Approaching Thirty Years in Science: What Has Happened, and What Should Have Happened, in That Time

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Describing my journey through my scientific career, from the end of my days as a student, through to working with the Center for Contemporary Sciences.

Part I: Starting Out, and an Epiphany…

As the twentieth century drew to a close, I had just completed my PhD in virus genetics/molecular biology, and embarked on a seven-year stint as a senior research associate at Newcastle University, England — my alma mater — studying human premature birth. Using human tissue samples from the hospital attached to the medical school, and tissue cultures made from those samples, I was involved in trying to find answers to a (still difficult and unresolved) problem: why are so many babies born too soon? Are there genetic factors? What are the molecular mechanisms involved in maintaining a womb in a quiescent state while a baby grows, but then, at the right time, turning it into a formidably strong organ that can expel a small human being from its mother?

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This remains an important issue, because when these mechanisms go wrong, the consequences can be high. Around 15 million babies are born too soon each year — more than 1 in 10 births — and one million of those babies die. Many of those who survive face lifelong consequences, including physical and mental disabilities, which can be severe. While there are recommended steps that mothers-to-be can take to lower the risk of preterm birth, there is still little we can do about it, in spite of considerable efforts to understand the biology. Once a baby is on its way, the best that can be done is to delay the birth for perhaps a couple of days, which gives doctors time to help the baby, and to get the mother to hospital, for example.

Working in this field was important to me, and remains so, due to my own experiences. My brother and I were born two months early. Another premature sibling was my brother for just a few days; he died not long after he'd been born, three months early. My surviving brother and I have some ongoing health issues that are strongly associated with being born prematurely. My daughter — my only child — was born two months too soon, and spent time in the special care baby unit, and in intensive care.

This issue, therefore, is serious. And yet, around two decades after I worked in the field, we still don't really know why premature human labor happens, and we still can't do much about it. Like many areas of biomedical science, it's difficult to unravel and tease apart: this is not an easy question to answer. However, I learned a very important lesson during my own work that shaped my subsequent career: if you're trying to answer a difficult problem, you need to use the very best tools you possibly can. And in many (if not most) areas of biomedical research, while many scientists have the very best intentions and convictions, I believe they're not doing that — for varied and sometimes complex reasons.

Ethics — Animal and Human

I learned something else important during my time at the laboratory bench. The ethical dimension of biomedical research is intimately entwined with the scientific aspect; they are not separate entities. Using the best available tools constitutes the best science, and the best science is demanded by human ethics. Anything less than this is failing the seven billion people on the planet who are depending on the best research using the most appropriate tools to provide a deep understanding of human diseases, their causes, their pathology, their consequences, and to find preventive and therapeutic interventions and cures for so many devastating diseases.

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On top of this human ethical aspect is, of course, is animal ethics. Some 200 million animals, including hundreds of thousands of monkeys, dogs and cats, are used globally each year. This is consistently opposed by much, even the majority, of the public in many countries due to welfare concerns, including in the US and the UK, and forms the basis of animal research practice and regulations around the world in the form of Harm-Benefit Analyses (HBA), in which the predicted harms to animals used in experiments must be weighed against anticipated human benefit from those experiments. There are, however, significant issues and concerns with the objectivity and accountability of the process, and there are many calls for its reform.

Increasingly, my long-held ethical unease over animal research, which had led me in the past to decline research posts that could not guarantee I would not be required to conduct animal experiments, was being augmented by a scientific one. I found myself asking why other scientists asking the very same questions that I was asking were using animal models. Why weren't they using human tissue samples and human tissue culture, like other researchers, and I, were? Why weren't they concerned that the differences in results that came from using different species, were likely to mislead and confound? I began to look at other areas of research and was led to ask the same questions. I thought of people I knew and loved who'd suffered and died from various diseases, and felt angry and frustrated that science was letting them down. This included my grandparents, with whom I was very close, who died of cancer. As is so often quoted, "We have cured mice of cancer for decades and it simply didn't work in humans."

Part II: "Doing Something About My Frustrations Over Animal Research: Moving Away from the Bench and Out of the Laboratory."

One lunchtime in the lab, the intensity of my epiphany urged me into action. Could I do something about this, as a scientist? Could I use the knowledge and experience gained in my 14 years of higher education and research, to help to change how biomedical science was conducted, for the better? Could I help reduce the misleading results and conclusions, to avoid the dead-ends, and to help to save animals in labs? And how?

One lunchtime, I sat at my office desk and wrote letters to more than 30 organizations that campaigned against animal research. I received some exciting responses, and began to work on a project in my spare time for one group. Soon, I was working full time for a UK-based organization campaigning for research modernization and for a safer and more effective drug development process. I became a consultant, working for several groups on this issue, on varied projects.

I have done this now for around 17 years. In this time, I have published dozens of scientific papers and book chapters on diverse topics, all addressing the human relevance of animal models in scientific research and product testing, and human-specific *in vitro* methods of investigation. Topics include:

Statistical analyses showing that animal testing of new human drugs is poorly predictive of safety

There remains no robust published evidence to support current regulatory paradigm of animal testing in supporting safe entry of new drugs into clinical trials. In fact, my own studies, along with two salient subsequent reports, actually support the contention that tests on rodents, dogs and monkeys provide next to no evidential weight to the probability of there being a lack of human toxicity from new drugs, when there is no apparent toxicity in animal tests. It is essential that the pharmaceutical industry and its regulators seek a roadmap to embracing a comprehensive and integrated human-biology based strategy for this purpose as a matter of urgency.

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Numerous and widespread genetic differences are at the root of poor human relevance of monkey and chimpanzee experiments

Critical analyses of the relevance of monkey studies to human biology indicate that genetic similarity does not result in sufficient physiological similarity for nonhuman primates to constitute good models for research, and that nonhuman primate data do not translate well to progress in clinical practice for humans. Salient examples include the drug testing/development, HIV/AIDS, Alzheimer's and Parkinson's diseases and stroke. Key molecular differences underly these inter-species disparities, with significant differences in all aspects of gene expression and protein function. The use of nonhuman primates in research must be considered of questionable value, particularly given the breadth and potential of NAMs.

Testing of substances in animals for potential harm to unborn children (developmental toxicity) are poorly predictive

Animal tests in this area do not provide reliable data that are predictive for human responses and, even if they did, the tests are too expensive and time-consuming for application to the very large number of substances that need to be tested. It is estimated there are already more than 100,000 man-made chemicals to which humans may be exposed on a regular basis, and it is therefore widely accepted that developmental toxicology tests using animals could not possibly be used to assess all new and existing chemical substances, due to the scale of its demand upon time and resources. It is therefore imperative that alternatives (such as those described here) are embraced, further developed, accepted and used — as a matter of urgency.

Chimpanzee research — prevalent in the US until funding was withdrawn in 2011 — was poorly predictive for humans. Areas included HIV/AIDS, hepatitis C, cancer, and others

Over 85% of chimpanzee published research is either not cited, or cited only by studies that do not report human medical advances. Of the few citing papers that do report human medical advances, chimpanzee research is not a contributory factor. Greater than 85 HIV/AIDS vaccines have been developed, almost all of which were successfully tested in chimpanzees, yet in 200 human trials none provided human protection or improvement of symptoms (this has since been updated in a paper in press). Hepatitis C

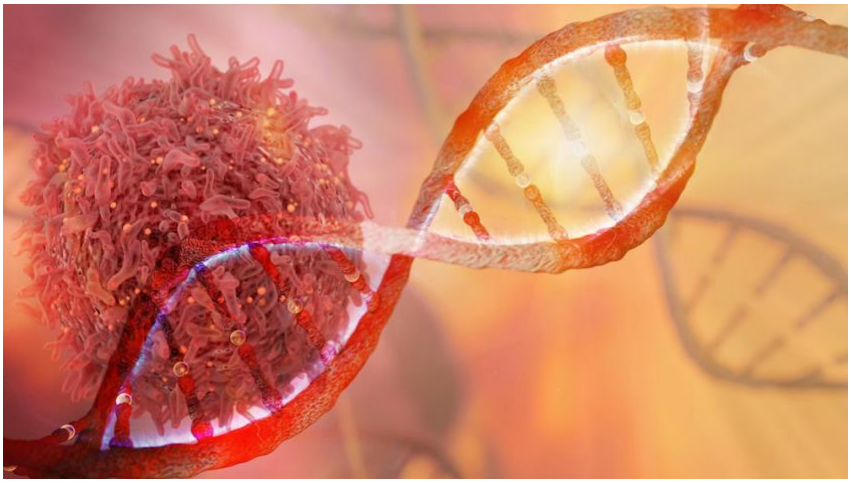
research with non-chimpanzee methods had increased 80-fold over two decades, while research involving chimpanzees declined by almost 70% to an historic low.

The human relevance and promise of clinical benefit from animal 'breakthroughs' are greatly exaggerated in the press.

Over-speculation and exaggeration of the human relevance of animal research is widespread in the UK national print media. Of 27 high-profile, unique published animal-based 'breakthroughs' promising imminent clinical benefit in 1995, only one had clearly resulted in human benefit, despite a time period of greater than twenty years to allow that research to come to fruition. Failures included therapies for cancers, HIV/AIDS, Alzheimer's disease, multiple sclerosis, deafness, and organ transplantation.

Substantial evidence warrants great concern over the poor efficiency and specificity of CRISPR-mediated genetic modification of animals, despite recent improvements.

These issues cause persistent, adverse, ethical, and scientific consequences for GM animals, which may never be sufficiently resolvable.



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Stress experienced by animals in labs significantly affects scientific results, and there is little that can be done about it.

Stress experienced by animals in labs is difficult to mitigate and can result in considerable psychological and physiological welfare problems. Physical consequences include adverse effects on immune function, inflammatory responses, metabolism, and disease susceptibility and progression. These effects must have consequences for the reliability of experimental data and their extrapolation to humans, in addition to causing welfare problems for the animals, and this may not be recognized sufficiently among those who use animals in experiments.

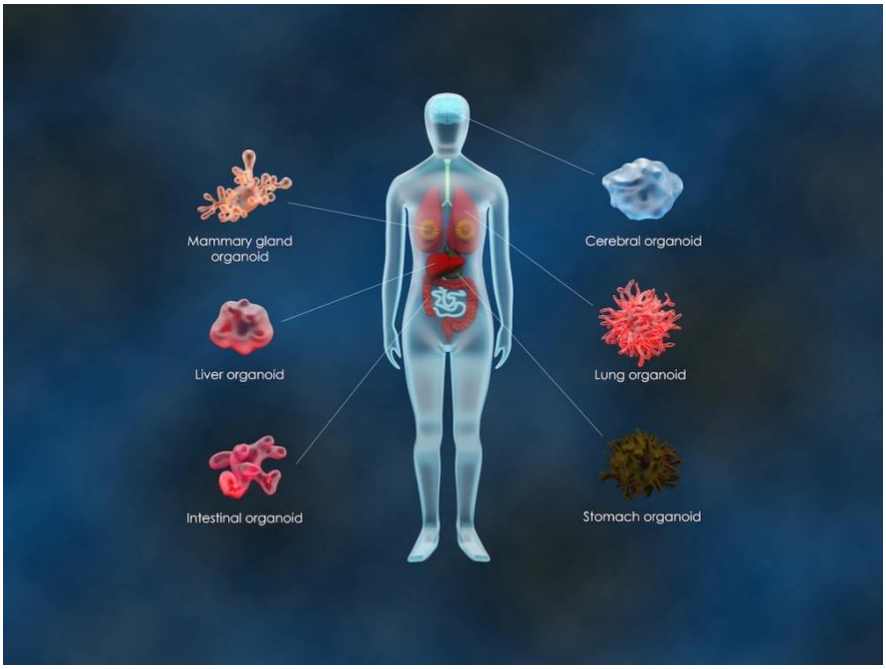
All in all, I, and many other authors over time, have published a considerable volume of such evidence. It is comprehensive, robust, powerful and makes a formidable case. Yet, the impact this evidence has had on changing how science is done, and on making it more human relevant and translate better to clinical success, has not been as great as it deserves. In the next, and final, installment of this blog series

Part III: "A Shift That Will Revolutionize Biomedical Science"

I outline how an increasing focus on what human-based research can do, rather than what other approaches cannot, could help expedite the urgently needed paradigm shift. I also describe how CCS came about, and what my colleagues and I are doing, and will do, to ensure that the change that science demands is realized.

In the previous installment (Part II) of this three-part blog, I described my move out of the lab and academic research, and some of my work over the past 17 years to elucidate how animal-based research is poorly relevant to human biology and medicine. The overall weight of evidence against animal-based research has grown very significantly over the past twenty years. For example, as well ever greater numbers of peer-reviewed scientific papers being published that are critical of animal-to-human extrapolation, multiple authors from a wide variety of disciplines are also contributing to edited books of high academic merit (e.g. here and here).
In more recent years, the burgeoning case against animal-based research has been augmented by rapid advances in so-called alternative methods, including New Approach Methodologies. Broadly, these are non-animal research and testing methods that involve human cell/tissue culture systems and other "test-tube based" methods (*in vitro*) and computer modeling/simulations.

These methods have contributed to a capacity to conduct biomedical research and to test new chemicals for safety with a human focus from start to finish. Unprecedented abilities to model human biology with astounding physiological relevance not only give researchers the option and the confidence to do this, but the science is strong that it *demands* that they do this. Standard cell/tissue culture methods involving two-dimensional monolayers of cells — such as those that I have used, and which formed the mainstay of cell culture for many years — have limitations, but have been improved over time and still have an important part to play in research. For example, 2D cultures of human hepatocytes (a major type of liver cell) are being used to detect liver toxicity of new drugs, to a much greater predictive level than traditional methods like animal tests. Yet, the power of advanced culture methods, involving 3D cultures, is astonishing.



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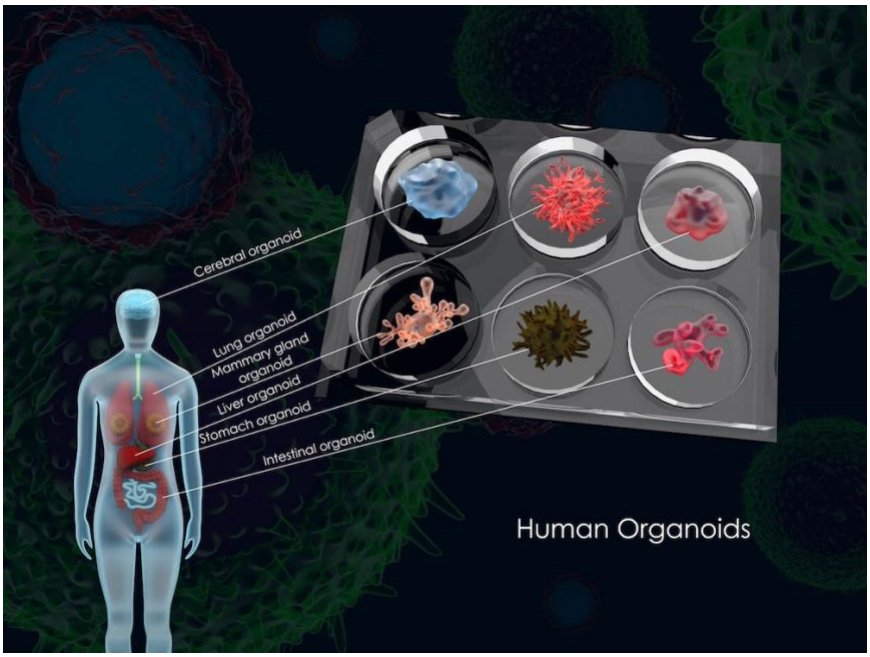
I reviewed some salient examples of this in an overview for the Center for Contemporary Sciences (CCS) website a little while ago, summarizing and describing the technologies, and detailing some exciting applications and examples of success. A few illustrative examples are:

- 3D cultures, including human "organoids" (tiny human organs grown in cell culture, with organ-like spatial arrangements of varied cell types that exhibit functional characteristics) are used in modeling:
- cancers more faithfully, including breast, lung, stomach, colorectal, renal, bladder, and others — providing more information about new how new drugs might work, and how safe and effective they might be the liver, permitting more predictive testing of new drugs for drug-induced liver injury (DILI)
- the heart, to investigate heart function, disease, and heart-drug testing
- human brain function and disease, including Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis (ALS); and the identification and testing of new drugs for them
- type 2 diabetes, and developing new drugs for it
- a system to test for toxicity to unborn children (embryotoxicity/ developmental toxicity)

Microphysiological Systems, or "Organ on a Chip" (OOAC) methods. These dynamic cultures of cells on small glass, silicone or plastic "chips" may be patterned with 3D printing, to help to provide geometry and physiological relevance. Microfluidic channels allow the circulation of blood substitute to provide nutrients, remove waste substances, and introduce drugs, for example. Other factors to potentiate physiological relevance may be imparted by the culture conditions and set-up, such as shear stress and physical pressure, replicating, for instance, physical factors such as heart beats, breathing and so on. Further, these chips can be connected together to provide interconnected organ functional systems, or even "body on a chip" simulations. The relevance to human organs has been so high that these approaches have been used in many ways, producing impressive results:

- Many organ chips have now been developed, including: brain, neurons, heart, lung (airway and alveolus), liver, kidney, intestine, blood vessels, skin, stomach, mammary gland, pancreas, testis, female reproductive system, and others.
- A first-pass model of testing of new human drugs: gut, liver and kidney chips were connected to facilitate the measurement of drug absorption, metabolism and excretion, and derivation of human pharmacokinetic and pharmacodynamic parameters, similar to those determined in clinical trials. As such, scientists believe these approaches can reliably predict safety and efficacy of new drugs prior to human trials — something current methods, based largely on animal testing, cannot do well. In fact, tests have shown such setups to correctly predict human drug responses — both toxic and non-toxic — that had not been predicted in animal tests.
- OOAC are being used to research many different human diseases, such as various cancers, liver diseases including hepatitis B, lung conditions like COPD, asthma and cystic fibrosis, ischemic heart disease, neurodegenerative diseases, brain injury, and more.
- COVID-19 research, including the infectious process, pathology, and screening for therapies.



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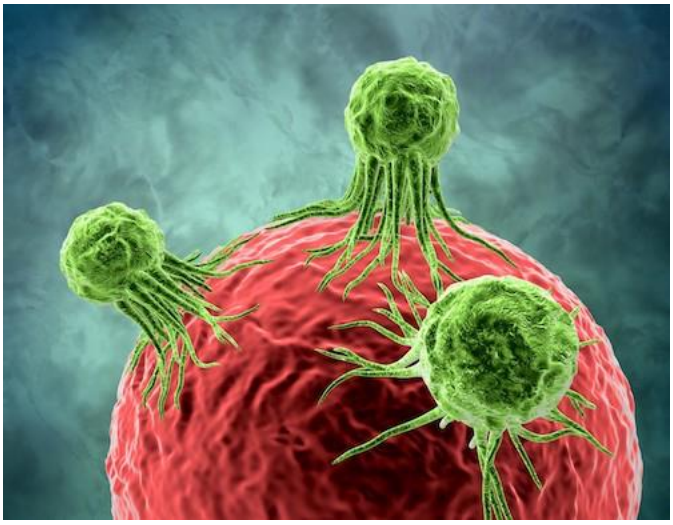
There are two major advantages to the use of methods like these: (1) they are human-specific, and therefore directly relevant to the species of interest from the start, without the confounding nature of inter-species extrapolation of data; and (2) because the cells that comprise the advanced cultures are derived from individual human beings and patients, they are able to reflect human heterogeneity, including variations in genetics, causes of disease, pathology, drug responses, and factors that contribute to these such as age, sex, disease, and diet.

Such is the power, promise and capability of these (and associated human-specific) approaches, the Founding Director of the Wyss Institute for Biologically Inspired Engineering at Harvard University recently published a Progress Report in the prestigious journal *Advanced Science*, questioning the ongoing dogmatic requirement of reviewers of scientific papers and grant applications that researchers "validate" results from *in vitro* methods in studies in animals. This reservation was based on the increasingly widespread appreciation that these approaches are able to recapitulate human biology, physiology and diseases, as well as predict human pharmacokinetics, better than animal models. A recent (May 2021) Editorial in a journal of the acclaimed Nature group also questioned the need for small animal models, at least, in biomedical research due to the increased sophistication and human mimicry of advanced tissue culture techniques.

On top of opinions and examples such as those above, there is empirical evidence. Many scientists believe that human-specific preclinical drug testing is a matter of time; regulators and governmental organizations such as DARPA, the FDA, EPA and NIH are increasingly getting on board, and embracing human-specific methods and their data, even setting targets for a complete elimination of animal use; industry are forming consortia that are working to address the issue; the level of venture capital and investment are soaring; and the numbers of users of human-based techniques and associated publications are taking off.



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A Scientific Organization to Pull it All Together — Moving to the Center for Contemporary Sciences

It was with this increasingly widely held viewpoint, and with similar ringing endorsements from sections of the scientific populace, in mind, that CCS was born, following a meeting of minds at Harvard Law School in 2019. I was asked to join them in the spring of 2020, and together we have spent our time setting up a purely scientific, single-issue organization to achieve a bold vision: to save and improve lives by catalyzing the world's transition to human-specific medical research. I was glad to do so for one major reason: the time is ripe to build on the formidable case showing what human-specific methods *can* do. CCS has been developing considered strategies to facilitate our mission: to pioneer a paradigm shift towards innovative, evidence-based research methods. I have worked with my colleagues to establish educational, academic and policy programs to expedite the sea-change in biomedical research that will help humans and animals alike. We are engaging with early-career scientists to raise awareness of the future of science, and to excite and attract them into it.

We are working with established researchers in academia and industry to try to solve persistent problems in biomedical research that have negatively impacted millions of people. We are envisioning strategies to work with legislators, with the support of diverse stakeholders, to potentiate change via revolutions in funding. All of this will result in science that is quicker, cheaper, humane, and which ultimately results in much greater clinical translation and human benefit. We are helping to facilitate investment for biotech companies that are furthering the reach of advanced research and testing methods that will replace animal use. And much more.

It seems clear, after almost two decades working in this effort, that, unfortunately and even unforgivably from some perspectives, the science "isn't enough". What I mean by that is that showing something to be poor, and showing something else to be better, doesn't automatically lead to change — at least, not a rate of change that is needed or acceptable. Indeed, I've participated in conference panel discussions with other scientists who, borne of frustration at a pace of change that is real, but nowhere near as great as the available evidence demands, have questioned why a biomedical paradigm shift is proceeding much more slowly than should be expected: why is there so much opposition and obstruction, and what needs to be done to expedite it?

At CCS, we believe our programs and our mission constitute an important part of the solution. I am excited and honored to be part of them.