

MEDICAL INNOVATION

Translational Medicine: An Engine of Change for Bringing New Technology to Community Health

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Bringing a new medical technology from the lab to the clinic is a daunting prospect, but making sure that same innovation is available to the average patient has proven to be even more challenging. Translational medicine is a movement intended to help bench researchers and bedside clinicians learn from each other for the benefit of patients. This goal can best be accomplished if a patient-centered focus is incorporated throughout the R&D continuum and changes are made so that biomedical innovation serves the broadest needs within the shortest period of time. All sectors of the biomedical enterprise must be engaged and committed for these changes to occur. If actions are taken in concert, we should see real change in one generation.

In a perfect world, basic research first elucidates the biological pathway for a disease, then ongoing screening for disease biomarkers, analysis of structure/activity relationships between potential drugs and their effects, or serendipity quickly identifies some likely compounds that will arrest or reverse the pathophysiology of the disease. Next, in vitro testing determines which of the leads has the best characteristics for formulation as a drug, and preclinical testing establishes basic safety and efficacy. Finally, human trials provide the proof of concept and sufficient clinical evidence to allow public health agencies to approve the drug quickly. But this is in a perfect world. In reality, drug development almost never happens this way!

In actuality, just validating that a biomarker is genuinely associated with a particular condition takes 3 or 4 years, and most potential biomarkers are discarded (1). Fewer than 1 in 20 compounds vaunted as promising in scientific publication of early findings makes it into medical practice (2). Last and most vexing, it can take 10 to 25 years for technologies that

have passed the R&D crucible and been acknowledged to work well in teaching hospitals to be commonly applied in the general community setting (3). In other words, most of us are using or receiving “the latest treatments” that were in reality developed not last year, but a generation ago! An example of one such treatment is photodynamic therapy with Photofrin, a light-activated photosensitizer drug, that



Fig. 1. Translational medicine must focus on the patient.

first showed promise in human trials over 30 years ago, received a regulatory approval some 15 years ago, and now is becoming commonly used in the clinical setting, especially for prophylactic treatment of blad-

der cancer and precancerous esophageal lesions (4). In many cases, this lag is unfortunate and unnecessary, and may in fact be unhealthy. The problem is both manifest and inscrutable at the same time. There is, in essence, a problem with the translation of new scientific knowledge into the everyday practice of medicine. Some caution in the process is inevitable and even desirable, but the process has become the problem. It moves in starts and stops, it frequently heads down blind alleys, and the players at one end aren't looking at what's happening on the other end.

Because it is integrative, communicative, and, above all, patient-centered, translational medicine (TM) is the engine of change for transforming this process. TM integrates basic science findings from the National Institutes of Health (NIH) and academic research institutions into the applied research activities at for-profit companies and other commercial enterprises. In effect, it brings together knowledge and expertise that are beyond the ken and capacity of any single company, institution, or investigator. It does this by attempting to create a common language for effective and productive communication among the various stakeholders, and by encouraging programs within the different institutions to foster the exchange of technologies and ideas. It has also led to the creation of a host of new training and degree programs at academic centers to teach a new cadre of clinicians and researchers how to think beyond the traditional—and outdated—boundaries of institutional scope, and to focus on one of the ultimate goals of basic research: improving health care by bringing newer and better treatments to the patient. To be successful, TM must put in to action the ethos of its operational mantra of bench-to-bedside (...and back) communication by adopting an emphasis on the person in the bed—the patient (Fig. 1).

The original impetus for the TM movement was concern that the speed at which new basic medical research findings were leading to important advances in health care had dramatically slowed in recent years (Fig. 2). In other words, fewer cures were resulting from

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the explosion of scientific knowledge about the cellular and physiological mechanisms of many debilitating and fatal diseases. Of equal concern was the fact that clinicians, unfamiliar with the capacities and capabilities of basic science, were not bringing

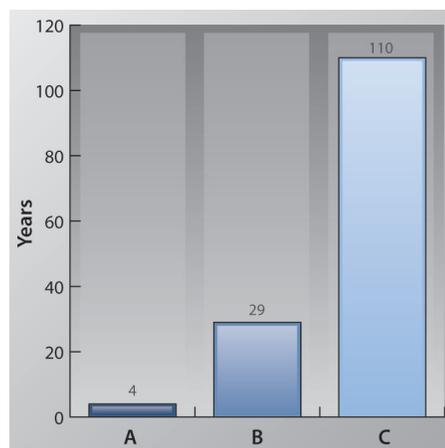


Fig. 2. Translational lag. This figure shows the extreme range in the translation lag for 32 promising medical interventions first cited in major science journals from 1979 to 1983 (2). (A) Time from patent to the first highly publicized clinical trial results for two HIV/AIDS drugs among the 32 discoveries analyzed. (B) Mid-point of range for all 32 discoveries from the earliest publication to the first highly cited article. (C) Mid-point of the interquartile range for all 32 discoveries from the first discovery to the first specific human use.

their clinical findings and fruitful insights to the attention of research scientists, thus impeding the latter phase of the bench-to-bedside paradigm.

A number of the first realizations to emerge underscored something of a paradox in the R&D process: Basic research was very good at uncovering the workings of biological pathways, just not necessarily human ones. There were problems in bridging the gaps between results from *in vitro*, *in vivo*, and *in silico* experiments. Animal models were often not predictive enough for human disease [famously demonstrated recently in the TGN 1412 trial in which six human volunteers suffered multi-organ failure despite the fact that monkeys had been administered a dose 500 times higher without apparent ill effect (5)], or were practically nonexistent for some biotechnology approaches [for example, monoclonal antibodies that target human proteins often have specific effects in humans that are not conducive to animal testing (6)],

and *in silico* modeling was promising but still premature.

Thinking began to change when the Human Genome Project (7), which focused the attention of clinicians on molecular biology, opened up the possibilities of personalized medicine and refocused science on the human laboratory. Other drivers of patient-centered focus played a role as well. One of these was the growth of patient empowerment, evidenced by the recognition of patients as consumers, who have choices about what products and services they will use and will pay for, either directly or indirectly. Patients are also players politically, through the expanding influence of patient advocacy groups, who not only lobby Congress and other decision-making bodies but actually are increasingly important in the innovative process, affecting R&D both operationally, through patient recruitment, and financially, by funding research (since 2000, their financial support of drug R&D has increased 13-fold) (8).

In addition, patient-reported outcomes (PROs), comparative effectiveness research (CER) (which seeks to determine whether a particular treatment is better than the alternatives), and patient preferences, especially for determining the success of home health care and disease management initiatives, are becoming increasingly important in clinical research. Consonant with this movement, the opportunities for the medical community to communicate with patients, and for patients to become informed and to communicate with other patients, via the Internet, support groups, and chat rooms, have increased dramatically with the onset of the information age and electronic connectivity. This phenomenon has several implications for TM: As patients become better informed, they are becoming more engaged in their own health care, giving clinicians better feedback, and demanding a greater voice in what types of treatments and services they receive. As the patient/physician relationship changes, so will clinical practice. Patients will increasingly demand access to the latest medical technology, or a very good explanation why it is not for them.

How will TM help bring about this change? The close nexus of TM and community health was first recognized in the health literature about a decade ago. It was said that both community health and TM share a common core of collaboration, with TM resting on the interaction between

bench scientist and bedside clinician, and community health relying on partnership and communication among constituents of the public sector, including clinicians, community health institutions, and patients (9). In the early 2000s, Elias Zerhouni, former head of NIH, expanded the definition of TM beyond bench-to-bedside research to encompass a goal of patient-oriented and population research, and translating discoveries to facilitate their use in the community (10). The plan for implementation of these efforts was detailed in the NIH Roadmap and included both the creation of centers of translational research at each of the NIH institutes, and the launching, in 2006, of the Clinical and Translational Science Award (CTSA) program. To date, nearly 40 CTSA-funded academic centers have been established, with the goal of having 60 centers funded by 2012. One of the key areas of support provided to CTSA centers is access to technologies and resources important to translational research, such as mass spectrometry, imaging, ultrasound, positron emission tomography, gene expression and proteomics data, and experimental cell and gene therapies (11). Zerhouni's vision was that CTSA-funded centers would address the transfer of knowledge between basic science and clinical medicine, and between clinical research, medical practitioner, and patient (12).

Meanwhile, in Europe, the National Institute for Health Research within the UK's National Health Service established the Academic Health Science Centres to integrate research, teaching, and clinical work under a unified governance model to improve patient outcomes. A prominent feature of these Academic Health Science Centres is a Patient Advisory Board that seeks to identify problems, concerns, and weaknesses, and offer suggestions to improve the quality of clinical care (13).

In concert with this momentum in the public sector, many major pharmaceutical companies in the private sector have formed TM units, whose goal in the broadest sense is to create a more direct connection between basic research and patient care. As the head of oncology at the international pharmaceutical company AstraZeneca put it: "We want to address the question of how our drugs actually work in man" (1). This aim is being pursued by conducting first-in-human studies (during which a drug is tested in humans for the first time) earlier in the development process of a promising

compound, by using healthy volunteers instead of patients to test efficacy through experiments instead of in time- and resource-consuming clinical trials. For example, there is an experimental medicine TM consortium working on, among other projects, an anxiety challenge study. In this study, anxiety is first artificially created in volunteers with a pharmacological agent in a laboratory setting and then the responses of the volunteers to a putative therapeutic agent are analyzed (1). Another approach associated with the expedited use of new drugs in human volunteers is the use of microdoses, which is considered to be acceptable on an ethical basis because these doses are so minute as to be pharmacologically inactive.

Payers are also driving the adoption of TM concepts. Philosophically, they favor an approach called the Medical Home concept, which focuses on a whole person rather than a single disease or organ. The emphasis is on personalized care and decision-making by patients in partnership with their physicians (3). On the practical side, payers are requiring more and more CER and PRO data on new and standard treatments, which has led to the rise of patient registries: databases containing information on patients with specific conditions. Patient registries have several advantages over randomized clinical trials (RCTs): (i) They can follow patients over a longer period of time than RCTs; (ii) they better reflect the management of a condition in its particular health microenvironment; (iii) they evolve over time, along with new data and changing influences on clinical practice; (iv) they bring into focus the impact of co-morbidities and concomitant treatments on patient outcomes; and (v) they can be effectively linked to electronic health records, patient questionnaires, and other complementary data (14). Also, patient registries have much less susceptibility to the usual factors limiting the scope of patient studies, such as time, geography, size of the sample, and participating health care providers. For example, the REACH registry for atherothrombosis encompassed over 60,000 patients and 4 years of follow-up, included patients in 44 countries, and involved close to 5000 health care providers (14).

What does the future hold? Clearly, the forces of TM and patient-centered medicine are well met and well meshed, but many obstacles are yet to be overcome.

Conflict-of-interest concerns threaten to hold the progress of medicine at bay. Oversight committees, laws, and professional guidelines are burgeoning. The proscriptive approach (regulating certain behaviors rather than addressing the root causes), however, is thought to be insufficient to help the changeover to patient-centered medicine for the following reasons (15): (i) It is reactive and can only identify problems, not anticipate them; (ii) it cannot encourage prospective researchers to select a TM path or adopt a patient-centered philosophy, as these are the purview of individual conviction and conscience; and (iii) it risks shifting funds and personnel away from patients and toward compliance for compliance's sake (15). For example, a complete prohibition on handing out free samples could impede doctors practicing in rural settings from helping the working poor in a way that maintains the dignity of their patients.

Resources could be better directed toward three intransigent problems at the heart of the transition to patient-centered care. First, patients need to be emancipated from paternalistic physician control in valuing which health preferences are important, but this change needs to occur in a way that strikes a balance between subjective needs and objective facts (16). Second, many clinicians, especially those working at the level of tertiary care, feel increasingly that medicine in Western industrialized countries has lost much of its focus on patients and is mostly preoccupied with highly expensive treatments and services that are tangential to the true quality and dignity of human life (16). Third, lack of access to medical technology plagues health care systems worldwide, not only in developing countries but also in developed countries; for example, one-third of the U.S. population lives in rural or small urban areas often dominated by just one hospital (17). Lack of access, however, involves multiple failures at the global, national, and local levels and can rarely be addressed by simply throwing more money or materials into the gap (18). New treatments and modes of delivery must be developed that take into account limitations in funding, infrastructure, and government willingness to pay. These goals can be accomplished without a massive reordering of the biomedical enterprise or reallocation of resources, by refocusing currently available

intellectual and investment capital (such as patient advisory boards; CTSA partnering programs; or powder technology for vaccines, an example of an advance that should expand access to health care in developing countries).

What would it take to achieve these goals? At NIH, small increments in CTSA funding over the long-term; at pharmaceutical companies, a culture shift out of the laboratory and into the community setting; at medical schools, more training programs focused on the commercial aspects of medical research; at academic medical centers, dedicated outreach programs up- and downstream, to pharmaceutical companies and the community; at community health centers, recognition that they are a lynchpin in the process of translating research from bench to bedside; and for patients, awareness that they are the most crucial stakeholders of all and that they need to be active participants, not passive recipients, in the health care system. Small changes across a variety of niches could have a large impact on the health care ecosystem, and within a generation could help us shed the status quo while shaping a new era of patient-centered care.

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