

# Improving the efficacy of translational medicine by optimally integrating health care, academia and industry

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Translational medicine has become a global priority, but there is still a major gap between the arrival of new treatments and the investment that many countries have made on this front. Here we discuss often unrecognized roadblocks in the translational process and offer potential solutions for further advancement through enhanced integration of health care, academia and industry.

Although understanding of biological mechanisms is on the rise, the process of translating fundamental knowledge to the clinic remains disappointing. Essential issues that have been widely recognized to account for the transitional gap include the need for increased investment in early-stage research and, in pre-clinical and early clinical work, the need for the capacity to stretch out beyond the boundaries of individual disciplines, for a more transparent dialogue between companies and regulators, for an approval process that does not always sacrifice efficacy in the name of safety and for other considerations that ultimately prevent new drugs from making it to the market<sup>1–8</sup>. However, there are additional problems that have not received sufficient attention and need to be addressed to improve success in translational medicine.

## Removing silos

The success of any translational process in medicine depends on a close integration of

government research institutes, academia and universities with hospitals and clinical care. Although the necessity for such an integration may seem obvious, it is anathema in most countries. The reality in most nations is that there are strict separations of revenue streams for hospitals on the one hand and for research resources that fund biomedical science on the other. Indeed, in some countries, hospitals and universities often report to different entities—to the Ministry of Health and the Ministry of Education, respectively. Funding streams from private or public insurance programs are kept separate from research revenue. Worryingly, this schism is widening as a result of the fact that health systems around the world are experiencing increasing pressure to treat more patients in shorter times. This fundamental split between research and daily clinical practice clearly reduces the efficiency of the translational initiatives that many nations seek to launch. It is illustrative to examine the way in which different countries are dealing with this fundamental problem.

Since the implementation of the Flexner Report 105 years ago, the US has had a tradition of integrating university-owned hospitals in the research and teaching processes<sup>9</sup>. Abraham Flexner supported a model system of medical education in which all schools were to be patterned after the Johns Hopkins University School of Medicine: university-based, research-oriented schools that owned their teaching hospitals<sup>10</sup>. Thanks to the Flexner Report, the Johns Hopkins model spread throughout the US. However, a new crop of US medical schools has been emerging in the last ten years in which there is a distinct separation between academia and health care. Moreover, the Flexner model has failed to spread globally, hampering the progress of the

translational initiatives launched by countries in which the separation between universities and hospitals is still the rule<sup>11</sup>.

However, there are exceptions. In the UK, a number of initiatives led by the National Institute for Health Research (NIHR) have promoted the integration of the previously separated health and mental health trusts and the academic sector. Such initiatives include the Academic Health Science Centre (AHSC) program, Biomedical Research Centres and Biomedical Research Units.

In Singapore, the prime minister has used his direct influence to bring together different ministries and governmental institutions to agree on a structure that truly fosters the integration of hospitals and universities.

Germany has also succeeded in promoting the translational process in technology with the Fraunhofer Institutes and by combining training programs with large companies in a manner that has helped contribute to the economic strengths of that country. Fraunhofer is one of the largest organizations for applied research in Europe, and the Fraunhofer Institutes have a strong link with industry and are focused on generating products for the market. A similar process has now been started in German biomedicine: the country has recently formed new health centers (Gesundheitszentren) for six major global health problems: diabetes, cancer, dementia, and infectious, cardiovascular and lung diseases. The new centers have brought together the five to eight leading universities in each area plus Helmholtz Institutes to form a decentralized network designed to bring basic scientific insights to the bedside. The Helmholtz Society is the largest science organization in Germany, with 17 institutes and numerous national and international collabo-

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rations. Its key mission is to combine research and technology development. In biomedicine, the vision of the Helmholtz center is built on the idea of 'leading science to health'.

Australia is in the process of setting up a network of Advanced Health Science Centres, through the National Health and Medical Research Council. Building on the experience of academic health centers from the US, the UK, Germany, Australia, Singapore and other countries, top universities, medical research institutes and healthcare providers are coming together to improve the way health care is delivered to the community. In addition, it has been proposed that the endeavor to build on the existing body of research and clinical knowledge should be a driving force behind healthcare reform in Australia<sup>12</sup>.

Brazil has a National Science and Technology Institute for Translational Medicine that cuts across institutions, states and areas of science. This institute consists of six member institutes and a core facility divided into four areas (institutional research, human resources, technology for the community and productive sector)<sup>13</sup>. This latter center constitutes a serious effort of a strong emerging economy to boost the development of new treatments and improved clinical care.

The economic and societal importance of integrating the efforts of academia and hospitals should not be underestimated, particularly by emerging economies. Although countries with rapidly growing economies, such as India, China, Vietnam and Korea, are making impressive investments in translational research, boundaries between their hospitals—entirely dedicated to patient care—and their newly built research institutes may foil their budding efforts. The silos that have been established by national bureaucracies represent a major pitfall in translational medicine. This challenge can be met only by a concerted action involving academia, government and, as we discuss next, industry.

### Rethinking academia-industry alliances

Historically, the financial support of the pharmaceutical industry for academic institutions has taken the form of investigator-driven research grants. Industry has now realized the obsolescence of this strategy and is seeking to establish new models in which academic institutions are true partners in the drug-discovery process.

Although specific models vary, they are similar in essence. In a nutshell, pharma researchers obtain early access to the scientific output of academic institutions. The experience of industry researchers is then useful to inform decisions on which projects have a greater

chance of success in the drug-development stage and on what steps need to be taken to, say, sufficiently validate a new target or lead compound. Academic institutions that welcome this input obtain benefits, because the value of their intellectual property increases as it meets the expectations of the pharma industry: the more validated a target, the more a potential license is worth.

The financial muscle of industry also comes in handy to support work that academic researchers have often regarded as uninteresting and routine (such as toxicology and pharmacokinetics) but that is nevertheless crucial for translational research. Partnerships of this sort are in their infancy, and only time will tell whether they will improve the translational process.

Another element of hope in this process is the proposed new National Center for Advancing Translational Science (NCATS) at the US National Institutes of Health. Strongly advocated by Francis Collins, NCATS would become a key catalyst and leader at the translational interface of government, academic institutions and industry<sup>14,15</sup>. The activities of that much-needed new center would include therapeutic target validation, chemistry, virtual drug design, preclinical toxicology, biomarker research, efficacy testing, phase 0 clinical trials (defined as very preliminary studies using as few as one or two human volunteers), treatment rescuing and repurposing, clinical trial design, post-marketing research and others<sup>14</sup>.

### Career advancement

The key battlefield of translational research is the issue of career advancement. A truly translational project involves many steps from basic discovery to a first-in-human clinical trial. Moreover, it is often the case that the description of a compound that will prove to be the basis for the development of an approved drug is published in the highly specialized literature, not in *Nature*, *Science* or this very journal. How are scientists, therefore, to reward the work of researchers who embark on translational projects, which take much longer than, say, tenure deadlines? Are they ready to go beyond the cult of scientific articles in high-profile journals and cumulative impact factors when evaluating young researchers who are being increasingly told to pursue translational research if they hope to 'make it' in science? What is the relative weight that employers should give to patents and to the generation of intellectual property when making major decisions on promotion, tenure and resource allocation? Or should they think entirely out of the box when evaluating translational researchers and come up with a totally new evaluation system?

There is, alas, no obvious way to deal with this elephant in the room. However, a key but underappreciated problem relates to the antientrepreneurial culture that still prevails in many places within the academic world. University leadership in many countries must overcome its traditional reservations toward a capital-oriented translational process, lest novel ideas fail to be translated into new therapies. Universities must foster innovation within their walls by openly rewarding young entrepreneurial members of their biomedical community. These future leaders of translational research might benefit from, say, additional time to be evaluated for tenure, funds specifically aimed at paying for the less exciting aspects of translational research (toxicology or legal paperwork quickly come to mind) or time off the lab to work with industry scientists, learning about aspects of translational research unknown to most academics.

Only this change in culture will foster outcome-oriented translational medicine. Moreover, implementing new ways to evaluate translational researchers and establishing a clear career structure for young academics interested in this path will go a long way toward counteracting the perennial decline in the number of physician-scientists, the ones who are best positioned to bridge the gap between bench and bedside.

At the same time, it will be critical to make sure that entrepreneurship does not run rampant at the expense of scientific integrity. In the past, conflicts of interest have greatly damaged the credibility and reputation of efforts to get academia and industry working together. If we are to foster entrepreneurship in academic institutions, it is therefore crucial that this culture flourish within a climate of full transparency and expert management of conflicts of interest. Mentoring programs for young scientists and the implementation of clear rules to manage potential conflicts will be critical for success.

### Accountability

Accountability is another underappreciated roadblock for translation. Universities and other research organizations are very good at making a case for the need to invest in translational research, and many of the national initiatives that we mentioned in the first part of this text are the result of such successful lobbying. It is, nevertheless, pertinent to ask whether, similar to the case of individual researchers, the right way to evaluate the success of these national initiatives is in place.

This is a relevant question, because the lack of proper evaluation mechanisms can lead to complacency and a lack of rigor on the

way money is spent. It is therefore crucial to develop appropriate criteria for measuring the success of translational initiatives. Investors, which include taxpayers, industry and clinical care institutions, will not maintain their enthusiasm for translational efforts unless there is a return on the investment. Historically, such returns have been poor.

How can this return on investment be best defined? Surely, the traditional yardstick of publishing in highly ranked journals and being listed as one of the top academic institutions in the world is not enough. In fact, one might even provocatively claim that the mere aim of publishing high-profiled papers is the antithesis of a successful translational process—evaluating publications rewards number and high visibility, whereas translational research is slow and the number of new therapies that make it to the clinic is very small.

Academic recipients of translational resources should be accountable for their resource usage. For example, a milestone-based model not unlike the one used by the pharma and biotech industries might be useful to evaluate large translational efforts at academic institutions: if a project fails to reach a milestone agreed upon from the start, one would unsentimentally pull the plug on such a project. Some may argue, however, that this model would interfere with the traditional expectations of academic outcomes, which are more intellectual than practical. This may be so, but translational research ought not to be measured in terms of impact factors, Hirsh indexes and the like, but rather by the numbers of patents applied for, licenses sold, drugs taken to the market, or public-health programs that are brought to fruition to improve human health. If such criteria are introduced into the evaluation process of translational institutes, their approach to science would probably change.

### Training

Returning for a moment to the issue of human resources and the vanishing physician-scientist, we would like to comment on the need to create a global workforce that can truly

build a bridge over the ‘valley of death’ that epitomizes translational research. In our view, novel translational medicine training programs would have to encompass several aspects: (i) training in emerging areas of medicine on the basis of translational paradigms that allow the identification, development and application of the appropriate strategies for a bedside-to-bench-to-bedside program; (ii) an internship or rotation in a pharmaceutical company, aiming at promoting a first-hand understanding of translational research out of universities and at facilitating the formation of true partnerships between industry and academia; (iii) training in regulatory aspects of drug development; and (iv) rotations in academic institutions in diverse countries and across different ethnic environments to understand the global challenges in translational research that go beyond the development of a new drug and that are outside of the scope of this piece—for example, how a new therapy is introduced into a new region and how it becomes the standard of care.

These types of training programs will create a new, global ‘translational physician scientist’ able to move the field forward. Such a person will be eagerly welcomed by both academia and industry to fill leadership positions in the future.

### Conclusions

Improving the efficiency of translational medicine has an unprecedented sense of urgency. The issues that we have discussed here—removing silos, developing new ways to evaluate translational researchers and institutions, rethinking the relationship between academia and industry and developing new training programs for budding translational researchers—need to be at the forefront of our conversations as we try to bridge the proverbial ‘valley of death’ once and for all.

At the same time, we want to make it very clear that the renewed push for translational research that we call for, and the concomitant financial investment that it will require, must

not happen at the expense of basic, investigator-driven research. We fully appreciate that fundamental research must be supported and funded as an integral part of translational science. Basic science should not be neglected, as translational research can simply not be envisioned in the absence of solid fundamental research. So, as we move forward trying to develop new therapies, we must never forget that basic research is always the first stone upon which we are building the translational edifice.

We hope that, as the issues that we have raised in this commentary are addressed collaboratively by new consortia of international translational centers, translational research will move from being the trendy topic that one needs to incorporate into the next grant application to becoming a reality of better and healthier lives for all.

### ACKNOWLEDGMENTS

We are grateful to Dr. Alan Schechter (US National Institutes of Health) for his insightful comments. This work was supported by a grant KFO 252/1 of the Deutsche Forschungsgemeinschaft (to S.R.B.) and the Center for Regenerative Therapies and by a grant of the German Federal Ministry of Education and Research for the German Australian Institute for Translational Medicine AUS 10/802 (to S.R.B. and J.L.).

### COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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