WHITE PAPER

Changing the Mindset in Life Sciences Toward Translation: A Consensus

Georg N. Duda,[1,2*] David W. Grainger,[3] Megan L. Frisk,[4] Leena Bruckner-Tuderman,[5,6] Andrew Carr,[7] Ulrich Dirnagl,[8,9] Karl Max Einhäupl,[10] Stephen Gottschalk,[11] Elliott Gruskin,[12] Christoph Huber,[13] Carl H. June,[14] David J. Mooney,[15,16] Ernst Th. Rietschel,[17] Georg Schütte,[18] Werner Seeger,[19,20] Molly M. Stevens,[21,22] Robert Urban,[23] Alex Veldman,[24,25,26] Günther Wess,[27] Hans-Dieter Volk[1,28]

Participants at the recent *Translate! 2014* meeting in Berlin, Germany, reached a consensus on the rate-limiting factor for advancing translational medicine.

The pace of basic discoveries in all areas of biomedicine is accelerating. Yet, translation of this knowledge into concrete improvements in clinical medicine continues to lag behind the pace of discovery. Stakeholders from around the world who seek successful biomedical translation met in May 2014 in Berlin, Germany, to identify barriers and redefine translation by critically analyzing characteristics of successful endeavors. The charge of this meeting was unique: to focus not on research data but instead on factors that have contributed to or hindered the successful translation of a variety of methods, technologies, drugs, or devices toward patient benefit. Together, the speakers presented different stories that, while varied, were consistent in emphasizing that improved translation of basic research to clinical benefit can happen only with widespread changes in mindset.

Here, we share key factors that could alter scientific, political, and industry perspectives on translation. Only through new ways of thinking and a new set of attitudes will the biomedical community more effectively initiate—and sustain—technology translation. This Commentary is the first in a collection of articles in *Science Translational Medicine* that emphasize the most important themes from *Translate!* and represents the participant consensus statement on challenges of changing the stakeholder mindset. Three articles in future issues will elaborate on major factors raised herein: specifically, infrastructure, funding, and derisking issues in biomedical technology translation to clinical use.

WHAT IS "TRANSLATION"? (AND WHO DOES IT?)

Translation is not the rebranding of old-style approaches that tentatively link basic biomedical research results to possible or potential clinical utility. It is also not simply the pairing of a clinical investigator with a basic researcher. Translation is innovation with a defined, specific clinical practicality and active engagement toward achieving that critical end goal of reduction to practice—a definition that highlights a mindset in which clinical utility, beyond scientific or medical concepts, is key to the process. The business sector often defines innovation as "value-creating novelty." For industry, new biomedical concepts and early-stage products are considered "innovative applications" when they create new health care value and impact. This is often defined by the clinical market, not in research publications. Academic circles define innovation as creative novelty—science or technology that has not yet been reported regardless of its application or commercial impact. These disparate views are often not reconciled in current discussions of biomedical translation.

Effective translational biomedical research addresses a clear clinical need and is typically based on a strong understanding of underlying biological mechanisms. To reach such quality in translation, an iterative approach [either bench to bed to bench or bed (clinical need) to bench to bed and back] is often necessary. Such a strategy goes beyond "reverse translation" and includes first-in-human study experiences, followed by more basic research to decipher the actual mechanisms behind the clinical need and the therapeutic results in humans. Such reciprocal translation allows substantial derisking for new therapies. Merely pointing to a distant goal of translation is not the same as actively building a conceptual, scientific, and then practical bridge to reach that goal. By insisting on improved translational efficiency, technical expert communities must take great care not to subvert or confuse basic and translational principles among experts or society at large.

Don't abandon the basics. Basic biomedical research drives the discovery engine of developed world economies and is essential to gain new knowledge about human biology for next steps in research and technology development. Although basic research may lead to innovative products, it is in itself insufficient for direct translation. Only select basic science discoveries are appropriate for translational consideration. An imaginative, large net must be cast within the research community to best

[1]Berlin-Brandenburg Center for Regenerative Therapies, Charité–Universitätsmedizin Berlin, Germany. [2]Julius Wolff Institut, Charité–Universitätsmedizin Berlin, Germany. [3]Department of Pharmaceutics and Pharmaceutical Chemistry, Health Sciences, University of Utah, Salt Lake City, UT 84112, USA. [4]*Science Translational Medicine*, American Association for the Advancement of Science (AAAS), Washington, DC 20005, USA. [5]Department of Dermatology, Medical Center–University of Freiburg, 79104 Freiburg, Germany. [6]German Research Foundation (DFG), Bonn, Germany. [7]NIHR Biomedical Research Unit, Botnar Research Centre, Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, UK. [8]Center for Stroke Research, Charité–Universitätsmedizin Berlin, Germany. [9]Department of Experimental Neurology, Charite–Universitätsmedizin Berlin, Germany. [10]Chairman of the Executive Board, Charité–Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. [11]Center for Cell and Gene Therapy, Texas Children's Hospital, Houston Methodist Hospital, Baylor College of Medicine, Houston, TX 77030, USA. [12]DePuy Synthes Biomaterials, 1302 Wrights Lane East, West Chester, PA 19380, USA. [13]Translational Oncology (TRON), Mainz University Medical Center, Germany. [14]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, Philadelphia, PA 19104, USA. [15]School of Engineering & Applied Sciences, Harvard University, Cambridge, MA, USA. [16]Wyss Institute, Center for Life Science Boston Bldg., Boston, MA 02115, USA. [17]Berlin Institute of Health, Luisenstr. 56, 10117 Berlin, Germany. [18]Federal Ministry of Education and Research, D-53175 Bonn, Germany. [19]Department of Pneumologie, Universities of Giessen & Marburg Lung Center (UGMLC), 35392 Giessen, Germany. [20]German Center for Lung Research (DZL), 35392 Giessen, Germany. [21]Department of Materials, Imperial College London, London, SW7 2AZ, UK. [22]Department of Bioengineering, Institute for Biomedical Engineering, Imperial College London, London, SW7 2AZ, UK. [23]J&J Boston Innovation Center, One Cambridge Center, 7th Floor, Cambridge, MA 02142, USA. [24]Monash Newborn, Monash Medical Centre, Clayton, Melbourne, Victoria 3168, Australia. [25]The Ritchie Centre, Monash Institute of Medical Research Prince Henry's Institute (MIMR-PHI), Institute of Medical Research, Clayton, Melbourne, Victoria 3168, Australia. [26]Department of Paediatrics, Monash University, Melbourne, Australia. [27]Helmholtz Zentrum München–German Research Center for Environmental Health, Germany. [28]Institute for Medical Immunology, Charité–Universitätsmedizin Berlin, Germany.
*Corresponding author. E-mail: georg.duda@charite.de

capture those few discoveries that might deliver products to the clinical marketplace. Thus, it is critical for researchers, funders, and the general public to understand that fundamental and often purely exploratory basic research is the platform from which major technical advances are launched. The history of technical innovation is replete with examples wherein hypothesis-driven research led to unanticipated, serendipitous observations that then served to open up entirely new fields. Attempts to divert or constrain the basic biomedical research's scope, diversity, or magnitude compromise innovation and possible health care advances.

For better or worse, an "invent and discover" approach is widely used in the life sciences, especially with technology-driven research. This eponymous approach centers on inventing new technologies and discovering new pathways, yet typically avoids the challenge of validating basic discoveries in a clinical scenario and further refining technologies to be reliable, robust, scalable, and capable of passing through regulatory hoops. When inventing and discovering, many researchers believe that they are also translating, when in fact they rely on the passing off of their research findings to someone else for possible future translation. In many of these cases, the most difficult decisions and work remain to be done after discovery: The hand-off requires that careful due diligence be done on the discovery to discern what is valued in translation. Movement of discoveries out of the basic science arena is rare, leaving the speculative promise of impact unfulfilled. According to the U.S. National Institutes of Health (NIH), 80 to 90% of research projects fail before they are tested in humans; and those precious few that do proceed to human studies require up to 15 years to see clinical use (*1*). Nonetheless, few basic research projects likely warrant translation beyond discovery. If the work is truly new, it often begets further discovery research instead, with its own intrinsic merits, before rational translational decisions can be made.

This focus on a basic research–oriented mindset leaves many potent basic research results in a technological no man's land, with translational feasibility and value frequently untested and unvalidated, without addressing the possible extension of further technological capabilities, product vision, and market- or investor-related aspects. Recognizing and addressing these challenges in moving select, promising ideas beyond basic research, while formidable, are precisely what counts in getting discoveries and inventions translated into both products and patients. Passive "hand-off" of early scientific discoveries (for example, by publishing details, hoping that someone else moves it forward) is inefficient and ineffective in vetting new biomedical technologies for translation. And although a deliberate systematic process might yield better results, it is difficult and tedious to identify only those few ideas uniquely qualified for translation.

Whose job is it, then, to bridge this difficult "in-between" step in order to shepherd early discoveries to the next level of translational impact? It is the responsibility of life scientists aimed at making a difference to patients and those who identify themselves as translational scientists. It is imperative that the global research and development community changes its attitudes to assume more active responsibility for ensuring best practices in translation, together with the appropriate structures, resources, and decision trees to make it happen.

A statement in this regard was published a decade ago: "Without mechanisms and infrastructure to accomplish this translation in a systematic and coherent way, the sum of the data and information produced by the basic science enterprise will not result in tangible public benefit" (*2*). This initiated a "call to action" that, in the United States, resulted in NIH's launching of the Clinical and Translational Science Awards (CTSA) program in 2006 and the more recent creation of the NIH National Center for Advancing Translational Sciences (NCATS), which focuses on improving the national translational medicine mission. NCATS currently funds a U.S. consortium of 61 medical research institutions.

In Germany six Centers for Health Research, launched by the German federal government, are addressing the challenge of translational research. As interinstitutional centers with a decentralized structure, knowledge and expertise from the best universities and their teaching hospitals and extra-university institutions are pooled in these Centers. The Berlin Institute of Health (BIH) is another example of the German commitment. The BIH is set up to provide a common research area designed to harness basic and clinical research within a joint approach and with a focus on systems medicine.

We now need an international discussion about who plays what role in producing translation: Who is actually responsible for catalyzing the transformation of useful ideas into products? Who matches clinical unmet needs with the risk of new technology developments? Who moves these products into clinical use or a competitive marketplace? How are these goals best molded into a concrete coordinated and efficient process (*3*, *4*)? The cost of translating every biomedical discovery is absolutely prohibitive and misses the mark, as most ideas are not worth translating. However, missing those few clinically impactful innovation opportunities because of poor selection processes is equally costly. Commercial vetting of academic basic discoveries is central to current translational strategies, a testament to the value and impact of profit-motivated product development. Yet, this process is not foolproof, and the industrial bottom line must balance; for a stable business, the costs of commercial translational failures are borne by the pricing of commercial product successes. While a profit motive is critical to the commercial process, the ultimate metric for translational success is an improved standard of health care and patient quality of life globally. To this end, all participants at *Translate!* agreed that the following considerations are needed upfront to improve translational success.

COME TOGETHER, RIGHT NOW

Because translation involves coordinated hand-offs and transitions between teams with different expertise sets and competencies, a multidisciplinary approach is required throughout in which players meet, transfer knowledge and know-how, and form teams for follow-through (*5*). In this scenario, clinical scientists and researchers in the biological and biomedical sciences and engineering would partner with health care providers, patent agents, industrial partners, and regulatory authorities, aiming for effective transfer of basic findings to preclinical models and then to early clinical validation. Cross-fertilization of ideas, capabilities, perspectives, and seamless interactions across both discipline- and funding-related siloes are essential to assemble the resources, inform of risks and benefits, and streamline the selection process. But all of this is much easier said than actually done: evaluations of translational processes and results have identified a complex matrix of issues that inform future action and

Join forces. Advancing clinical medicine to improve health care value and outcomes requires professional translators—competently trained translational scientists who are educated across the diverse spectrum of translational components and capable of efficient communication with diverse stakeholders across multiple disciplines and areas of expertise required to vet early-stage ideas into products.

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decisions (*3*, *4*). The decision to translate or not to translate hinges on expertise, evidence, resources, and engaged dialogue at each step in the process.

Most basic and applied research is pursued in academic settings, whereas most product development and late-stage clinical trials, regulatory approval, manufacturing, and distribution are accomplished by industry and requisite commercial efforts. Logically, the two efforts should be linked to share expertise and facilitate transfer of ideas. Nonetheless, barriers persist in priorities, culture, philosophy, and process. Current academic structures and career pathways reward individual scientific merit, chiefly based on novelty and innovation regardless of practicality. In most academic institutions, translation-oriented efforts are rewarded less well than the "classical" measures, such as publication output or awarded grants.

Academic reward systems should focus on not only publication quality, number, or journal impact factor, but also tangible impacts of research on medical treatments and patient benefits. Naturally, effective translation requires team-based expertise and coordination throughout the bench-to-bedside-and-back, ideally as a developmental continuum; however, a team-based approach may not lead to clear individual credit and visibility as other, more classical academic pursuits. Junior academics have only a few years to demonstrate their intellectual creativity and scientific impact to obtain tenure and career stability. This timeline is often not commensurate with one that recognizes the benefits from clinical translation, which requires longer development timelines. New academic incentives should be tailored to allow demonstration of longer-term benefits from team-based approaches and provide metrics for promoting and defining career stability. This would encourage the best and brightest minds to engage in translation-oriented basic research and the risks of participating in clinical proof-of-concept trials.

Although a creative, productive scientific career is essential for a junior academic to thrive, an open ear and eye toward other complementary disciplines are frequently necessary for shaping long-term career success (*5*). Current funding mechanisms and graduate-student training and mentoring too often focus on narrow science or technology topics, lacking a big-picture perspective important for understanding the context of moving early-stage ideas toward medical applications and the pitfalls of uninformed or hasty vetting methods. Graduate students and young investigators should be educated in the challenges, rewards, and multidisciplinary nature of translating basic research into medical applications (*6*, *7*). Multidisciplinary approaches in teaching can unexpectedly produce benefits by marrying seemingly unrelated biomedical disciplines in graduate and medical professional training.

Translation also benefits from carefully considering the mindset of stakeholders not directly involved in the research. Clinical and patient representatives and product end-users are essential resources and partners (*3*). Patient advocates can help to generate support for research and first-in-human trials, which best inform the path to translation. Most clinical indications require costly multicenter approaches for reliable and reproducible clinical assessment. Such a goal may be best accomplished with international interactions among scientists, industrialists, commercial authorities, patient advocacy organizations, and clinical investigators.

PROFESSIONALIZING TRANSLATION

Investigators who consistently aim to change standards of patient care should seek training and experience as "professional translators." A key to professionalization is early, dedicated training on the diverse spectrum of translational components. Such a mindset requires (i) strong roots in basic science to realize the importance of mechanism; (ii) an understanding of funding and related barriers across basic, applied, and clinical research and development; (iii) dedicated knowledge about clinical trial requirements and how these follow from preclinical studies and regulatory mandates; and (iv) product development awareness surrounding simplicity, good manufacturing practice (GMP), and end-user requirements. Understanding the risks and adverse, wasteful impacts of improper translational selection is a powerful negative reinforcement to the process. If proper design requirements for clinical trials are included early in preclinical research, guided by informed product design and quality system expertise, unnecessary and often costly product redesigns and trial repetitions can be avoided. Young scientists are then essentially trained on the job to fulfill critical translational requirements.

Professional translators recognize that many preclinical disease models and laboratory scenarios lack the expected predictive reliability to ensure transfer of the concept to a treatment in people within real-life settings (*8*, *9*). This gap results from inherent limitations in common disease models (physiological, pathological, anatomical, metabolic); a lack of understanding of the medical indication or human pathologies being modeled; or poor study design. Systematic reviews of preclinical research have

revealed low internal validity, such as a lack of randomization and blinding or insufficient statistical power, as well as low external validity (for example, modeling diseases of elderly humans in young, healthy mice). These limitations often preclude translation of basic findings to any kind of relevant clinical application. Post-hoc "prediction" of clinical trial failures might help to improve or innovate preclinical models to be more reliable, reproducible, and predictive.

To enhance reproducibility, some journals, including *Science Translational Medicine*, *Science*, and *Nature* (*10*–*12*), and funding bodies, such as the U.S. National Institute of Neurological Disorders and Stroke (NINDS) (*13*), have devised technical study reporting checklists (fig. S1) and publication requirements. Although these requirements are more often imposed at the manuscript revision stage, their implementation even sooner in the process—for example, at study conception (hypothesis generation and study design)— would better transform the mindset of translational scientists to ensure that preclinical studies are designed to yield higher clinical success rates.

Appreciating and discerning that failure is an efficient mode of drug and target selection is also requisite to improving translation and to providing teaching examples for young researchers. Too frequently, basic academic research lacks the inherent ability to fail early and quickly, as is now the common mindset for product-pipeline development in the pharmaceutical industry. Negative results have few publication venues. On this issue, journals are also working to fight this publication bias, with certain journals introducing a "negative results section" and other new journals starting only to report significant negative results (*14*). It is not clear yet if these are equalizing solutions or are just another way to segregate negative results. One mechanism for highlighting the importance of negative results may be to publish them alongside positive ones when the negative results illustrate something fundamental and distinct about therapeutics discovery or human pathophysiology (versus simply descriptive results of a failed investigation).

Unfortunately, failed studies and negative results often have no respected place in an academic portfolio. The tenure and promotion systems do not rate such studies highly, however important they are for accurate reporting and translation. Many in-depth mechanistic analyses lack relevance to human biology, but instead reflect only the experimental context in which they were generated (that is, the lab bench); yet, these studies are viewed more positively than those that report a failed clinical trial in which direct knowledge and insight are learned about human disease, about a new drug's mechanism of action, or about human toxicity. Learning how to fail quickly in a clinically relevant setting, to gain and exploit the knowledge from these failures, and to better educate the community to value failures are essential for professionalizing translation and should be actively embraced, discussed, and rewarded.

INFRASTRUCTURE

Education alone—including professionalization—cannot single-handedly improve translational success. A well-oiled research infrastructure represents a central backbone in a system designed to vet and sort innovations, identify potential solutions that address medical needs and therapeutic concepts, and move even the simplest but most reliable technologies forward, culling from the system those that fail. In some cases, academia provides consultancy hubs, linking industry and academia as a one-stop service with integrated access to clinical needs, cutting-edge technologies, intellectual property management, knowledgeable business development capacity, and even bridge financing. Other solutions hand basic research to an internal business development team that carries an idea through development to product concept, production, and marketing. Industry has also set up its own technology scouting teams to broadly survey emerging, early-stage ideas and steward only select innovations forward through translation. Something can be learned from each of these infrastructures about changing the mindset of stakeholders and promoting a culture of translational medicine in academia; this topic is tackled in-depth in a forthcoming partner article in *Science Translational Medicine*.

ELEPHANT IN THE ROOM

Ask investigators what the elephant in the translational research room is, and most will say "funding." Adequate bridge funding, economic incentives, and market forces are essential to driving and directing successful translation. Current basic research funding [NIH in the United States, the German Research Foundation (DFG), and the Federal Ministry of Education and Research (BMBF) and European Commission across Europe] cannot cover all clinical trial costs (although some new government programs now seek to ease this problem). Industry is eager to take over projects after success in phase 2 and beyond, after substantial derisking has occurred. Despite major efforts by the above-mentioned authorities, funding for early-phase (that is, 1 and 2) development in this riskier gap remains a fundamental challenge. Few resources exist

Never forget the elephant in the room. It's about the money. Lack of funding mechanisms and selection processes for riskier, early-phase development blocks translation.

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for bridging early-stage, unvetted research to more mature, validated technologies. In addition, precious resources should be expended on identifying only the most meritorious concepts to move forward while avoiding the majority of less promising or more costly, riskier ideas.

Once the mindset of translational investigators changes—in other words, once participants have been educated in the various dimensions of translational medicine, are supported by their institutions, and recognize how to develop and vet products for translation—the next challenge is to interest investors and industry in setting up partnerships. Pharma has pulled out of several fields, citing costly struggles with a lack of predictive models and low success rates for drugs in clinical trials (*15*). Derisking and adding value are major challenges. The mindset of a translational researcher should, at the outset, recognize these challenges in engaging industry and be diligent in seeking partnerships and collecting market data. Two future articles in *Science Translational Medicine* will take on funding barriers and derisking.

Go–no go. Responsible product-development parameters modeled from commercial decision-making algorithms help turn red lights green on the road to clinical translation.

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THE RUBBER MEETS THE ROAD

Translate! 2014 brought together voices on the translational process, the keys to success, the regulatory requirements, the clinical needs, the partnering essentials, the value of proper resource use, and the possible (and very real) pitfalls. Every translational researcher is a stakeholder as well as an important cog in the translational medicine machine. With an improved definition of "translation" in place, the interest groups identified, and the tools chosen, the process of changing the attitudes that historically have limited this process can begin. This transformation at academic levels will be accomplished by revamping traditional funding schemes, better partnering with experts in commercial-product translation, adding to academic promotional and performance incentives, altering publishing priorities and reliability, and updating graduate and postdoctoral education priorities.

Another component is establishing stronger partnerships between academia and commerce that better informs the process with industrial development strategy, market opportunities, and critical interactions with both patenting and regulatory bodies. Ideally, this business relationship also provides a direct path to economic forecasts and intelligent financing decisions for product investments. Focus on responsible product investment timelines helps to establish parameters for determine product development "go–no go" points, providing some early derisking guidelines. This essentially mirrors aspects of industrial product selection processes for new technology adoption and makes translation an economically driven process. Discoveries at the bench cannot reach the bedside without the third "B": business. Translation necessitates consistent, intelligent, and prudent financial guidance—knowing when to "pull the plug" on a project (that is, to fail confidently and efficiently)—and the essential manufacturing and marketing resources from business. Partnering early and then continuously with industrial technology transfer experts appears critical to the endgame of improving success in providing innovative products for patient care.

Overall, effective translation will require a change in the scientific mindset to value much more interactive and collaborative relationships. This starts with young investigators who learn to maintain a trained open eye and ear to other disciplines beyond their individual educational experience. Translational investigators should be skilled at properly identifying unmet clinical needs, matching appropriate strategies and partners, and including nonscientific parameters in their evaluation. This approach requires interactions across fields within medicine and scientific disciplines and across the various stakeholder, patient, and interest groups. Success also requires involvement of funding agencies, intellectual property experts, and regulatory authorities as accessible consultants early in the process of innovative thinking and translation-oriented basic research. As the conference title *Translate!* implies, translation is not a passive process, it is an imperative to improve health care value, health outcomes, and patient quality of life.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/6/264/264cm12/DC1

Manuscript checklist

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