in the US

The Institute for Safe Medication Practices calculated that in 2011, prescription drugs were associated with **two to four million** people in the US experiencing "serious, disabling, or fatal injuries, including **128,000 deaths**."

Ref: *Quarterwatch*, 31 May 2012

Animal research – a broken model?

Writing in the *British Medical Journal*, Dr Pandora Pound and Michael Bracken, Professor of Epidemiology at Yale University Schools of Public Health and Medicine, advise that: "urgent attention needs to be paid to the quality of animal research for important reasons.

Much clinical research follows on from animal research. If the foundations of the biomedical research enterprise are unsound, then whatever is built on these foundations will be similarly precarious.

The current situation is unethical. Poorly designed studies and lack of methodological rigour in preclinical research may result in expensive but ultimately fruitless clinical trials that needlessly expose humans to potentially harmful drugs or may result in other potentially beneficial therapies being withheld.

... if research conducted on animals continues to be unable to reasonably predict what can be expected in humans, the public's continuing endorsement and funding of preclinical animal research seems misplaced."

BMJ Editor Fiona Godlee suggests that: "Funds might be better directed towards clinical rather than basic research,



where there is a clearer return on investment in terms of effects on patient care."

She quotes John Ioannidis, Professor of health research and policy at Stanford University, who wrote in his 2012 paper "Extrapolating from animals to humans" (*Science Translational Medicine* 4: 1-3) that it is "nearly impossible to rely on most animal data to predict whether or not an intervention will have a favourable clinical benefit-risk ratio in human subjects."

Fiona Godlee concludes her Editorial by asking: "Where would you place the balance of effort: investment in better animal research or a shift in funding to more clinical research?"

Ref: *BMJ* 348, 7 June 2014

Dogs do not predict safety



FRAME (Fund for the Replacement of Animals in Medical Experiments) has recently published an analysis of the value of studies in dogs for predicting the safety of human medicines. The salient feature of this study is the use of appropriate statistical metrics, which have not previously been applied to such data. The results shine a new light on our reliance on dogs for this purpose, suggesting that they contribute little or nothing to ensuring our safety. The paper and a presentation by lead author Dr Jarrod Bailey can be viewed from our website.

Ref: *ATLA* 41, 335-350, 2013

Mice mislead research

A major study by a large consortium of researchers has revealed why every one of nearly 150 drugs tested in patients with sepsis (the leading cause of death in intensive-care units) has failed. The trials were based on studies in mice. The study shows that 'sepsis' in mice is very different from the condition in humans and that the mouse model has been totally misleading for at least three major killers: sepsis, burns and trauma. The researchers commented that many years and billions of dollars have been wasted following false leads as a result. Furthermore, they added that their results raise troubling questions about other diseases that involve the immune system, including cancer and heart disease.

The investigators tried for more than a year to publish their paper. They submitted it to the journals *Science* and *Nature*, hoping to reach a wide audience. It was rejected from both.

"They are so ingrained in trying to cure mice that they forget we are trying to cure humans" – Ronald W. Davis, Professor of Biochemistry and Genetics, Stanford University School of Medicine and Director of Stanford Genome Technology Center

"When I read the paper, I was stunned by just how bad the mouse data are. It's really amazing — no correlation at all" – Dr Mitchell Fink, Vice Chair for Critical Care and Professor-in-Residence, University of California, Los Angeles

"It argues strongly – go to the patients. Get their cells. Get their tissues whenever you can. To understand sepsis, you have to go to the patients" – Dr Richard Hotchkiss, Professor of Anesthesiology, Medicine, Surgery, Molecular Biology and Pharmacology, Washington University School of Medicine

Ref: *New York Times*, 11 February 2013

The journal *Nature Medicine* commented on the study in an editorial entitled: "Of men, not mice" (4 April 2013):

"Although the message that mice are an imperfect model for human disease is far from new, these recent results should prompt some soul-searching among disease researchers... Rather than over-relying on animal models to understand what happens in humans, isn't it time to embrace the human 'model' to move forward?"

USA acknowledging the problem

Dr Elias Zerhouni, former Director of the National Institutes of Health (the world's largest financial supporter of medical research), laments that researchers have over-relied on animal data, saying:

"We have moved away from studying human disease in humans. With the ability to knock in or knock out any gene in a mouse—which can't sue us—researchers have over-relied on animal data. The problem is that it hasn't worked, and it's time we stopped dancing around the problem... We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans."

Ref: *NIH Record*, 21 June 2013

Dr Francis Collins, the current Director of the NIH, has made many powerful appeals to challenge the status quo, e.g.:

"The use of animal models for therapeutic development and target validation is time consuming, costly, and may not accurately predict efficacy in humans. As a result, many clinical compounds are carried forward only to fail in phase II or III trials; many others are probably abandoned because of the shortcomings of the model... With earlier and more rigorous target validation in human tissues, it may be justifiable to skip the animal model assessment of efficacy altogether... We must move forward now. Science and society cannot afford to do otherwise."

Ref: *Science Translational Medicine*, 6 July 2011

Dr Margaret Hamburg, FDA Commissioner, has written:
"We must bring 21st-century approaches to 21st-century products and problems."

Most of the toxicology tools used for regulatory assessment rely on high-dose animal studies and default extrapolation procedures and have remained relatively unchanged for decades, despite the scientific revolutions of the past half-century.

... The FDA is ... working to eventually replace animal testing with a combination of *in silico* and *in vitro* approaches... Policy-makers, industry leaders, and the scientific community have the opportunity and the power to answer this call to action. It cannot wait any longer."

Ref: Editorial, *Science*, 25 February 2011



Why Are All the Cancer Cures Going to Mice? We're Still Waiting

US charity, Gateway for Cancer Research, collected nearly 30,000 signatures for their petition (above), saying:

"We don't fund research to cure mice, we fund research to cure people. We are changing how cancer research is done. It should always and only be about the patients, not about interesting research findings. Please sign this pledge today to join us and demand cures today."

According to Azra Raza, MD, Professor of Medicine at Columbia University: "An obvious truth that is either being ignored or going unaddressed in cancer research is that mouse models do not mimic human disease well and are essentially worthless for drug development."

Her answer to the Edge.org annual question 2014: "What scientific idea is ready for retirement?" was: "Mouse models." She concluded:

"The time is here to let go of the mouse models at least as surrogates for bringing drugs to the bedside. Remember what Mark Twain said, "What gets us into trouble is not what we don't know; it's what we know for sure that just ain't so."

Human cells shown to predict toxicity more accurately

Newly published research demonstrates the ability of BioMAP Systems, a unique set of primary human cell and co-culture assays that model human disease, to identify important safety aspects of drugs and chemicals more efficiently and accurately than can be achieved by animal testing.

Data from 776 environmental chemicals, including reference pharmaceuticals and failed drugs, were analysed as part of the US EPA (Environmental Protection Agency) ToxCast Programme.

"This publication examines an unprecedentedly large data set... Our results show such systems to be a highly useful and reproducible tool for predictive toxicology" – Dr Ellen Berg, Scientific Director of DiscoverRx's BioSeek division.

Ref: *Nature Biotechnology*, 18 May 2014

Computer models highly reliable

German company PharmaInformatic has developed a computerised expert system, called IMPACT-F, that calculates human oral bioavailability (drug uptake) much more precisely than animal trials. This system will increase the prospects of successful clinical trials in humans. "Now we have proof that they are significantly more efficient and reliable than animal trials and we hope they will replace useless animal trials soon" - Dr Wolfgang Boomgaarden, founder and CEO, PharmaInformatic.

Ref: *Medical News Today* 21 May 2013

Organ-on-a-chip models

Exciting progress is being made in the field of 3D microfluidic replicas of human organs, using human cells, to study disease processes and to test drugs and chemicals for both effectiveness and safety. Suction can be applied to the small, flexible devices to simulate the mechanical effects of breathing, in the case of the lung-on-a-chip, or peristalsis, in the case of the gut-on-a-chip. Along with the realistic blood-like flow of fluid, this allows the cells to grow and behave in a more life-like way than static cultures, greatly enhancing their predictive capabilities.

Several other organ mimics are under development, including kidney, spleen, liver, bone marrow and heart. Most exciting of all, these organ chips can be linked together to replicate coordinated organ systems. This is the ultimate aim of many of the projects, including Harvard University's Wyss Institute, who have a number of excellent short video-clips on their website, some of which can also be viewed from our website.

NIH Director, Dr Francis Collins is impressed, writing that the lung-on-a-chip is already a game changer:

"This nifty little thumb-sized device offers a new way to model human diseases, and a cheaper and faster way to screen potential drugs."

Explaining how the chip was used to model the serious condition pulmonary edema and how it revealed, for the first time, that the motion of breathing contributes to the problem *and* how it could be alleviated, he pointed out:

"This is something that would have been very hard to appreciate in an animal model – you can't ask the animal to stop breathing!"

Ref: *NIH Director's blog*, 26 November 2012

Hepregen's human 'HepatoPac' micro-liver is predictive of liver damage from fialuridine (a potential treatment for hepatitis B) – an effect that was not predicted by animal studies, resulting in severe liver damage in 7 of 15 people in the 1993 clinical trial: five of whom died.

Ref: *Nature* 471, 661–665, 31 March 2011

New paradigm for Alzheimer's research

A review paper by Dr Gill Langley, senior science adviser to Humane Society International, says: "It's time to move dementia research into the 21st century."

... Alzheimer's is one of those disease research areas still very much dominated by the standard approach: studying the wrong condition in the wrong animal. The legacy of that approach is that despite a decade of effort using genetically modified mice, more than 300 potential treatments have been successful in animals but not a single one has proved effective in human patients.

... From patient-derived human brain cells in culture, to powerful neuroimaging machines, and super-computers combining multiple data to reconstruct the disease pathways, Alzheimer's can be mapped within the framework of human biology in order to understand why and how the illness occurs and how best to treat it. These advanced techniques will allow a complexity of understanding of this uniquely human disease never before achieved using animal models."

Ref: *Drug Discovery Today*, 21 May 2014

BBC series "Bang Goes the Theory" featured the work of Dr Rick Livesey's team at the Gurdon Institute, Cambridge, who are growing 3D human 'mini-brains' to study Alzheimer's disease. An iPlayer clip features presenter Liz Bonin enthusing:

"It's only because they can grow living brain cells that they can see the disease spreading – and can now test a multitude of different drugs on live human brain cells and watch the effects on a cellular level. It's a very exciting time for Alzheimer's disease research because this breakthrough – allowing us to understand the disease at its early stages, using live human nerve cells – is completely transforming our understanding of how to find a cure."

Ref: bbc.co.uk/programmes/p01wd83n

Animal Free Safety Testing of New Medicines



A symposium was held in Utrecht, Netherlands in May 2013 by Utrecht University and the Medicines Evaluation Board, in collaboration with Nefarma and Top Institute Pharma. Two expert panels with members from industry, regulatory authorities and academia were asked to design a scheme – if possible – to develop a medicine safely without the use of animal testing.

Both panels concluded that such a scheme would be challenging but feasible.

One of the organisers, Dr Peter van Meer wrote his PhD thesis on: "The scientific value of non-clinical animal studies in drug development". His studies concluded that "animal studies to assess the safety of new drugs are not always needed and can be, in fact, unscientific, uninformative or irrelevant. This, in turn, increases the costs and limits the efficiency of drug development".

He recommends a thorough revision of regulatory guidelines, increased dialogue between pharmaceutical companies and regulatory authorities, increased investment by pharmaceutical companies in technologies to improve safety assessment, along with economic and political incentives from governments. Another key necessity is that animal study reports need to be made available for research. This would enable unprecedented scientific analysis and discussion of the predictive value of animal studies and, he says, "an opportunity to reconsider when and how (and for how much longer) we use animals in drug development. This does require considerable effort and trust by pharmaceutical companies and regulatory authorities alike but the trade-off is an efficient non-clinical drug development process which is based on science."

Ref: tipharma.com, Project T6-301
P.J. K. van Meer, 2013

Leaflets

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Newsletters

Safer Medicines

Safer Medicines Trust


Briefly
Landscape for Medical Progress Trust

26 minutes
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A CRITICAL LOOK
AT

ANIMAL
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Booklets

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impact of animal experimentation
on research into cancer, AIDS,
neurological disorders and others,
as well as outlining more valid
human-based methods of research.

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.

[illegible]

Donate

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

Regular gifts by standing order help us to plan ahead with confidence – if you would like to help us in this way, we will be delighted to send you a standing order form: please contact us or download one from our website.

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.

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