TRANSLATIONAL RESEARCH

Changing Models of Biomedical Research

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Thanks to the revolutions in information technology, human "-omics" research, and intricate medical device development, academic health centers (AHCs) now have an unparalleled potential to become translational engines that both generate basic science advances and then translate them into human studies and, ultimately, into improved health care. However, AHC infrastructures have traditionally been optimized to foster basic research. Now modifications must be made to meet these expanded roles of AHCs, from providing fundamental biomedical insights to first-in-human interventions and, if warranted, to larger randomized clinical trials. Eventually, AHCs must integrate these improved treatments into patient care. Challenges to this process have been defined by the Institute of Medicine. Building the appropriate infrastructures for human investigation and stabilizing the careers of young physicians essential to these translational events have become critical needs that will require systemic investments if AHCs are to respond to these biological revolutions and fulfill their promise.

HISTORICAL PERSPECTIVE: THE "BUSH MODEL" OF BIOMEDICAL RESEARCH

Toward the end of World War II, U.S. President Franklin Roosevelt requested the director of the Office of Scientific Research and Development, Vannevar Bush, to develop a vision for the future development of the nation's science. In the resulting landmark report, *Science: The Endless Frontier* (*1*), Bush laid out a bold plan for America's biomedical research, a vision that has provided a fundamentally stable blueprint for the nation's scientific efforts over the past 64 years. Bush's model placed the highest value on investments in basic science, which was envisioned as the wellspring of a cascade that ultimately concluded with testing in humans (Fig. 1). Building on the previous advances in physics and chemistry from the first half of the 20th century, the robust framework provided by the Bush model engendered advances that include the harnessing of nuclear energy for medical diagnostics and therapeutics and laying the groundwork for the chemical basis of pharmaceutical development. In the fostering of basic science innovation, the Bush model has served our nation well. However, in terms of transferring these basic advances to improvements in medical care, the Bush blueprint now requires more in-depth analysis (*2*).

The Bush model has had profound implications for science policy, the organization of biomedical research communities, and science funding both locally and globally (Fig. 1). For example, the model logically suggested that medical schools and academic health centers (AHCs) should preferentially recruit basic scientists and that their careers be well supported by generous allocations of research space, facilitated promotions, and prestige. An unintended consequence of the Bush model was that human research became relegated to a far downstream component of the scientific discovery process, essentially serving as little more than proof of a given scientific principle, rather than as either a means of defining new science or a real opportunity to influence health care. This final step of the translation of basic science discoveries to humans became viewed as more of a challenge in execution than an exercise in innovation. Thus, these functions were largely relegated to academic hospitals, which were populated mainly by physicians, many of whom had studied in basic science laboratories but left them for a variety of reasons. Hospitals and physician researchers thus were viewed not as the drivers of scientific discovery but rather as its end point, making academic investments in human investigation and its infrastructure scant.

A second feature of the Bush report that had a profound impact on AHCs was its ground-breaking suggestion that the public should fund the nation's scientific endeavors. The ultimate consequence of this recommendation was the founding of the National Institutes of Health (NIH), which became the major funder of AHCs and their affiliated institutions in the United States. This funding fueled an explosion of basic research in these centers that previously had focused solely on care delivery, particularly to the disadvantaged. The resulting NIH budget funded more basic than clinical research by a wide margin (~2:1) that has been stable for some time (*3*) and changed the face of our universities in general and AHCs specifically. Government funding converted their status from almshouses that provided medical care for the indigent at the beginning of the 20th century into dynamic research centers that spawned numerous Nobel Prizes by its end.

A third consequence of the Bush model was that the translation of basic science advances into drug development, testing of drugs in humans, and their fashioning into medications became largely the responsibility of the pharmaceutical industry (Fig. 2). However, this translation required the well-

Fig. 1. Policy Consequences of the Bush Doctrine

Issue	NIH	Medical schools	AHCs
Emphasis/ investments	Basic research funded 2:1 vs. clinical research	Facilitated basic research promotions and space allocation	Facilitated basic vs. clinical research space allocation and core infrastructures
Recruitment and retention	Basic researchers	Ph.D.'s nearly exclusively	M.D./Ph.D.'s => ? clinical investigators of the future
Clinical research	Intramural programs and draft	Nonexistent	Largely relegated to industry and pharmaceutical trials
Populations	Import patients with rare diseases; no health care system affiliations	Left to AHCs	Left to industry Proof of principle General Clinical Research Centers (came later)

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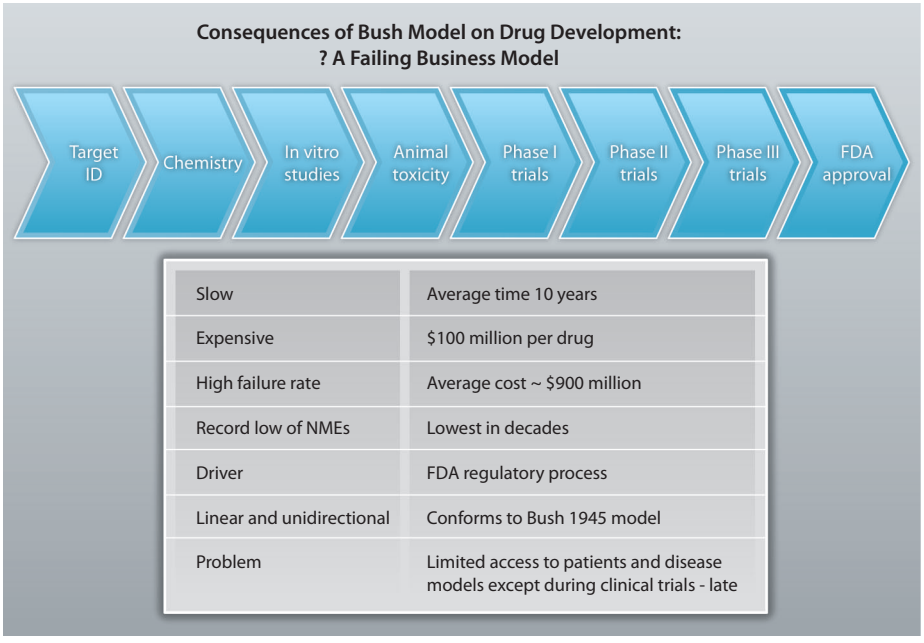

Fig. 2. Vannevar Bush model of science as applied to drug development. NMEs, new molecular entities.

phenotyped patient populations found in AHCs. Participation of these patients in drug development was supported by a transient, study-specific infrastructure and by collaborations focused on the drug approval process, with no abiding commitment to the support services required for the long-term health of the drug development industry. This culture resulted from the absolute requirement for drug testing in humans with well-characterized diseases [which is regulated in the United States by the Food and Drug Administration (FDA), established by President Theodore Roosevelt in 1906] and from the scale of drug development costs and pharmaceutical competitiveness. This model has represented the state of affairs in the United States for the past six decades (Fig. 2).

PROBLEMS EMERGE

The past three decades have produced substantial evidence that the clinical research infrastructure and the human components of translational research in AHCs have been poorly served by these Bush policies. In their newfound positions of authority and national prominence, basic scientists were reluctant to share resources with hospitals and clinical investigators, and universities neglected to invest in the infrastructure required to facilitate the complex and expensive process of translating basic science advances to studies in humans. Several Institute of Medicine (IOM) reports produced since 1980 documented the consequences of this skewed allocation of resources within universities and AHCs, which gave rise to bottlenecks that hindered the efficient translation of basic science into medical practice (so-called "translational blocks") (Fig. 3) (*2*, *4*–*8*). Still, little was done to address these difficulties. Consequently, problems in the recruitment, training, and retention of clinical investigators within academic medicine deepened (*6*–*8*). In his Presidential Address to the American Federation of Clinical Research in 1977 (*9*), Sam Thier first referred to clinical investigators—who were absolutely required for human testing of any biological advance—as an "endangered species," a designation that became popularized when used by NIH Director James Wyngaarden in a subsequent publication (*10*).

THE TIPPING POINT: THREE IMPORTANT CHANGES OCCUR

The appearance of powerful new clinical investigative tools. Beginning in the 1980s, several major advances began to change this status quo. Novel genetic technologies were applied directly to human DNA, allowing scientists to begin to unravel the molecular triggers of rare diseases (*11*–*25*) and learn powerful new truths about their underlying pathophysiology. These successes led to the concept of sequencing the entire human genome (completed in 2003) to discover the basis for all inherited disorders, an endeavor that spurred the development of potent new analytical tools that empowered studies of the genetic underpinnings of common human diseases. Perhaps the most striking generalization that emerged from these studies was that the genes and associated biological pathway abnormalities unearthed by the new genetic and genomic tools frequently were not the traditional ones being investigated by basic scientists, who had based their approach largely on late-stage disease phenotypes that they then modeled in experimental organisms.

Thus, the study of humans brought truly novel information to the attention of basic scientists, making the human a valid experimental organism for discovery research, while also providing new hope to patients with devastating diseases. This fundamental change in the direction of innovative information flow (now from bedside to bench) was the first element of the tectonic shift that is now occurring in medical science. For example, many of these newly discovered genes, such as the *huntingtin* gene, which can harbor a mutation that causes all cases of Huntington's disease, were previously unknown to basic scientists (*23*, *25*). Other genes, such as the *superoxide dismutase 1* gene, which is mutated in certain forms of amyotrophic lateral sclerosis, encode well-studied proteins that had not yet come to the attention of scientists in the field of neurodegeneration (*22*). The discovery of new disease triggers and their respective biological pathways not only inspired astute basic scientists to refocus their research programs but also revealed potential new therapeutic targets for drug development.

The engineering of intricate new imaging tools, such as functional magnetic resonance imaging, opened yet another avenue to early disease diagnosis and investigation, which, like molecular genetic studies, reinforced the concept of human disease as a potentially protracted pathogenic process whose clinical expression is only a late-stage phenotype. Together with sensitive imaging techniques, the so-called "-omic" technologies (genomics, proteomics, and metabolomics), which were derived from the Human Genome Project, clearly demonstrated the importance of clinical phenotyping, unbiased molecular profiling, and human genetics, while also highlighting the shortage of scientists trained to investigate the human research components of these new and powerful pathways of scientific discovery.

IOM's Clinical Research Roundtable. The second major contextual change was the formation of the Clinical Research Roundtable by the U.S. IOM in 2000. For the first time in U.S. history, this group convened all health care stakeholders to deliberate the paradox that was becoming apparent to all observers. On one hand, as a result of the advances described above, human studies yielded a burgeoning collection of basic science discoveries. In parallel, a growing shortfall in infrastructure, personnel, and policies interfered with the translation of these discoveries into advancements in clinical medicine. The Clinical Research Roundtable comprised basic and clinical scientists, health care providers, insurers (both governmental and private), AHCs, patient groups, the business community, government and regulatory agencies (the FDA, NIH, Centers for Disease Control, and Veterans Administration), the pharmaceutical and biotechnology sectors, and the media. This multidisciplinary group met for 4 years, during which all constituent groups registered similar complaints and expressed frustration over the general untimeliness, rising costs, and decreasing efficiency of important basic science advances being "lost in translation" into new therapies for human diseases. Each group also decried the fact that these problems were occurring in parallel with spiraling health care costs, increasing NIH budgets, and considerable press coverage touting the advances in basic science without corresponding improvements in health care.

The group authored two seminal papers in the *Journal of the American Medical Association* (*2*, *26*), the first of which clearly enumerated the component blocks involved in translating basic science into superior therapies. The current translational system was inefficient, they observed, in part because it was a disjointed cottage industry composed of individual silos that communicated poorly. They proposed a more modern system to replace the currently fragmented model of inefficiently interdigitating components, each viewing itself as performing a discrete role rather than functioning as part of a continuum. To frame the direction in which the group thought a new system should evolve, they coined the aspirational term the National Clinical Research Enterprise (NCRE) (*26*). Ideally, this new ensemble was designed to bear the collective responsibility for translating basic advances into new treatments (*26*).

The Clinical Research Roundtable also characterized two major translational blocks (Fig. 3). The first was the movement of a basic research finding into the first-in-human level of clinical testing (*2*). Empowered by the rapidly growing repertoire of tools from the Human Genome Project, all participants recognized that this flow was becoming increasingly bidirectional. Studies in patients, families, and their tissues and DNA were now able to provide as much novel information to basic researchers as basic science advances provided to clinical researchers. These changes created a new opportunity to speed the scientific discovery process and avoid communication and cooperation inefficiencies. NIH provides most of the funding to address this first translational block. Moreover, the early steps of translation occur almost exclusively within AHCs, which assumed the role of translational research engines. Information gained from this initial innovation step empowered the subsequent harvesting of these truths by biotechnology and pharmaceutical companies as drug therapies, through a subsequent series of coordinated drug development steps and, ultimately, randomized clinical trials.

The second translational block (Fig. 3) was then defined by the Clinical Research Roundtable as the failure of new therapies to be swiftly incorporated into routine medical practice. Examples include the lack of widespread use of aspirin, β blockers, and angiotensin-converting enzyme inhibitors, all of which were shown in large randomized clinical trials to save the lives of patients who had suffered myocardial infarctions (*27*). This "implementation gap" was closely intertwined with the evolving complexity and spiraling costs of the health care delivery system.

In a second paper, the Clinical Research Roundtable suggested several novel remedies for these two major translational blocks (*26*). The first was a requirement for all current health care participants to form, fund, and actively participate in a new representative national effort (called the NCRE) to address these blocks. Only such a central body with a budget contributed to by all, the group reasoned, could sustain the fruitful discussions and strong sense of shared destiny that had developed during the Clinical Research Roundtable's collegial interactions. All felt equally strongly that the NCRE should not be governmentally based, because nearly all solutions required public-private partnerships, which are difficult to establish and maintain under a solely governmental aegis. Although many stakeholders in the drug development process attempted to enhance the efficiency of their internal

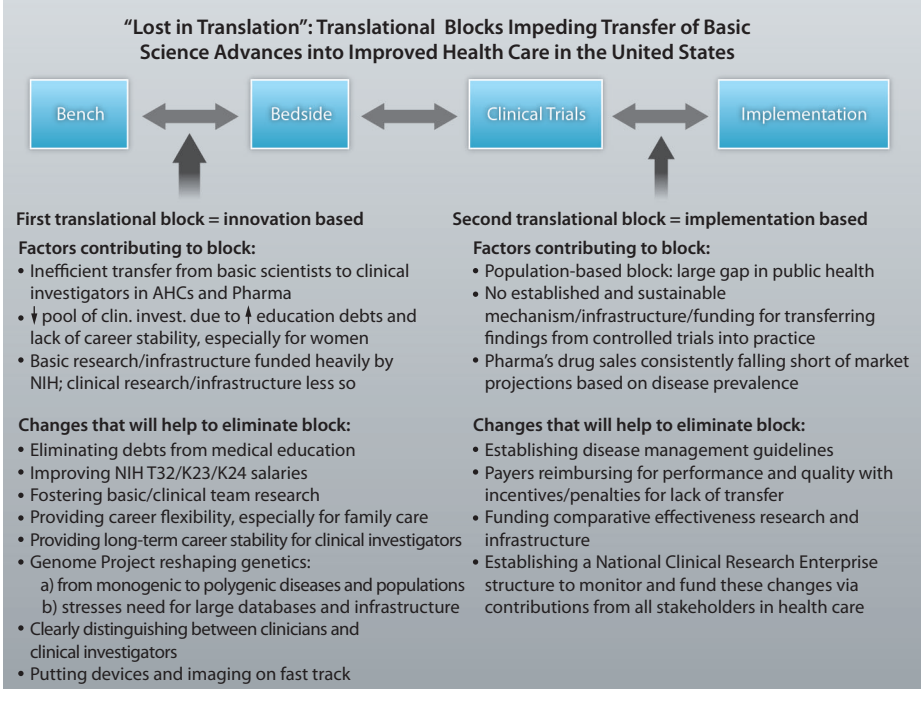

Fig. 3. Continuum of clinical research mapped on translational blocks.

translational processes, others were prohibited from doing so legislatively (such as the Centers for Medicare and Medicaid Services) or viewed such investments in infrastructure as reducing their market competitiveness (for example, the insurers). Nonetheless, all stakeholders agreed on the need for a bold, centralized, national-scale effort. The cost of continued noninvestment was simply too high.

Lack of infrastructure: NIH's response. In recognition of the dismal translational track record, NIH acted to correct the negative trends by establishing a spectrum of research career awards for young and midcareer clinical investigators [(K23s and K24s]; training programs at the master's degree level in clinical research (K30s); a loan repayment program for scientists choosing careers in human research; and the establishment of a new network of Clinical and Translational Research Centers (CTSCs) designed to replace the older General Clinical Research Centers, whose programs were increasingly viewed as ineffective and provincial in nature. Although it is still too early to judge the results of this transition, these CTSCs potentially represent the most dramatic change in the infrastructure of AHCs to facilitate support of clinical research in U.S. history since the original establishment of the General Clinical Research Centers over 40 years earlier, and they set the stage for dramatic remedies for the translational blocks.

FUTURE POLICIES IN BIOMEDICAL RESEARCH

Although the growing importance of genomics-based investigative tools and approaches clearly points to a bright future for biomedical research, it also has profound implications for future policies within AHCs (Fig. 4). Given their constellation of well-characterized patient populations, strong historical investments in basic research and its infrastructure, and deployment of the limited number of physician-scientists who are well trained in the techniques of human research, AHCs should become the major translational engines of our nation's biomedical research investment in the 21st century. This is the moment for AHCs to assume such leadership (or not). Like so many other chances for leadership, however, this opportunity knocks at the doors of the AHCs accompanied by many less-attractive companions, including a societal financial crisis, a recession, reduced philanthropy, rising health care costs, and urgency for health care reform with considerable associated controversy.

Fig. 4. Policy Consequences of the New Model

Issue	NIH	Medical schools	AHCs
Emphasis/ investments	Increases in clinical research funding	Revamp promotions and space allocation to reward multidisciplinary teams	Incentivize team research Foster women's careers Fund clinical research cores
Recruitment and Retention	Basic AND clinical researchers	Ph.D.'s and clinical investigators in departments	Clinical investigation + basic science collaborations = keys to the future
Clinical research	CTSCs * Intramural programs Repay ALL loans Adjust K23/24 salaries	Key teachers and thought leaders	Recognize that clinical research is key to their future Foster basic/clinical research collaborations and teams
Populations	Import rare patients Link with clinical trials Link with AHCs	CTSCs, epidemiology, genetics, OMICs, and bioinformatics	CTSCs Core labs Team research Career flexibility

* CTSCs, Clinical and Translational Science Centers.

The infrastructure for recruiting, consenting, phenotyping, and perturbing the physiology and pathophysiology of patients and normal populations is unique to the environment within AHCs. The scale of investigations that adhere to the postgenomic model of clinical and translational research requires considerable investment in large-scale human subject research capabilities and information technology, such as electronic patient registries and consenting processes, vast biological repositories, core scientific platforms for analyses, rules of governance, and data sharing. In addition, such studies require career stabilization for the multidisciplinary teams required, all of which are not yet well established in the research community. Our current academic reward system provides incentives chiefly for principal investigators with novel ideas. The leaders of AHCs are only now beginning to design reward structures for the building, sustaining, and functioning of the multidisciplinary scientific teams required to achieve success in translational medicine. In particular, polygenic disorders, clinical trial design and orchestration, outcomes research, the assembly and analysis of vast amounts of data, and the accumulation of large numbers of samples and their corresponding phenotyping all are daunting logistical challenges that demand a far more robust infrastructure for human research than is currently available in any single AHC, a reality that strongly argues for networking capabilities across like-minded institutions. Early successes in investigating polygenic disorders via genome-wide association studies and large-scale clinical trial networks have occurred only when dedicated resources were assembled by individual clinical research groups with longstanding commitments to specific diseases or in countries where large national epidemiological infrastructures exist. These infrastructures have enabled the accumulation of substantial, well-characterized populations, often over decades. National registries associated with socialized health care systems, specific ethnic or disease populations or foundations, and/or populations in which familial relationships have been characterized are especially well positioned to capitalize on postgenomic and bioinformatics discovery tools.

Such studies clearly argue for a future realignment of centers that can multiplex: that is, focus simultaneously on several patient populations, genes, and diseases across several centers. Over time, a robustly funded CTSC network may well be a part of this solution. Finally, and perhaps most importantly, these changes require a fundamental redefinition of the relationship and shared responsibilities between physician-scientists, our patients, their patient

groups, and society as a whole. Without a view of true partnership between AHCs and their patients, all of the infrastructure in the world will not be enough to achieve our goals.

These changes that are required in our scientific landscapes should not be allowed to drive wedges between basic and clinical researchers. On the contrary, the transformations must be framed in such a fashion that they serve as catalysts to building ever tighter working relationships across diverse research disciplines. Dual mentorships and co–principal investigators, and teams with shared goals and destinies, need to become the norm. That said, some realignment of resources within AHCs must occur once the impact of these changes is fully understood by senior leadership. Whenever such a rebalancing occurs, resistance and opposition invariably follow, especially when it occurs in tight fiscal environments and is accompanied by a failure to explain that this is the tide that will ultimately lift all ships. In environments that tend to focus on zero-sum analyses, such opportunities can be divisive. These resistances can be addressed only by airing these strategic issues openly; viewing the changes as new opportunities to alleviate human suffering; and building a collective will to act.

Finally, from these strategic discussions, a new resolve must emerge from the AHC leadership to establish, support, and reward the new interdisciplinary teams required to address the evolving complexities of the translational processes. This shift will require a critical rethinking of the criteria for academic promotion that addresses the complex issues of career independence versus synergistic interdependence and the progressive loss of well-trained female faculty members at every level of their training (*6*, *7*).

NIH instituted a widespread series of helpful programmatic changes nearly a decade ago, but the key programs (K23s, K24s, K30s, and the loan repayment program) need to be contemporized. Salaries (those for K23s in particular) are now substantially out of date. Young scientists who are well into their 30s, often married with children and attempting to repay their education loans, cannot sustain careers on the current K23 stipends. Similarly, the loan repayment program offers loan repayments of only $30,000/year for 3 years, whereas 22% of graduates now leave medical school with debts of $200,000 and 39% have debts larger than $138,000 (*28*). If these crucial programs are to remain successful, they need to be adjusted periodically to the scientific opportunities at hand.

The biotechnology and pharmaceutical industries' support of AHCs and their clinical research enterprises through sponsorship of individual projects currently is aligned strictly with highly focused corporate goals. This support generally does not contribute materially to sustaining the training, infrastructure, and career pipeline that are fostered by AHCs and that companies ultimately rely on for successful completion of their missions. Industry sentiments that such attributes are supported by their governmental taxes may have some truth but fail to reflect the fact that many companies do not pay their full complement of taxes, as a result of the vagaries of the complex U.S. tax system. Because the long-term successes of industry require contributions from AHCs, such as basic science innovation, professional training, access to well-phenotyped patients, FDA review of their studies, and the education of physicians about new therapeutic advances, it is in the best interest of companies to enhance their support of AHCs. The magnitude of the required investments is often small enough to represent rounding errors in industry budgets, and, with the increasing conflict-of-interest restrictions imposed on academic researchers by AHCs, a timely review of industry's commitment to investments in AHCs and their infrastructure is warranted.

CONCLUSIONS

For biomedical research, it is simultaneously the best and worst of times. The tools for discovery have never been more powerful. Their speed, swiftness, and accuracy are astonishing. It is equally clear, however that the infrastructure and resources of the NCRE have probably never been less well-proportioned to the opportunities at hand. This is not a surprising truth when one realizes that the current infrastructures were established more than 50 years ago for an enterprise that was only a fraction of its present scale and had little of its current power, complexity, and regulatory requirements.

Within academic centers, most new investments remain targeted to basic science facilities. The power of these basic science enterprises remains enormous, and continued investment in them should remain a high priority for AHCs. Thus, although a new model of biomedical research is developing, it should not be viewed as replacing the old one, but rather as offering a complementary dimension for innovation and scientific opportunity. To capitalize on these opportunities, however, AHCs need to better balance the allocation of new resources between basic and clinical research infrastructures. Paramount is the recruitment of our most promising physician-scientists into clinical investigation and their training in contemporary techniques in a fashion that matches the rigorous training of basic scientists. Partnerships between basic and clinical researchers at every level—including didactic programs and co-mentoring of young physician investigators by both basic and clinical scientists—will be a winning path to our collective futures and ensure mutually stabilizing career paths for both, especially those skilled at interacting with their counterparts.

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