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TRANSLATION

Moving medicine forward faster

THE EFFICIENT TRANSLATION OF BIOMEDICAL SCIENCE AND ENGINEERING TECHnology to the clinic is one of the most pressing research and development issues worldwide. Why? Because the path leading from knowledge about basic human biology and disease mechanisms to clinically applicable diagnostics, therapeutics, and prevention measures presents a variety of hurdles and bottlenecks. Here, we attempt to resolve the paradox that more scientific knowledge does not automatically yield improvements in clinical medicine and to explain why the functionality of individual steps in the translation process is paramount.

Success at each step of translation depends first and foremost on close cooperation between the universities and other institutions that conduct biomedical and clinical research and the facilities that deliver clinical care. These different worlds must be brought together in order to bridge information gaps between basic and translational scientists, physician-scientists, and physicians. Spatial vicinity of patient-care facilities and research laboratories facilitates communication, inspiration, and interactive research; therefore, in a decade dominated by e-mail, teleconferencing, and internet-based crowdsourcing, a major challenge for translation is to transcend physical barriers between disciplines, departments, and institutions. Close cooperation is obviously needed, but there exists a wide range of elementary hurdles—conceptual, ideational, and financial. To clear these hurdles, we may make use of new collaboration structures for knowledge integration, new ways of dissecting knowledge-integration blocks, and alternative approaches to education and training.

One solution is the formation of multidisciplinary centers, which guarantees a geographical and organizational proximity of clinical and basic research. In Germany, the German Research Foundation (DFG) has a highly competitive, coordinated program (called Collaborative Research Centers) that comprises institutions that are established at universities and maintained for a period of up to 12 years. These institutions enable researchers to pursue investigator-initiated research programs that cross the boundaries of disciplines, institutes, departments, and facilities. Collaborative research centers facilitate scientifically complex, ambitious, long-term research projects by concentrating, complementing, and coordinating the necessary resources available at a university—a model that is suitable for translational research consortia (www.dfg.de).

The notion of organizational proximity of basic, translational, and clinical research also inspired the founding, between 2009 and 2011, of the German Centers for Health Research, an initiative of the German Federal Government and the Länder (German; Federal States). These health research centers focus on six major global health problems: diabetes, cancer, cardiovascular, infectious, lung, and neurodegenerative diseases. The goal of the centers is to join the best biomedical researchers in Germany, irrespective of institutional and disciplinary barriers. Thus the structure houses university clinics and their departments of medicine and natural sciences as well as extra-university institutions such as research centers of the Helmholtz Association, Leibniz Institutes, and Max Planck Institutes. Similar initiatives exist internationally, such as the U.S. National Institutes of Health's (NIH's) National Center for Advancing Translational Sciences (NCATS), University of Pennsylvania's Institute for Translational Medicine and Therapeutics, Colorado Clinical and Translational Sciences Institute, the Broad Institute of MIT and Harvard, and the UK Medical Research Council (MRC).

The latest example in Germany is the Berlin Institute of Health (BIH), which was founded in 2013. The BIH is being designed so as to provide a common biomedical research arena that will harness basic, translational, and clinical research using a systems medicine paradigm. It is a new type of translational research center that brings together, into a joint institution, the Charité (one of the largest university hospitals in Europe) and the Max Delbrück Center for Molecular Medicine.

Despite the various international translational initiatives, the scientific community continues to face substantial barriers that delay the process of successful and efficient translation and, therefore, health benefits for individual patients and society. These limiting gaps are now being acknowledged, dissected, and addressed.

Communication gaps. The successful integration of the two worlds and cultures of basic science and medical care depends on the ability to communicate, share data, and func-

tion as a collaborative entity. Teamwork is essential, but basic scientists and physicians speak different languages and often do not understand each other. Physician-scientists (*1*), who have been trained in both medical practice and laboratory science, are key players in mediating fruitful communication between the groups.

Research time for clinicians. Physicians at university clinics have increasingly less protected time for translational and clinical research. One central reason is the growing density of tasks. Another factor is that focal areas of clinical research are chosen, in part, on account of their economic potential. This practice does not necessarily suffice, because physician-scientist–led translational and clinical research could provide a much-needed molecular and systems-based understanding of the natural histories of human diseases as well as the entities that alter disease progression in the context of distinct environmental inputs, genetic and epigenetic backgrounds, and comorbidities. Such knowledge may be crucial for effective translation; an in-depth understanding of human physiology and pathophysiology could foster fewer phase 3 failures and forge innovations in clinical medicine.

Proper research metrics. Translational research is a complex process that can take decades. Today, research centers are challenged to improve results and shorten the time between a scientific discovery and resulting practical innovations. Performance assessment can identify improvement areas that will help reduce translational delays. Currently, there are few standard techniques for performance assessment in the translational realm, and the current models used for basic researchers in academia are not entirely adequate; thus new models must be devised, tested, and perhaps implemented.

Although many metrics have been suggested over the past couple of years, a consensus has yet to emerge on what constitutes the appropriate criteria for assessing translational success for researchers and institutions. As a start, we welcome the initiative taken by the German Centre for Lung Research (DZL) on metrics for research programs. These include assessments of research output (publications, number of patents filed, third-party funding, increased collaborations), research outcome measures (such as experimental programs established and targets identified or introduced into clinical studies), clinical programs (initiation of and participation in clinical studies), the completeness and contributions of the infrastructure, as well as researcher participation in networking, data sharing, training of the next generation of translational researchers, and patient outreach. These metrics can be expanded and developed further.

Changing mindsets. One would expect academia and industry to focus on research areas that present the greatest medical needs. But this is not necessarily the case. For example, the pharmaceutical industry has partly shifted its efforts to the most commercially attractive disease areas (*2*, *3*). As a result, there has been a reduction in investment in basic and early-stage translational research (such as first-in-human clinical studies or phase 1 and 2 clinical trials). In comparison with industry, academic biological scientists work to dissect the molecular mechanisms that underlie as yet uncharacterized biological processes and do not necessarily select research areas strategically according to unmet clinical needs. Because academic scientists depend heavily on public funding and, therefore, must comply with their grant review processes to obtain financial support, many scientists are not active in priority areas of industry and may have difficulty in finding industrial partners. As a result, some potential therapeutic advances that stem from mechanistic insights have difficulty being developed.

Industry is now seeking to establish new models in which academic institutions are true partners in the drug-discovery process. The expectations are high that academia can deliver and fill the pipeline gaps. Partnerships of this sort are in their infancy. To improve collaborations between publicly funded research and industry, several models of subcollaborations could be addressed and synchronized—an effort that might lead to a new paradigm of future medicine. These include joint (academic-industry-regulatory) science teams with common goals; academic science–driven drug, diagnostic, and device discovery with industry support; interdisciplinary teams for drug, diagnostic, and device discovery; separate funding streams for joint projects, each with defined milestones for obtaining additional research funding; and systems for project review and selection.

The rather slender resource of public funds for academics and private investment is still a major barrier to progress, because the cost of investigator-initiated clinical trials is inherently high. To increase the success rate of major investments by industry or science organizations, preclinical studies or small first-in-human studies should show sufficient scientific evidence

for proof of concept before the approaches are tested in large clinical trials. The ongoing financial challenges of hospitals as well as different research goals and reward mechanisms can complicate fruitful translational collaborations between clinical and research facilities.

Viable career paths. Last but not least are challenges associated with career advancement and the obtaining of tenured faculty positions in academic medical centers or in university science departments. Current criteria for promotion still rely heavily on individual research output, such as high-impact publications, grants, and invited lectureships. Scientists involved in team-driven translational research projects, which take many years to complete, may not be able to produce traditional evidence of their contributions (multiple first- or last-author publications in top journals, principal investigator on multiple grants) in the prevailing tenure-review time period (6 to 8 years). To ameliorate this situation, institutions may have to ensure that their tenure and promotions systems adequately recognize and evaluate the contributions of scientists conducting translational research. Some academic institutions are already working on moving away from traditional assessment criteria for professors toward new evaluation systems and career structures for young academic scientists (*4*, *5*).

Building sturdy bridges for career advancement will help to attract the brightest and most innovative students in the field of translational medicine. This influx will ensure the development of a new mindset for future biomedical and health research as well as clinical medicine.

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