



Spring 2020

Safer Medicines Trust welcomes new Director

We are delighted that Dr Jan Turner joined us in January 2019 as our new Director, taking over the role from Kathy Archibald, our founder and director for 15 years. Kathy remains the Chair of Trustees and continues to manage supporter communications as the charity moves from strength to strength.

She says: "It has always been my ambition for Safer Medicines Trust to be led by someone with high level experience of the paradigm-changing technologies we champion, so Jan is the perfect choice. We are excited to have someone of her calibre leading our expert team, to help to realise a future where better science will improve health and save lives."

Dr Turner has a wealth of experience in developing and promoting human-relevant in vitro technologies, including directing validation studies and influencing organisations such as the FDA (US Food and Drug Administration) to introduce such technologies into the early safety testing of drugs.

After completing her BSc in Biochemistry & Pharmacology, followed by a PhD and postdoctoral research in Genetic Toxicology, Dr Turner worked for

Amersham Biosciences, subsequently GE Healthcare Life Sciences. Her roles included Global Product Manager and Product Management Operations Leader. Latterly, she was Senior Product Manager at BBI Solutions, directing global cross-functional teams and driving adoption of innovative technologies.

She says: "I am passionate about human-focused biomedical research, and thrilled to have joined Safer Medicines Trust. It is an honour to work with so many talented and inspirational people towards our shared vision of a future where safe and effective treatments for patients will be delivered by scientifically valid, human-relevant research."



Dr Jan Turner

“We don’t have to look for model organisms any more because we are the model organism”

Nobel Laureate Sydney Brenner CH FRS

Safer Medicines Trust is a patient safety charity whose mission is to change the way medicines are tested, to a system based on *human* biology: the only way to ensure safety for patients.

Safer Medicines Campaign exists to challenge the regulations that still require animal-based safety tests when superior methods exist.

Help us put patient safety first

OUR PATRONS



Sir David Amess MP



Caroline Lucas MP



Grahame Morris MP



Mat Fraser



Carol Royle



Dr James Le Fanu

Meet some of the team:



Left-right: Pandora Pound, Kathy Archibald, Jan Turner, Gerry Kenna, Rebecca Ram

Dr Turner's first year with us has been a whirlwind! Some highlights include:

A presentation (available on our website) on Safer Medicines Trust's chapter (Replacing Animal Tests to Improve Safety for Humans) at the London launch (8 March 2019) of the book "Animal Experimentation: Working Towards a Paradigm Change", available as a FREE e-book: <https://brill.com/view/title/35072>. Jan gave another talk on the chapter at the annual Advances in Cell and Tissue Culture international conference in Cardiff (5 June), and at a further book launch event in the European Parliament in Brussels (4 December).

Gerry Kenna spoke at the 2019 British Toxicological Society Annual Congress. His slides and a recording are available on our website.

Kathy Archibald spoke via Skype to the Institute of Bioethics at the Pontificia University Javeriana in Bogotá, Colombia. Her slides and a recording are available on our website. Jan and Pandora Pound both gave presentations at the 22nd European Congress on Alternatives to Animal Testing in Linz, Austria, in October 2019.

Also in October, both Jan and Gerry contributed to a very positive Evidence Based Toxicology Collaboration workshop at the European Food Standards Agency meeting on using human-relevant Adverse Outcome Pathways in toxicology.

In November, Pandora and Jan both participated in an interesting and unusual "Pioneer-2-Policymaker" conference in Utrecht, hosted by the Dutch Transition

Programme for Innovation without the use of animals (TPI). The conference hosted 150 international scientists, entrepreneurs, research funders, NGOs, regulators and policy-makers in an interactive forum for participants "daring to pioneer" with innovative animal-free research. Pandora gave a keynote lecture at a symposium preceding the conference. Her slides are available on our website.

In December, Jan and Pandora attended an event on Strategies for Innovation in Life Sciences with Alliance for Human Relevant Science partners UPM and CN-Bio at the European Parliament in Brussels, and Jan also gave a presentation to MEPs at a Eurogroup for Animals event, on the subject:

"What's on the Horizon for Animals in Science – Changing the Paradigm."

Pandora gave a seminar: 'Towards a new ethics of animal research' at the Centre for Ethics in Medicine, University of Bristol, in February 2020. Her slides are available on our website.

Welcome to our new Patron



Grahame Morris MP

We are delighted to welcome Grahame Morris, Labour MP for Easington, as our new Patron. Grahame is a passionate campaigner on many issues, including health. Prior to his political career, he worked as a scientific officer in the Sunderland Group of hospitals. Over the past 10 years, he has led many campaigns in Parliament, including improving access to lifesaving advanced radiotherapy treatment for cancer patients, from which he has benefited personally.

He says: "I am pleased to support Safer Medicines Trust because I agree it is high time medical research focused on humans, rather than animals."

Latest Publications

Pound P, Ram R. Are researchers moving away from animal models as a result of poor clinical translation in the field of stroke? An analysis of opinion papers. *BMJ Open Science* 2020.

<http://dx.doi.org/10.1136/bmjos-2019-100041>

Given the failure to develop treatments for acute stroke despite decades of animal research, this study analyses the opinions of researchers who conduct animal studies of stroke. Scientists conducting animal studies of stroke agreed that the field was in crisis, and many robustly criticised the science in this area. When it came to identifying the causes of this crisis, most scientists focused on the poor quality of animal studies. Similarly, when it came to solutions, most proposed improving the quality of animal studies in the hope that this would ultimately translate into benefits for stroke patients. A small number of researchers proposed using human in vitro methods alongside animal studies and one proposed using human focused methods instead of animal studies. Although there is evidence then, that a minority of scientists are beginning to consider human focused approaches, our study indicates a strong resistance to relinquishing the use of animal models in stroke research, despite decades of their failure to produce any benefits for stroke patients.

Pound P. Animal models: problems and prospects. Chapter 18, p239-52. In Fischer B (Ed) *The Routledge Handbook of Animal Ethics*. 2019, Taylor and Francis, New York. <https://doi.org/10.4324/9781315105840>

This handbook is intended as a resource for philosophers and philosophy undergraduates and the chapter on animal models aims to bring readers up to date with recent developments in the field. It discusses recent evidence relating to weaknesses in the design, conduct and reporting of animal studies and explores how these weaknesses raise significant doubts about the validity of findings derived from animal studies, and their translation to humans. The chapter goes on to argue that this burgeoning evidence relating to poor scientific conduct and lack of human relevance challenges the existing ethical frameworks that govern animal research, such as the harm-benefit assessment. The case is made that philosophers and bioethicists need to grapple to a much greater extent with such evidence if bioethical theory is not to stagnate or become too abstract. The hope is that the chapter will provide philosophers with the evidence necessary to reinvigorate and update animal research ethics,

particularly as it relates to the harm-benefit assessment.

Pound P, Ritskes-Hoitinga M. Can prospective systematic reviews of animal studies improve clinical translation? *Journal of Translational Medicine*, 18 (15) 2020. <https://doi.org/10.1186/s12967-019-02205-x>

Some researchers suggest that systematic reviews of animal studies conducted prior to human trials would aid decisions on whether or not human trials should proceed. This paper argues, however, that individual studies in animals are not necessarily able to reliably predict the safety and efficacy of an intervention when trialed in humans, and so systematic reviews of these individual studies would likewise fail to offer reliable predictions of safety and efficacy. As a result they would not be able to reliably safeguard humans participating in clinical trials. Also, animal and human studies are often conducted concurrently, which not only makes prospective systematic reviews of animal studies impossible, but suggests that animal studies do not inform human studies in the manner presumed. Thus it is time to review our expectations of what animal studies can deliver and focus instead on investigating how clinical knowledge is actually produced.

Baker EJ, et al. Advancing nonclinical innovation and safety in pharmaceutical testing. *Drug Discovery Today*, 24 (2) 2019.

Open Access: <https://doi.org/10.1016/j.drudis.2018.11.011>

Researchers, academics and representatives from the pharmaceutical industry and advocacy groups, including Dr Gerry Kenna of Safer Medicines Trust, joined together as the 'Nonclinical Innovation and Patient Safety Initiative' to call for a significant and urgent shift to prioritise predictive, human-based nonclinical tests. Recommendations include:

- Change the language of policy requirements from 'animal' data to 'nonclinical' data
- Increase funding for development of human-based approaches
- Create a central hub to communicate existing training, funding, and educational opportunities in human-based regulatory science and/or new approaches
- Develop additional training and educational opportunities in human-based nonclinical approaches.

Links to all publications are available on our website.

White Paper

As we go to press with this newsletter, we are preparing to launch a white paper, which we co-authored with the Alliance for Human Relevant Science, entitled:

Accelerating the Growth of Human Relevant Life Sciences in the UK.

The paper is available from our website and from www.HumanRelevantScience.org. Its message is that investment in human relevant science offers a golden opportunity to revitalise biomedical research, save money, create wealth and improve public health.

Executive summary:

Significant advances in science and technology have provided a variety of new research methods that are based on the use of human tissues and cells. These are increasingly being used by researchers to gain unique and valuable insights into human biology and disease and to develop new treatments. With numerous human diseases remaining poorly understood and lacking effective treatments, urgent action is needed to develop and implement these new human relevant methods. Animal models are limited in their ability to translate to humans – of the drugs that have proved promising in animal trials, 86-90% fail in human trials. It is now time to

invest in methods that focus on human biology, to transform our ability to understand human disease and develop new medicines.

To accelerate the development and uptake of human relevant methods and technologies in the UK, this white paper calls for:

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- Government-backed infrastructure to provide practical support in transitioning towards human relevant approaches
 - Strategic funding to incentivise the development and usage of human relevant methods and technologies
 - Improved education at all levels on the potential of human relevant technologies, as well as skills training in their use
 - Drawing together of multidisciplinary expertise
 - Incorporation of human relevant methods into regulatory guidelines on medicines development.

Achieving these objectives will require support from the UK government, universities, pharmaceutical companies and regulatory agencies. The outcome will directly benefit the UK science base, help improve human health and wellbeing, and enhance the efficiency and profitability of industries which make vital contributions to the UK economy.



Moving from animal-based to human-based research

Many encouraging developments show that the tide is beginning to turn. For example:

- Two of the UK's largest mouse research facilities have announced their impending closure. In May 2019, the Wellcome Sanger Institute in Cambridge announced the closure of its animal facility, saying: "The Sanger Institute is increasingly using alternative* technologies to deliver its scientific strategy and this has led to fewer mice being needed." Similarly, in June 2019 the Medical Research Council recommended the closure of the Harwell Institute's Mammalian Genetics Unit near Oxford as a "reflection of the changing scientific landscape."

*i.e human relevant

- The US Environmental Protection Agency (EPA) announced in September 2019 that it will eliminate testing on mammals by 2035 – and instead focus on more informative and efficient technologies based on human biology, such as organs-on-chips and predictive modelling. Administrator Andrew Wheeler opened the first annual EPA conference on the development and use of new approach methodologies (NAMS) by saying: "Scientific advances exist today that allow us to predict better without the use of tests on animals... We can and will eliminate animal testing, while protecting human health and the environment."

Is enough being done?

It is clear that progress is now underway – but does this level of response reflect either the scale of the challenge or the pace of scientific advances?

We believe that the situation is analogous to the challenge of climate change and our collective societal response to it. There is a major crisis affecting the entire global population, which demands immediate action from all governments and unprecedented levels of international cooperation. Many technological and political solutions are already available, which would massively reduce the impact of the crisis if they were adopted universally and urgently. But many governments fail to recognise the scale or the urgency of the problem and are failing either to implement the solutions or to stop the practices that cause or exacerbate the crisis in the first place.

While failing to use the human relevant technologies already at our disposal does not threaten the extinction of life on earth, it does leave us all vulnerable to diseases and harmful substances from which we could be better protected if we relied on more accurate, predictive, modern, efficient and appropriate science.

To use the climate change analogy to illustrate how close we are to positive change and how simple it could be: cars are a significant contributor to greenhouse gases. Electric cars (powered by renewable energy) could make a big difference if all drivers were to switch to electric power tomorrow. Electric cars are available but are not yet mainstream because they are currently more expensive and charging points are not universally available. All that is needed is government



intervention, to subsidise the transition and to make charging points available. As with solar panels and other renewables: if governments are serious about enabling change, all they need to do is redirect their subsidies from destructive to constructive systems. Incentivise and invest in solutions and divest from harmful practices.

Currently, many human relevant technologies that could help cure diseases or identify toxins are languishing in academic laboratories and small biotechnology companies, for want of serious interest or investment from the government in enabling them to become ready to scale up and market. We acknowledge that much work and many projects are underway, including several international collaborations with funding from governments and industry, such as the EU-ToxRisk project (eu-toxrisk.eu), which aims to drive a paradigm shift away from 'black box' animal testing towards an understanding of how chemicals can harm human cells. Yet even these excellent relatively large consortia are tiny compared to the edifice of the global scientific enterprise, comprising multinational industries, academia and national scientific bodies.

While there is much to celebrate, in terms of exciting new scientific solutions, their actual uptake into routine practice lags woefully behind. Government support, especially in the UK, is simply not proportional to the challenge. The burdens of technology evaluation, scale-up and market integration are simply out of reach for many of the smaller companies with the most promising technologies. Consequently, we are witnessing a gradual, piecemeal evolution towards a scientific approach fit for the 21st century, rather than the revolution we need right now. Treatments for many diseases are inadequate or non-existent, or have troubling side effects. Drug development has an unsustainable rate of failure. Every year in the UK, adverse drug reactions cause more than a million hospital admissions and kill more than 10,000 people. Clearly there is something wrong with the way we investigate disease and develop medicines.

Human relevant technologies have the potential to deliver safer and more effective medicines, more quickly and at less cost. Some are already in use; many more are available but need optimising to make them accessible and ready for use. If the government made it a priority to divert existing funding from poorly performing animal-based to human-focused research, the benefits to public health and to the economy would be immense.

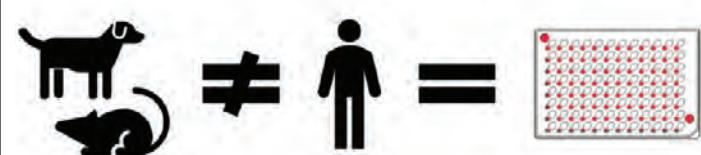


IMAGE CREDIT: MATTEK

How to accelerate the transition?

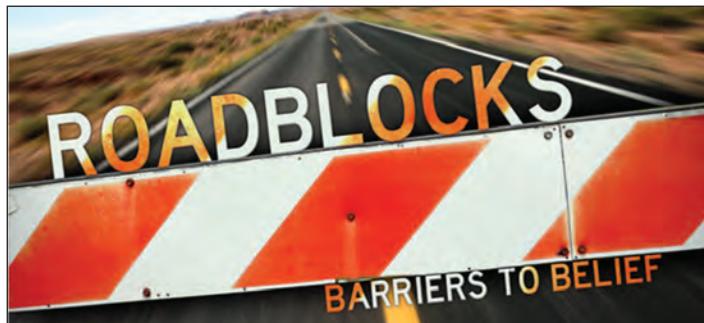
Some examples of efforts to realise this vital opportunity include:

- MEPs are calling on the European Commission to establish a concrete strategy with milestones and deadlines to phase out the use of animals in specific areas of research, education, and testing. At a roundtable event "Strategies for innovation in life sciences" and exhibition at the European Parliament on 3-5 December 2019, stakeholders explained the urgency for a transition to human relevant science. Speakers including our Director, Dr Jan Turner and some of our partners in the Alliance for Human Relevant Science, helped MEPs and policy makers to understand the need for a human focus in research and education.
- The Dutch Transition Programme for Innovation without the use of animals (TPI) aims to increase the pace of animal-free innovation. They say: "Start-ups are game-changers in animal-free testing" and launched a booklet on 26 Dutch start-up companies: "*26x better and faster without use of animals*" at their November "Pioneer-2-Policymaker" conference, to show that animal-free testing is both possible and promising. They want to shift the perspective from the dominant paradigm based on the 3Rs (Reduce, Refine and Replace) of animal testing towards safety assessment based on human measurements and data.
- The Indian Council of Medical Research is establishing a "centre for excellence in human pathway-based biomedicine and risk assessment" and urging their government to increase funding and international collaborations for human relevant technologies. In a paper in the *Indian Journal of Medical Research* (volume 149(5): 584–592, 2019), Dr Soumya Swaminathan (now deputy director general of the World Health Organisation) and co-authors argue that: "**Greater emphasis on human relevance will bring about a true paradigm shift**" and that: "**Funding for research focusing on human-based biology, rather than 'improved' animal models, should be prioritized.**"

All of these and many other developments should influence others, through positive feedback loops and virtuous circles, so that the progression of the transition will not be linear but exponential.

As Dr Thomas Hartung, Professor of Evidence Based Toxicology at Johns Hopkins University, USA wrote in his 2017 ALTEX article: "Opinion Versus Evidence for the Need to Move Away from Animal Testing": "**We need a 'scientific enlightenment movement', a type of restart as Life Science 2.0."**

What is holding us back?



Despite the multitude of positive developments, there are still major obstacles holding back the transition and consequently holding back medical progress. The following 4 examples illustrate the 4 major barriers to change:

1. Lock-in (the current system is so well established that it is rarely challenged. See: <https://faunalytics.org/wp-content/uploads/2015/05/Citation393.pdf>)

There is a rapidly growing epidemic of non-alcoholic fatty liver disease (NAFLD and NASH), linked to obesity and diabetes and thought to affect ~10% of the adult population in Western countries. Notwithstanding the fact that the most effective treatment for most people would be simply to eat less sugar and refined carbohydrates, there are currently no medicines available to treat the

disease, which can progress to liver fibrosis, cirrhosis, and cancer. In the race to develop an effective drug, 772 clinical trials have been conducted so far. While every drug candidate has shown promise in mice, none has shown success in humans.

Meanwhile, Swiss company InSphero has launched a game-changing in vitro testing model (3D InSight™ Human Liver Disease Discovery Platform), engineered to include all the human liver cell types necessary to replicate progression of NASH in patients, from fatty liver (steatosis) to inflammation (NASH) and scarring (fibrosis) of the liver. It will be interesting to see how many companies will follow InSphero's advice to break the bottleneck in NASH R&D and move away from mouse models to human-based options.

<https://insphero.com/blog/animal-nash-models-2/>



2. The 3Rs

Paradoxically, the very framework for aiming to Reduce, Refine and Replace experiments on animals may now be restricting progress. The concept of the 3Rs was born over 60 years ago, with the publication in 1959 of the seminal book by William Russell and Rex Burch: "The Principles of Humane Experimental Technique". Admirable efforts to put those principles into practice, to benefit both animals and science, have led to the establishment of national 3Rs centres (including the UK NC3Rs) and national and international regulations, such as Directive 2010/63/EU, which aspires to "*the final goal of full replacement of procedures on live animals*". Much has been and continues to be achieved, in terms of creating 'replacements' for procedures that previously used animals. Yet by framing the issue as one of animal welfare, where there is a need to seek 'alternative' methods so as to spare animals, our thinking is constrained and deterred from truly revolutionary avenues of thought that seek to answer scientific questions using the most appropriate methods, which are directly relevant to the object of study; usually humans. As Safer Medicines has always argued, continued reliance on animal research is seriously detrimental to the progress of human biomedicine, which should simply focus on humans in all their infinite variety.

Professor Michael Balls is a towering figure in the 3Rs field, having been the Chairman for 32 years, and now Life President of the Fund for the Replacement of Animals in Medical Experiments (FRAME), editor of the journal ATLA (Alternatives to Laboratory Animals) and the first Head of the European Centre for the Validation of Alternative Methods (ECVAM). In November 2019, he gave a keynote lecture (["On the Replacement of Animal Testing: Yesterday, Today, and Tomorrow"](#)) at the Center for Alternatives to Animal Testing (CAAT) at Johns Hopkins University in Baltimore, USA. While there is no greater advocate of Russell and Burch's Principles, Professor Balls argues that it is now time to move on from the 3Rs and to focus on modern human-relevant methods, rather than on the replacement of animal tests. Acknowledging that retirement allows him to speak more freely, he explains that the main messages of the Principles have not been fully appreciated and that 'lip-service' has often been paid to the 3Rs, under the guise of genuine commitment. In his speech, the thrust of which is captured in a November 2019 editorial in Expert Opinion on Drug Metabolism and Toxicology, referenced below, he says:

"We need to realise that animal welfare is not the only issue. We're really talking about a human welfare issue. If the drugs don't work, then human patients who need treatment aren't getting it, and huge resources are wasted [...] We should reduce animal use because the results aren't really worthwhile, and increase investment in what we can do with humans instead. We should stop talking about replacement [...] because what we need to do is to develop methods which have a sound mechanistic basis, using modern techniques, where we identify the questions which need to be asked, and find ways of answering them which are directly relevant to humans, rather than involving the need for the kind of extrapolations which we've had to put up with in the past."

The 3Rs concept has served its purpose: to show that there are more humane ways to do science. Now that there are better ways to do science, perhaps a necessary 4th R is to Retire the concept. As we have said before; animal experimentation is not only one of the major moral issues

of our time, it is also one of the major scientific issues. It is time to stop viewing science through the prism (or prison) of animal models and recognise that the ultimate goal is human relevance. If it weren't for the near-total dominance of the idea that we must model our diseases in animals, who knows how much further ahead we might be?

As John Maynard Keynes said in 1935: **"The difficulty lies, not in the new ideas, but in escaping from the old ones."**

And as Einstein said: **"We will not solve the problems of the world from the same level of thinking we were at when we created them. More than anything else, this new century demands new thinking."**

"How viable are alternatives to animal testing in determining the toxicities of therapeutic drugs?"
<https://doi.org/10.1080/17425255.2019.1694662>

See also shorter lecture: [The Principles at 60: What Next?](#)

3. Outdated regulations

Vanda Pharmaceuticals has been pursuing legal action against the FDA, to challenge their demand for a 9-month safety study on dogs (in addition to numerous animal and clinical studies already conducted) before allowing Vanda's candidate drug tradipitant to progress into longer-term human clinical testing. Dr Mihael H. Polymeropoulos MD, Vanda's President and CEO, says:

"We believe that there is no scientific justification for the requirement that tradipitant be tested in a nine-month dog study, given its currently understood safety profile in both animals and humans, and further, that these studies should not be a routine requirement for all sponsors. The FDA is ignoring a large body of published scientific evidence which concludes that these chronic dog studies do not offer any additional useful information. That policy is based on old, outdated science [...] yet, companies have been reticent to stand up to the FDA and demand that it change its policy. Vanda is unwilling to accept the status quo [...] It is time to demand that the pharmaceutical industry and government regulators abandon unscientific, low-resolution animal testing and adopt modern, human-based scientific methods to advance human drug safety."

In January 2020, a judge ruled against Vanda's assertion that FDA failed to demonstrate that canine studies are predictive of effects in humans, saying that:

"Vanda's argument is unpersuasive for the basic reason that the statutory and regulatory scheme here explicitly contemplates that the results of animal studies are predictive of the results of human trials." In other words, animal studies are predictive because the FDA believes they are. Vanda is now considering its options.

Safer Medicines also believes that updating regulations is key to enabling transition. We have launched a new petition (see back page) calling on the UK government to mandate the use of the most reliable safety tests. Please sign and share! We will soon be delivering our old petition to Number 10 Downing Street and will report on that in our next newsletter.

<https://vandapharmaceuticalsinc.gcs-web.com/news-releases/news-release-details/vanda-pharmaceuticals-takes-stand-against-unnecessary-animal>

4. Under-funding

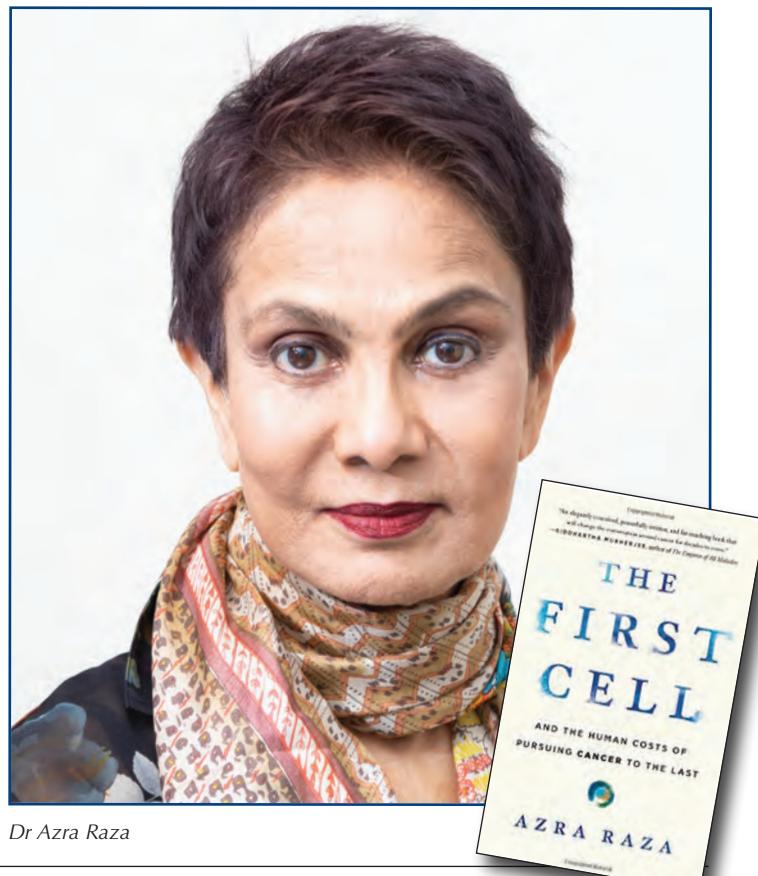
Dr Azra Raza, Professor of Medicine at Columbia University in New York, international authority on leukaemia, and Science Adviser to Safer Medicines Trust, has written a remarkable and highly recommended new book published in October 2019: *The First Cell: And the human costs of pursuing cancer to the last*. In amongst highly moving stories of her patients, including her own husband, Dr Raza explains why the global cancer research effort should make two major changes of direction:

- 1) to focus on prevention and early detection, to find the first malignant cell instead of attacking late-stage disease; and
- 2) to focus research exclusively on humans and their tissues, rather than on mice, rats and other futile animal models.

To that end, she has founded the **First Cell Center**, to study her tissue repository of more than 60,000 samples collected from her patients over the past 35 years. These samples hold the key to unlocking new early detection strategies, with which the First Cell Center aims to challenge and replace the current ineffective and costly paradigm.

Dr Raza's inspirational approach is our best hope of halting cancer. Significant funds are needed to analyse this unique treasure trove of samples – but appropriate funding has not been forthcoming, despite Dr Raza's heroic efforts,

since her approach does not conform to the current paradigm. If you or anyone you know is looking to donate to a truly promising cancer research charity, you may wish to look into <https://firstcellcenter.com>.



Dr Azra Raza

Paul Flynn MP 1935-2019

We were deeply saddened by the death of Paul Flynn MP. It was a great honour for us to have his support as a Patron. He was a politician of courage and conviction and a fearlessly talented communicator, which made him a powerful advocate for causes he cared passionately about, including social justice and improving the safety of medicines. He was a towering figure in the House of Commons and in his beloved Welsh homeland and is greatly missed.



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 a generous legacy bequeathed to us by Carole Hayman, a wonderful friend and supporter from our earliest days twenty years ago, before we became Safer Medicines.

How to help

If you would like to fundraise for us in any way, we would be 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 leaflet. If you can distribute 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!

Ask your MP to sign Early Day Motion 256, calling on the Government to support and accelerate the growth of human relevant life sciences in the UK. A template letter / email is available on our website.

