Comment

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Biomedical Research Must Change — But a Shift Toward Human-specific Research Methods Is Only Part of What Is Needed

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The poor translation of animal research to human biology and clinical benefit is more widely acknowledged than ever before. Much of my work over the past 17 years has made a scientific case for the replacement of animal experimentation with human-specific methods for this reason, also arguing that such a paradigm shift has a human ethical basis, as well as being based on animal welfare. Over this time, the debate has grown from being largely argued by animal rights groups, to a movement that now involves stakeholders from every area of science, including academia, industry and regulators. Initiatives and roadmaps to expedite *replacement* specifically — not just the Three Rs generally — are ongoing, gathering momentum and finding success (for example[1–8]). Furthermore, acknowledgements of poor translation/human relevance of animal-based approaches are stated frequently in papers in mainstream journals in a huge variety of specialist fields, as researchers increasingly look to new approach methodologies (NAMs) to find a better way forward.

This is all very welcome, naturally. However, it may be a serious mistake to assume that this paradigm shift, when it happens, will be enough for biomedical research to reach its full potential. There are long-established and growing concerns among some academics around how biomedical research is conducted, over and above the methods and approaches it adopts. These concerns deserve much more attention than they currently receive. I recall many and regular conversations with my scientist colleagues during my time in academic research, lamenting certain aspects of how academia operated, how science was funded, the unfortunate weight of the 'publish or perish' mantra, and how research and researchers were assessed and assigned relative value. While this all took place almost 20 years ago, it is perhaps even more relevant today. No matter how good the very best, most human-relevant NAMs may be, if the drivers of research and the modus operandi of biomedical investigation are not optimal, then biomedical research itself will remain, at best, sub-par — and this has serious human ethical consequences. There must be a significant change in this respect, too, which would potentiate, enhance and maximise the capabilities of NAMs and human-specific research, ensuring significant increases in clinical translation and benefit. This limitation of research potential and translation to human benefit is a critical point. Notably, it is distinct from other calls for change in how research is conducted, calls for intellectual/academic freedom, complaints surrounding unnecessary 'regulatory burden' and so on. These concerns are not borne of frustration with the job and career, but of the purpose, goals, and main raison d'être of biomedical research: i.e. clinical impact and human benefit.

The issues involved are many and varied, but are far from intractable, and have been summarised by many authors and researchers.[9–16] They include:

- A culture and system that pushes scientists towards 'self-preservation' over tackling the correct, most burning scientific questions and seeking the truth.
- Measuring success by incorrect and superficial metrics: grant money received, number of papers published, where those papers are published (elite journals?), and the level of interest in their field of research from the public and media.
- Rewarding scientists who are best able to play the system and achieve 'career milestones', rather than the ones who can do the best and most successful research (typically measured by impact factors and grant income, rather than the impact of their research on human diseases, for example).

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- The existence of selection pressures favouring poor methods and safe hypotheses.
- The manipulation of research and of metrics that are used to assess researchers: for example, research fraud, fake peer-review, artificial inflation of citation rates, and self-plagiarism are frequently reported.
- The presence of bias and lack of transparency in some peer-review processes associated with research funding.
- In some cases, encouraging lower quality research that can potentially yield significant volumes of data and publications, but which may not add useful information to the knowledge base and/or lead to clinical benefit.
- In other cases, researchers striving towards the accumulation of large amounts of potentially useful and clinically relevant data more likely to be accepted in top-tier journals, instead of publishing smaller communications in a much timelier manner. Conversely, in some research areas, encouraging the rapid publication of a greater number of brief reports, instead of fewer, higher quality papers.
- Disincentives to publish 'negative data', regardless of its merit and importance, resulting in duplication of research and a substantial waste of money, time and animals' lives.

The above predicaments make biomedical research risk averse, this can lead to 'bad science' that negatively impacts on the breakthroughs that could lead to the greater understanding of human biology, human diseases/pathology and, ultimately, the discovery of safe and effective new therapies that are of clinical benefit.[15,16] Some stakeholders in the field have, however, suggested ways in which biomedical research must change to be more successful and less wasteful.

Examples of such changes were elegantly summarised in a review by Charlton and Andras, who proposed a "new specialist research system", in which research could be free from these constraints and forces.[16] In this new system, scientists could do what they believed would be fruitful and make a real difference, instead of what was conducive to the system and to self-preservation. *Inter alia*, they advocated international, independent research institutions, where researchers are employed not based on the above, traditional, flawed criteria, but based on creativity, aptitude and research skills that incorporate truth-seeking, risk and translation to clinical benefit. In such an environment, radical strategies and transformative ideas could be developed and utilised to their full extent to solve problems not being solved by historical, established approaches. The impetus for these institutions may well come from the increasing public frustration that biomedical research is failing to result in sufficient true breakthroughs leading to clinical benefit for millions of people — in other words, the idea that numerous researchers need to stop "doing ever more of the same old stuff" and embrace more ambitious strategies, such as the panoply of human-specific NAMs. The authors also provided a useful analogy to illustrate their views: the development of Compact Disc technology was a genuine, revolutionary breakthrough in high quality music reproduction, compared to the diminishing returns of incremental progress with tape/cassette technology. The biomedical example they provided alongside this is that of cancer research. In this field, at least until recently, the development of new treatments had plateaued, as a result of a reliance largely on old methods.

For many areas of research, breakthroughs are sorely needed, in order to discover safe and effective new treatments, and a shift in how research is conducted is key to this.[17] There are numerous other cases, in addition to cancer, including: Alzheimer's disease,[18,19] Parkinson's disease,[20,21] neuroscience generally,[22] the testing of chemicals for cancer risk,[23,24] the testing of new drugs for safety and efficacy,[25] amyotrophic lateral sclerosis,[26,27] HIV/AIDS vaccines[28,29] and sepsis.[30] In so many areas of biomedical research, progress is slow, understanding is poor, and researchers continue to rely on the often-misleading animal-based approaches that have led to countless frustrations.

One simple solution — achievable, given adequate funding — would be a much more prevalent establishment of research institutes that tackle these areas of research with long-term attitudes and strategies, without the limiting factors and pressures mentioned above. These institutes could be physical, one-site establishments, or multi-site virtual collaborative entities. Scientists, selected based on their visions, knowledge of human-specific methodologies and integrated approaches, and on their ambitious, forward-looking (rather than traditional) criteria, would be free to pursue the research they believed would be most relevant and productive; to tackle with absolute focus the difficult questions that must be answered instead of those that would provide the most, and most-publishable, data; to pursue their investigations free of worry about short-term funding and repeated grant applications, and they would be answerable only to 'science'. One salient example of this type of approach is Harvard University's Wyss Institute (wyss.harvard.edu), which was launched, and has been largely maintained, by significant philanthropic gifts. It has forged cross-institutional and cross-disciplinary collaborative research programmes, and encourages high-risk, innovative research that might not otherwise be pursued in 'traditional' academic research or industry.[31]

There are other institutes, foundations and collaborations worthy of mention, of course. Salient examples include: the US-based Milken Institute (milkeninstitute.org), which has a 'FasterCures' think tank, aimed at "accelerating medical solutions" via patient-centric

research and outcomes. In turn, this FasterCures think tank founded 'The Research Acceleration and Innovation Network' (TRAIN), which is a collaborative network of more than 100 foundations that are committed to these goals and approaches. Their aim is to overcome the obstacles they see in biomedical research in general, to accelerate clinical translation, and to achieve this by so-called 'venture philanthropy', involving the significant funding of higher risk, innovative approaches, with greater multi-centre collaboration and collaborative evaluations of progress. One notable member of TRAIN is the Michael J. Fox Foundation (MJFF), which is committed to the funding of "high-risk, high-reward research targets" in Parkinson's disease research, and de-risking the field to make it more attractive for researchers, funders and investors.

The not-for-profit Bill and Melinda Gates Medical Research Institute states "It's time to use the latest innovations to improve all lives. We will combine advances in biomarker profiling of the immune system and infectious organisms and bioassays, quantitative sciences and statistical computing, and expertise in chemistry and manufacturing to move potential solutions from the laboratory into human trials". The Howard Hughes Medical Institute (HHMI) focuses on providing talented scientists ample funding to pursue research they believe will be productive in collaborative ventures, and provides greater than $1 billion annually to over 300 researchers at more than 60 institutions. One measure of its success is 29 Nobel laureates resulting from its programmes.[31]

The Simons Foundation has an autism research initiative, which provides support grants to encourage scientists to validate new hypotheses, helping to encourage innovation and to increase chances of greater funding subsequently. The international Aligning Science Across Parkinson's (ASAP) initiative accepts that limiting factors in Parkinson's disease research include the risk aversion of researchers to novel concepts, and lack of decent funding levels to investigate new ideas. In accordance with others mentioned in this Comment, they believe that philanthropic funding helps with these issues, supporting risk-taking and new avenues of research, as well as collaboration and data sharing, increasingly seen to be absolutely crucial by many.[32]

Academic observers have commented on the failure of 'traditional' funding approaches (such as those of the National Institutes of Health (NIH) in the US) to keep up with the times and to respond effectively to the evidence and their own researchers' needs. They describe the NIH's intramural programme, for instance, as short-sighted, slow to react, not bold enough, and paying too little attention to bold early-career researchers. They also urge the NIH to take a leaf out of the book of philanthropic donors, for all the reasons already given herein, and cite the Parker Institute for Cancer Immunotherapy, the Chan Zuckerberg Initiative, and others as shining examples of how things should be done.[33] Yet another of the many published articles championing and bemoaning the same issues with scientific funding and conduct, highlights the benefits that philanthropic funding of collaborative projects brought to, for example, the Scripps Institute, the Broad Institute of MIT and Harvard, the Burroughs Wellcome Fund, the Michael J. Fox Foundation, and others.[34]

Philanthropic funding is considered to encourage new and unconventional approaches, risk-taking and innovation, and to expedite proof-of-concept, all via a long-term focus on translation to clinical benefit. This is in direct comparison to, for example, governmental funding/traditional research funding, whose success is measured by such criteria as meeting the goals of the grant, publication numbers and publishing journal status, etc.[31] In addition, philanthropic funding/institutes tend to require the sharing of data prior to publication, which traditionally funded investigators may understandably be reticent to do, but which is also acknowledged to expedite research and generate ultimate benefits.[35] The Milken Institute has put forward a number of considered new metrics — both tangible and intangible — that it proposes to be better indicators of scientific talent and contribution to eventual clinical benefit than current, established measures. These include fruitful collaborations (including with industry), follow-on funding, infrastructure and workforce development, development of new and innovative ideas, and demonstration of scientific ambassadorship.

A much greater number of institutes set up and operated along these lines would demand a considerable outlay of funding but, given the wasteful nature of research as it is often conducted presently, it would be no more expensive to fund (probably even cheaper to fund) going forward. My colleagues and I — and many other biomedical researchers — believe this is the future of biomedical science. However, like the proposed sea-change in research away from animals and towards human-specific NAMs, this is a discussion that must be conducted much more widely and frequently, and positively acted upon so that this much-needed change is actually realised. Everybody — human and non-human, scientist and non-scientist — stands to benefit.

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