

Obstacles facing translational research in academic medical centers

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ABSTRACT Over the last quarter of the 20th century, there has been a boom in biomedical research discoveries that, for the most part, has not been successfully exploited for improving medical therapy or diagnosis. This lack of success is surprising because there is a broad consensus within academic medical centers (AMCs) that a primary mission is to move scientific discoveries into meaningful clinical outcomes, and there are numerous opportunities for doing so. We illustrate the latter point with 10 clinical opportunities for translating scientific discoveries from our field of vascular biology and transplantation. We attribute the limited success of translation to various factors, chief of which is that translation is rarely straightforward and requires continuing research in both the clinic and the laboratory. Translational research is hindered by insufficient targeted resources, a shortage of qualified investigators, an academic culture that hinders collaboration between clinical and laboratory-based investigators, a traditional structure of the AMC that favors departmental efforts over interdisciplinary programs, an increasing regulatory burden, and a lack of specific mechanisms within the AMC for facilitating solutions to these problems. We offer several suggestions to reduce these impediments.—Pober, J. S., Neuhauser, C. S., Pober, J. M. Obstacles facing translational research in academic medical centers. *FASEB J.* 15, 2303–2313 (2001)

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THE PAST 25 years of biomedical research have witnessed a scientific revolution based on the application of molecular biology to mammalian, especially human, systems. A highpoint of this endeavor was reached earlier this year with the release of the sequence of the entire human genome. Despite these enormous advances in basic biomedical research, there are relatively few examples during the same period of the successful application of the findings of such research to the practice of medicine. Such applications are commonly described as ‘translation’, as in the “process of translating discoveries in the laboratory into clinical interventions for the diagnosis, treatment, prognosis, or prevention of disease with a direct benefit to human health”

(1). Although there are both a perceived need and perceived opportunities to improve clinical care through the translation of basic research findings, there is no consensus on how to do this. The lack of a generally applicable model arises chiefly because the process of translation must vary depending on the current state of the applicable science and the nature of the clinical problem. However, we believe there is a more deep-seated reason for the uncertainty in how to proceed, namely, that translation is rarely straightforward and that the process of translation must be understood as a new form of research that “involves the application of basic scientific discoveries into clinically germane findings, and, simultaneously, the generation of scientific questions based on clinical observations” (2). In other words, laboratory discoveries are not typically made in a form ready for adoption into the clinic, and research cannot end when a pertinent laboratory finding is made.

Translational research is a new discipline that must incorporate aspects of both basic science and clinical research, and therefore requires skills and resources not usually available in a single laboratory or clinical setting. For this reason, translational research cannot readily be accomplished by research institutes, university science departments, or isolated molecular medicine centers because these institutions lack the clinical investigative expertise needed. Translational research is equally difficult to conduct in free-standing clinics or hospitals that lack investigative expertise in the laboratory. Academic medical centers (AMCs), which combine medical schools and hospitals, are therefore the institutions most suitable to conduct translational research since they house both clinical and laboratory-based investigators.

AMCs have much to gain from conducting translational research. First, in many instances translational research offers a path to improved clinical care, which is the fundamental justification in the U.S. for public funding of AMCs through the National Institutes of

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Health (NIH) and other governmental health agencies. Consequently, translational research programs create opportunities for garnering increased grant and contract support, a key element in financing the medical school component of AMCs. Second, the clinical component of AMCs benefit because successful translational research brings with it increased patient referrals to the AMC hospitals. Translational accomplishments can define a hospital as 'cutting-edge', providing an advantage in competitive clinical markets. Finally, translational research also brings new professional scientific and clinical opportunities to the faculty working at AMCs. For example, translational research creates opportunities for basic science researchers to participate in human studies and clinical trials, thus validating efforts spent on model systems. At the same time, it allows full-time clinicians to participate in cutting-edge laboratory science. Many clinical faculty consider such opportunities a major reason to choose to work at AMCs for generally less compensation than they can obtain in other settings. Thus, the key constituencies in the AMC—namely, the medical school, the hospital, and the faculty—all have an interest in the success of translational research.

Despite the benefits to the AMC that can accrue from successful translation, there is a widespread appreciation that translation has made little headway. As Charles Marwick, Editor of the *Journal of the American Medical Society*, has recently written, "In the past fifty years, there has been a major growth in biomedical knowledge. But there has been a gap between findings from the laboratory bench and their application to patients" (3). Similarly, the American Association of Medical Colleges has noted that "Landmark developments in genetics, bioengineering, neuroscience, and molecular and structural biology will mean little in practical terms if clinical researchers are unable to translate this science into new and effective medical and health practice" (4). In this article, we will identify what we believe are the real impediments that have limited success in translational research and propose some potential solutions.

OPPORTUNITIES IN TRANSLATIONAL RESEARCH

One possible explanation for the paucity of examples of successful translational research is that the alleged opportunities for translation may not be as real as they seem. We disagree. As members of a newly organized translational research program at Yale Medical Center, Vascular Biology and Transplantation, we have little difficulty in identifying opportunities to combine basic and clinical research in our own field. We list 10 such examples here to illustrate this point (**Table 1**).

1. Reducing atherosclerosis

Atherosclerosis is the major cause of death in the U.S. (5, 6). Epidemiological and genetic evidence point to

TABLE 1. Ten translational research opportunities in vascular biology and transplantation

1. Reducing atherosclerosis
2. Protecting against acute coronary syndromes
3. Treating chronic anginal syndromes and preventing restenosis after angioplasty
4. Preventing post-stent restenosis
5. Preventing or treating acute vascular rejection of allografts
6. Preventing or treating chronic vascular rejection of allografts
7. Addressing the allograft organ shortage
8. Instituting angiogenic therapies
9. Instituting antiangiogenic therapies
10. Preventing ischemia-reperfusion injury

elevated levels of low density lipoproteins (LDLs) in the plasma as a primary cause of atherosclerosis; a treatment introduced recently for preventing atherosclerosis involves lipid-lowering drugs, collectively referred to as statins or, more precisely, as HMG CoA reductase inhibitors (7). These agents block cholesterol biosynthesis in the liver and thus reduce hepatic secretion of very low density lipoproteins, the precursors of LDLs. The development of statins is one of the few triumphs of translational research deriving from the pioneering efforts of Michael Brown and Joseph Goldstein, winners of the Nobel Prize in Medicine and Physiology in 1985, who elucidated the basic features of LDL metabolism. However, recent laboratory findings in mice have strongly suggested that in addition to elevated levels of LDL, a chronic immune/inflammatory response within the arterial wall can contribute to and may be necessary for the progression of atherogenesis (8). This model has lent support to the hypothesis that human atherosclerosis is an inflammatory disease (5). Inhibition of the chronic arterial inflammation has become an additional target for further improving the efficacy of statin therapy. However, anti-inflammatory or immunosuppressive drugs carry significant risk of infection and other side effects. To use these treatments safely and effectively, they must be tailored to the specific inflammatory process; the nature of the chronic immune/inflammatory response within human atheromas therefore must be better characterized. A translational research effort combining laboratory and clinical studies is needed to convert this important research insight into a useful therapy.

2. Protecting against acute coronary syndromes

Acute coronary syndromes, such as unstable angina or myocardial infarction, are precipitated by occlusive thrombosis of epicardial coronary arteries; the thrombosis is initiated by degenerative changes (e.g., fissure or erosion) in atherosclerotic plaques (9). Thrombolytic therapy is effective at reversing thrombosis and can limit the extent of myocardial infarction after thrombosis has occurred (10). However, since thrombolysis is instituted after the process has begun, it cannot com-

pletely prevent heart damage. Anticoagulation therapy offers a chance to actually prevent thrombosis, but it is only moderately effective. An alternative therapeutic strategy would be to reduce the incidence of plaque fissures or erosion that are caused by acute intraplaque inflammation (11). Consequently, anti-inflammation therapy may have an important role in preventing acute coronary syndromes as well as reducing atherogenesis. However, the nature of the inflammatory process may not be the same in these two settings; once again, choosing or developing effective anti-inflammatory strategies will have to follow a focused translational research effort in both the clinic and the laboratory to determine the precise nature of the process.

3. Treating chronic anginal syndromes and preventing restenosis after angioplasty

Until recently, it was widely thought that chronic coronary ischemia and associated anginal pain were caused by the expansion of arterial atheromas to the point where they physically obstructed the lumen of the coronary arteries. It is now appreciated that inward 'constrictive' remodeling of coronary arteries that reduces the diameter of the vessel, not atheroma expansion, is actually responsible for limiting blood flow through atherosclerotic coronary arteries (12). The cause of inward remodeling is not known, but may relate to scarring of the vessel adventitia due to extravascular inflammation associated with atheromas. Coronary artery angioplasty can re-expand constrictively remodeled vessels, but the benefits are often lost within 3 months to a year when the artery again remodels and re-constricts, a process commonly referred to as 'restenosis' (11). Restenosis after angioplasty, like chronic angina, is not caused by expansion of intimal atheromas but by constrictive remodeling. Therefore, therapies designed to inhibit the growth of vascular smooth muscle cells within atheromas are unlikely to prevent angina or restenosis.

One successful approach to prevent recurrence of constrictive remodeling after angioplasty is placement of an intravascular stent. Though highly successful, this approach is not always possible. To benefit those patients in whom stents cannot be used, a combination of clinical and basic (i.e., translational) research is needed to define the mechanisms of inward constrictive remodeling before and after angioplasty, so that an alternative therapeutic approach can be developed.

4. Preventing post-stent restenosis

As we have noted, the combined approach of angioplasty and stenting is an effective means of reversing inward remodeling of coronary arteries and preventing its recurrence. However, stents can fail by provoking progressive intimal hyperplasia, mediated largely by proliferation and matrix deposition by intimal vascular smooth muscle cells. Much is known about vascular smooth muscle behavior from animal models, offering

an opportunity for preventative therapies (13). However, the biology of smooth muscle cells can vary with vessel type and with species, and improving post-stent outcome in coronary arteries will likely require more translational research into human coronary artery cell behavior involving both clinical and basic investigators.

5. Preventing or treating of acute vascular rejection of allografts

Allotransplantation is the best and sometimes only effective therapy for end-stage heart, kidney, liver, or lung failure. Immunosuppressive therapy has evolved to the state where it can effectively prevent or even reverse host immune cell-mediated (parenchymal) rejection of allografts. However, current immunosuppressive therapy often fails when the rejection process involves graft arteries (vascular rejection) (14). The mechanisms of acute vascular rejection appear to involve both T lymphocytes and antibodies, and probably differs from the mechanism of cell-mediated rejection of graft parenchyma. This difference in immunological mechanism probably accounts for the lack of response of vascular rejection to existing drug regimens. Translational research will be needed to develop different immunosuppressive strategies that can protect graft vessels and parenchyma. Alternative approaches to reducing vascular rejection, such as the induction of host immune tolerance to the allograft or cytoprotective strategies to prevent vessels from injury, represent additional opportunities for translational research

6. Preventing or treating chronic vascular rejection of allografts

Although acute rejection rates have declined steadily because of better immunosuppressive regimens, reductions in the rates of late graft failure have not kept pace. Parenchymal changes in late graft failure of hearts and other organs frequently reflect injury due to ischemia, not immune-mediated rejection. The cause of this graft ischemia is a progressive immune-mediated graft arterial remodeling, called either chronic vascular rejection or allograft vasculopathy (15). Chronic vascular rejection is now the major cause of cardiac allograft failure. The precise immune mechanisms of chronic vascular rejection are disputed and animal models offer only limited insights into chronic diseases. Translational research, combining clinical and basic studies, is needed to develop strategies that prevent or reverse the process. An additional opportunity for translational research in this area is to develop approaches for the diagnosis and inhibition of tissue ischemia before irreversible changes occur.

7. Addressing the allograft organ shortage

The dramatic success of organ replacement therapy since the advent of successful immunosuppression has triggered a demand for transplants that greatly exceeds

the supply of donor organs. Most observers agree that increased donation rates from beating-heart cadaver donor and living donors will not be adequate to meet demand (16). New approaches for organ replacement therapy are needed. Candidate strategies include increased use of nonbeating heart cadaver donors (17), development of synthetic organs (18), and development of suitable (genetically modified) animal organs (19). Creating and preserving adequate graft perfusion is a common problem facing these three approaches and may be the largest impediment toward their use in the clinic. Solutions to these problems will require extensive translational research in vascular biology and transplantation immunology involving clinical and basic components.

8. Instituting angiogenic therapies

In some settings (e.g., in diabetics), impaired perfusion of tissue develops as a result of progressive loss of microvessels (20). This microcirculatory loss often leads to ulceration of the skin and damage to other organs. The ulcer problem is compounded because such wounds often fail to heal, a problem related to the fact that these same patients have a diminished ability to form new blood vessels from preexisting ones (angiogenesis), and angiogenesis is a critical feature of the wound healing process. Stimulation of angiogenesis by a single agent such as vascular endothelial growth factor has failed, emphasizing that we really do not yet understand the complex set of signals and events that comprise physiological angiogenesis (21). Translational research incorporating both clinical and laboratory investigation will be needed to improve natural angiogenesis or develop alternative approaches for tissue revascularization, e.g., by turning on vasculogenesis (forming blood vessels from stem cells) or transplanting differentiated endothelial cells.

9. Instituting antiangiogenic therapies

Whereas inadequate angiogenesis can be a cause of disease, inappropriate angiogenesis may also be harmful in specific settings such as tumors, diabetic retinopathy, rheumatoid arthritis, and growth of atherosclerotic plaques (22). This is because these pathological processes all involve new tissue growth, which is dependent on new blood vessel formation, principally by angiogenesis. Several therapeutic trials are under way, especially in the tumor field, to treat disease by inhibiting blood vessel growth (23). Preliminary reports have suggested that novel agents such as endostatin and angiostatin may offer some benefit, but that the inhibition of angiogenesis is not complete. Once again, more research in the clinic and the laboratory will be needed to develop better strategies and regimens.

10. Preventing ischemia-reperfusion injury

Ischemia-reperfusion is a common mechanism of tissue injury that occurs in several settings: in thrombotic

stroke, after therapeutic thrombolysis to treat coronary artery occlusion, after cardiac bypass surgery, and in transplantation. The agents of injury are free radicals, especially reactive oxygen intermediates and reactive nitrogen intermediates produced by recruited leukocytes; the principal target of injury is the vascular endothelium (24). Endothelial damage by free radicals leads to thrombosis, further exacerbating the extent of injury. Much is known about the basic mechanisms of both processes, but translational research in the clinic and the laboratory will be needed to develop effective strategies to prevent leukocyte recruitment and activation within reperfused vessels and/or to protect endothelial cells from free radical-mediated injury.

The 10 examples we chose are all instances in which recent insights in basic research have presented opportunities for new therapies or are applicable to diagnosis. These examples also share another common feature: they require additional clinical studies to validate and refine the conclusions of laboratory findings. Additional laboratory studies suggested by the clinical research will be needed to refine clinical approaches. In other words, our examples of clinical opportunities all require translational research defined as a bidirectional, iterative process between the laboratory and the clinic (2). The opportunities for such translational research do exist, but they cannot be realized simply by expecting clinicians to convert laboratory findings into effective therapies. We believe that the complex nature of such opportunities can be exploited only through an organized team approach, combining the expertise of clinical and laboratory-based investigators. The availability of clinical and laboratory investigators in the same institution is precisely why the AMC is the logical place for conducting translational research. Nevertheless, AMCs generally have not fostered such interdisciplinary programs, and we will discuss some impediments to realizing this goal within the AMC.

IMPEDIMENTS TO TRANSLATIONAL RESEARCH (Table 2)

Inadequate financial support

Translational research is expensive. Support for translation is complicated because it requires support of the basic and clinical components, usually from separate sources. Although there are multiple sources of fund-

TABLE 2. *Impediments to translational research*

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- Inadequate financial support
 - Shortage of “translational investigators”
 - Impediments in the academic culture to collaboration
 - AMC Structural organization often hinders collaboration
 - Regulatory impediments to translation
 - Absence of mechanisms for facilitation of translational research
-

ing these components of translational research, each has its own limitations.

The National Institutes of Health and other governmental health agencies

The main source of basic biomedical research funding in the U.S. is the National Institutes of Health (NIH), which supports basic, clinical, and translational efforts largely from the same pot of money. The NIH has been urged to increase its support of translational research on many occasions. A recent study in the *New England Journal of Medicine* noted that, “remarkable advances have been made recently in our understanding of the molecular and genetic bases of disease. The potential therapeutic opportunities offered by these scientific findings have led to broad-based congressional support for increases in the National Institutes of Health budget. These developments have put into sharp relief the question of how to allocate growing budgetary resources among the various categories of medical research. In addition to the need to support basic-science research, investigators and policy analysts alike have recently emphasized the need to invest in translational research” (25).

In fact, significantly more money has been given to the NIH to spend on research as the U.S. has committed to a doubling of the NIH budget over a 5-year period. The principal limitation of the NIH as a funding source for translation is not in numbers of dollars, but rather a failure to develop mechanisms that allow translational research to compete effectively against basic research, the traditional recipient of the lion's share of NIH research funding (26). This is because the NIH allocates most of its extramural funding through peer review, conducted by study sections comprised of non-NIH scientists, and most study sections strongly favor hypothesis-driven research designed to discover basic mechanisms over ‘mere’ applied research that assumes that the basic mechanisms of disease are understood and seeks ways to apply the knowledge. Even when specific hypotheses are identified in a translational project, such research is penalized because definitive tests of hypotheses are much more difficult to carry out on human subjects, for ethical and logistical reasons, than they are in model systems. Simply put, clinical work does not stack up well against laboratory models when the primary criterion is scientific rigor. In a survey taken at the University of California at San Francisco Medical Center, 83% of faculty (including both clinical scientists and basic scientists) thought that clinically based research does not receive equal support, recognition and credit for promotion when compared to basic research (27). The history of NIH funding has shown that patient-oriented research (POR) grants, a category that includes translational research, do well only when evaluated on their own standards (i.e., not against basic grants). According to the Division of Research Grants’ (presently called the Center for Scientific Research) Clinical Research

Study Group, “In contrast to those study sections with a low POR [patient oriented research] application load, in those with a substantial load (greater than 50%), POR applications have success rates that are similar to LOR [laboratory-oriented research] applications in general. Thus, the study section composition is likely to affect the outcome of a POR grant application” (28). In other words, in an NIH peer review culture where basic research is given far more credence, basic research grants score better; clinical research, including translational research, often goes underfunded.

Clinical income

Because of these impediments within the NIH peer review system, clinical research has traditionally been supported by excess income from clinical practice rather than by grants. In the past, insurance companies and health maintenance organizations (HMOs) subsidized AMCs to support clinical research. As the costs of health care have grown, the payers of health care costs, which are either profit driven or at least committed to breaking even, have progressively all but abandoned unprofitable ‘philanthropic’ activities such as research. As explained by Jerome P. Kassirer, former Editor-in-Chief of the *New England Journal of Medicine*, “Managed care organizations, particularly those owned by investors, are required to apply only existing knowledge to routine patient care. Academic medical centers, on the other hand, also create new knowledge, develop and assess new technologies, evaluate new drugs, educate medical students, train tomorrow’s physicians, and care for the sickest patients. The costs of these programs as well as other factors (for example, local economic and demographic variables) make academic medical centers some 30 to 40% more expensive than nonacademic hospitals” (29). Thus, the AMC has gone from a cause to be supported to a cost to be avoided.

The clinical faculty at AMCs may feel directly the financial squeeze from health care payers. In the current climate of cost control, clinical faculties are pressured to see more patients and take on added clinical responsibilities in order to maintain their salary. As this happens, “Many [faculty] reported that excessive clinical responsibilities prevent them from working on grants and the projects funded by grants” (27). NIH grants, which could support some of the salary of clinical scientists, are increasingly unobtainable except by those who are able to devote most of their time to basic research and slow steady research accomplishments. Thus, clinician-investigators who undertake to do research and clinical care are forced to meet demands from both sides and, “In this atmosphere of highly polarized needs, it is a tall order to succeed on both fronts” (2). New sources of salary support for clinical investigation must be identified to protect time for translational research.

Pharmaceutical and biotechnology companies represent an additional source of financial support for the clinical aspects of translational research. Although these entities, like insurance companies and HMOs, are largely profit driven, they are a natural source of support for translational research because translation is the core of drug development. However, for-profit companies are usually unwilling to support programs that fail to show a clear market opportunity or may actually diminish the market for an existing drug or therapy (i.e., developing immune tolerance to replace immunosuppressive drugs). Furthermore, the clinical divisions of pharmaceutical companies are rarely willing to support basic investigation once a clinical trial has begun.

There is also a cultural divide that separates industry from the AMCs. Companies are typically highly focused on specific milestones whereas the AMC's research environment is more flexible and opportunistic. Thus, translational research efforts supported by these sources are often selective, limited, and unlikely to sustain independent activities at AMCs. Some previous ventures in providing broad support to AMCs have left the companies feeling frustrated, and commitments of this type are less likely to occur in the present competitive environment.

Private foundations

Philanthropic organizations, such as the Howard Hughes Medical Institute (HHMI), represent another source of funding. Indeed, HHMI, along with the American Cancer Society and the Burroughs Wellcome Fund, has recognized that translational research "will command center stage, requiring team approaches and the collaboration of many individuals from vastly different fields, ranging from computational mathematics to clinical science" (30). So far, funding commitments in support of this principle are relatively small compared to total research spending. We hope these institutions understand that "the need for team approaches to scientific research suggests that private funders can make a significant difference in building expertise and collaborations by providing support to clusters of faculty" (27). It remains to be seen whether they will become major sources of support for translational research in the future.

Academic medical centers

Finally, AMCs themselves can directly support translational research. Self-funding is often limited to the availability of endowment. Furthermore, institutional support frequently is allocated through departments, and translational research is, as we shall discuss, more often interdepartmental and therefore less likely to receive support than departmental-based activities. Consequently, translational work does not generally fair well in competition for

limited internal resources. It is uncertain whether the current structure will change.

Shortage of 'translational investigators'

In addition to the financial constraints, many observers believe there is a shortage of individuals who are suitably trained to perform translational research. Traditionally, the onus of bridging the gap between laboratory and clinic has fallen to M.D./Ph.D.'s or other physician-scientists with training in both the clinical and laboratory realms. Despite the perceived need for dual trainees, the number of such individuals continues to dwindle. Leon Rosenberg, former dean of the Yale School of Medicine and former President of the Bristol-Myers Squibb Pharmaceutical Research Institute, has described this problem as a "defect in the structure of the country's medical research edifice, which must be repaired soon and well, lest it threaten the entire construct [of academic medicine] . . . I speak of the progressive, dangerous decline in the number of physician-scientists" (31). The shortage of physician scientists begins with training. Joseph Goldstein and Michael Brown note that "the path to an M.D./Ph.D. degree is torturous" (32). Rosenberg adds, "there has been a progressive increase in the number of years of postdoctoral training required for physicians undertaking careers in research, often stretching to 10 or more [years]" (31). Even after M.D./Ph.D.'s have completed training, other obstacles prevent them from pursuing careers as physician scientists. As we have already noted, clinical investigators, like other medical practitioners, are pressured to see more patients and spend less time in the laboratory. At the same time, laboratory investigators who obtain salary support from NIH or other grants are pressed to pursue a more traditional, basic science career that is better suited to earning grant support, which minimizes their clinical time. Thus, the need to cover one's salary promotes polarizing career choices that limit efforts in 'bridge' research.

The pressure to avoid a career in translation is driven by forces other than finances. Alvan Feinstein, Sterling Professor of Medicine and Epidemiology at Yale School of Medicine, has noted, "An important intellectual source to the problem is the ideologic belief that scientific importance is inversely proportional to the size of the investigated entities. With this belief, the title of basic is excluded from the fundamental question in any research that does not occur at the level of cells and molecules. Although recent changes in NIH policy may augment the decreasing number of physician-investigators, the more serious intellectual problems of constrained scientific creativity will continue until the current ideology is revised" (33). The net result is to drive physician-scientists away from messier, POR activities into more traditional laboratory problems. This drive into the laboratory reduces the time available to sustain clinical skills (especially in fields such as surgery) and produces an inverse pressure on clinical scientists who continue to see patients. Consequently,

likely physician-scientists spend more time in the laboratory and often lose their credibility in the clinic.

The cumulative effect of these pressures is that there are fewer individuals able to bridge the gap between bench and bedside and play a major role in both spheres. There is no solution to this problem, but it can be circumvented. The alternative approach, which we favor, is to conduct translation by creating teams that include dedicated clinicians as well as laboratory-based investigators. Physician-scientists who are able to play a bridge role will fit well into such teams; yet they need not carry the whole burden. Collaborations create opportunities for polarized specialists to apply their unique skills to translational efforts. However logical this solution may seem, collaborations face difficulties from both the academic culture and the structure of AMCs.

Impediments in the academic culture to collaboration

We believe that the only sustainable approach to translational research lies in the creation of collaborative teams of clinicians, laboratory scientists, and physician-scientists. Brown and Goldstein, who have exemplified this approach to translation, have also argued for “collaboration between specialists rather than through comprehensive performance by individuals” (32). However, the academic culture of the AMC inhibits such collaborations in several ways. First, the standards set by appointment and promotions committees often discourage collaboration. To become promoted, one must gain recognition for one’s work. As a UCSF study group recently noted, “being a principal investigator on an independent NIH R01 (or equivalent) grant was essential for promotion, whereas participation in program project grants, serving as an essential collaborator in research with other PIs [principal investigators] or pursuing research supported by other mechanisms was less valued” (27). The NIH grants have only one spot on the sheet for a principal investigator, undermining the rewards for collaboration.

Second, there is often an inability of the participants themselves to appreciate the contributions made by their own colleagues. Dale Dauphinée, Executive Director of the Medical Council of Canada, and Joseph B. Martin, Dean of the Faculty of Medicine at Harvard University, note “[because] it requires the crossing of once-sacrosanct boundaries and the breaking down of longstanding institutional walls, the scholarship of integration has been slower than the other forms of scholarship to gain acceptance as an integral activity of the professorate” (34). In other words, clinicians and basic science researchers have fundamental difficulty recognizing the merits of research from the other sphere. According to Emil Freireich, Professor of Medicine at the University of Texas M.D. Anderson Cancer Center, clinical research is not adequately valued by basic researchers because it does not have its own criterion: “It is important for us to recognize the achievements of clinical scientists by different criteria than those that have been used for laboratory-based

research” (35). Likewise, basic science research is often dismissed by clinical investigators as too reductionist because, “although the reductionist paradigm that informs most contemporary biomedical research has facilitated the design and execution of elegant, well-controlled experiments, generalizing from these results to whole-body systems remains a challenge” (36). Indeed, clinicians have trouble applying this knowledge gained: “in the modern era, the gap between scientific theory and clinical practice is closely linked to the reductionist approach that is the animating spirit behind science today. In our excitement about the progress of science, we cannot forget that determining the DNA sequence of a gene, or understanding how two proteins bind to each other in a test tube, or learning how a particular type of cell grows in a Petri dish, is not equivalent to developing treatments and cures for complex human disease” (37). This existing academic culture will have to change if collaborations between clinicians and laboratory-based investigators are to be successful.

AMC structural organization often hinders collaboration

Even when the relevant parties favor the idea of collaboration, the structure of the AMC provides additional impediments. For example, basic scientists and clinical researchers are often separated physically within AMCs. This separation, correlating with assigned space to departments, limits opportunities for spontaneous interactions and mutual inspiration, and departments will rarely provide space for members of other departments to rectify this problem. As Michael Brown has noted, “departments used to contain a mixture of pure physicians, physician-scientists, and even a few basic scientists, all united in their quest to understand and treat human disease. Now, these departments are split. An enormous gap separates those who practice medicine from those who practice science. Rarely do they attend the same conferences and barely do they communicate. As a result of this isolation, most scientists have left clinical departments, including those who hold the M.D. degree” (38).

An alternative to departmental models are interdisciplinary centers. There is no doubt that centers are better poised to support translation than traditional departments. However, centers threaten the power base of departments and, unless they are independently endowed, are rarely successful in such struggles when pitted against better financed opponents.

Regulatory impediments to translation

There is a broad consensus (which we heartily endorse) that patients must be protected from undue risks associated with research and that they must be educated so they can give truly informed consent before being enrolled in acceptable protocols. However, the pendulum is moving rapidly toward ever more strin-

gent regulation (39). Areas of new regulation involve reducing instances of actual physical harm to participating subjects, protection of privacy rights (including genetic privacy) from the growing capacity to disseminate data electronically, and eliminating financial conflicts of interest on the part of clinical investigators that may compromise their ability to act in the patient's best interest. The primary response to these concerns has been to increase regulatory oversight through institutional review boards (IRBs). As IRBs shoulder more responsibility, many have increased the burden of work for investigators to meet these higher standards. Although there are no firm figures to support these contentions, there is a widespread sense among clinical investigators that worthwhile studies are increasingly abandoned simply because the burden of regulatory compliance has become too high. There are certainly cases when IRBs have asked investigators to modify study design in an attempt to protect subjects in ways that ultimately negatively affect the data collected (i.e., by leaving out control groups). IRBs have become the subject's advocates, which may be appropriate, but there is no one left to champion the value of the research other than the investigator. Thus, although we support the role of IRBs and applaud their vigilance, we believe that the current system increasingly undervalues the benefits of research. Since patient protection and conduct of research may sometimes be in conflict, we believe that IRBs must consider both the value of the research as well as the risks involved in order to find a proper risk-benefit balance.

We also concur with the general proposition that physicians should not be placed in the position of choosing between their patients and financial gains. However, there is a special issue regarding financial conflict of interests of investigators that applies to translational research. This is because it is increasingly likely that a bench scientist participating in a collaborative team will have intellectual property related to a new therapy. Prohibition of participation, as opposed to disclosure and regulation of such relationships, could undermine the collaborative approach and may hinder the back-and-forth exchange between the clinic and the laboratory. We believe that IRBs or other AMC oversight committees need to find solutions to allow increased rather than decreased participation of laboratory scientists in clinical trials while continuing to vigilantly protect study subjects from harm.

Absence of mechanisms for facilitation of translational research

Perhaps the least appreciated hindrance to translational research is the limited availability of administrative support for translation at most AMCs. We mean two things by this. First, on a day-to-day basis, research programs require support staff. Such resources usually come through departmental structures and generally are not available for interdepartmental collaborations. Centers could provide these resources, but must have

revenue and jurisdiction to do so. The second point is that translational efforts generally are not adequately represented in the top leadership of the AMC. Heads of programs or centers rarely have the influence of departmental chairs within the highest echelons of the AMC. This makes it difficult to champion the idea of translational research and, when problems arise, to muster sufficient influence to resolve them expeditiously.

PROPOSED SOLUTIONS

Having identified what we believe to be the primary impediments to translational research, we outline some proposals to address these problems (see **Table 3**).

Recognize the nature of translational research

The first step is for AMCs to recognize that translation depends on translational research and that this will not occur unless the AMC is committed to such efforts. Once the decision is made, then specific solutions can be implemented.

Provide access to adequate funding

If successful translation is a national goal, then current NIH funding mechanisms should be changed so that translational research receives adequate funding. The NIH can, through restructuring of the peer review system, create review panels that are constituted to fairly evaluate translational research. The ongoing restructuring of the study sections within the Center for Scientific Research (formerly the Division of Research Grants) provides a unique opportunity to do this (40, 41). In addition, the NIH should explore other models of funding. One such model is the Immune Tolerance Network (ITN) set up by the National Institutes of Allergy and Infectious Diseases, in which a 7-year contract has been awarded to a consortium of investigators to support translational efforts outside the traditional peer review system (42). The ITN is really an experiment to explore alternative funding in which review panels try to improve rather than merely rate proposals (43).

Funding sources outside the NIH and other governmental health agencies (such as HHMI) can also play a role, but they must be convinced to support transla-

TABLE 3. *Proposed solutions*

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- Recognize the nature of translational research
 - Provide access to adequate funding
 - Increase the pool of translational investigators
 - Restructure the academic environment
 - Remove the physical barriers blocking collaboration
 - Provide support for regulatory compliance
 - Provide administrative facilitation for translational research
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tional as well as basic research. We single out HHMI because it is the largest such private funding agency in the U.S. and we are encouraged by its newly expressed interest in clinical research (44). We hope that other private agencies now follow suit. It is unlikely, in our view, that private health insurers or HMOs will voluntarily increase their support of research, but incentives may be developed to encourage such support. AMCs as well as governmental agencies will need to cooperate if they are to broker such arrangements. In the case of pharmaceutical and biotechnology companies, which do support some targeted translation, we believe that AMCs must assume a more active role in developing corporate partnerships that support translational research programs with not-for-profit outcomes as a price for having AMCs participate in company-run clinical trials. Finally, AMCs must take the lead in building up endowment for support of translational research, providing a means to support interdepartmental programs and centers. None of the other funding sources stand to gain as much as the AMCs themselves, and translational research must become a priority for fund-raising efforts.

Increase the pool of translational investigators

We support the training of several types of investigators who can participate in the field of translational research. The limited pool of physician-scientists needs to be expanded, which can be done in three ways. First, create new and/or more securely fund existing M.D./Ph.D. programs at AMCs. However, for reasons we have discussed, many such trainees become polarized either as clinicians or laboratory-based investigators during the long training period that follows graduation from M.D./Ph.D. programs. Therefore, our second recommendation is to create and support postdoctoral programs such as the Specialty Training and Advanced Research (STAR) program at the University of California at Los Angeles, which combines a clinical fellowship with Ph.D. postdoctoral research training. Continued dual exposure postpones and should ultimately reduce the extent of polarization. Our third idea is to provide opportunities for further training of young clinicians in laboratory research, expanding the pool beyond graduates of M.D./Ph.D. programs. An example is the new Investigative Medicine Ph.D. program at Yale University School of Medicine, which provides an accelerated but rigorous Ph.D. program for M.D.'s who have completed clinical residency and fellowships.

Even with such training opportunities, we believe that the bulk of translational work must be conducted by scientists and clinicians who are more polarized in their specialties rather than by an expanded, cadre of bridge physician-scientists. To take full advantage of the expertise provided by these specialized individuals, clinicians and basic scientists must learn to understand and communicate with each other. To this end, we propose that AMCs provide in-service courses to train laboratory researchers in clinical issues and clinicians

in laboratory approaches. Such training opportunities will help ease the communication barrier, although true collaboration must develop by doing rather than by training.

Restructure the academic environment

The AMC must learn to recognize and reward collaborations in translational research teams. Champions of translational research should sit on AMC committees where they can promote the cause of translational research and bring it to the attention of AMCs. Most important, they must sit on appointments committees and serve as advocates for members of translational teams, ensuring that the committees recognize and reward collaborative efforts in addition to work done by individual principal investigators. Other activities (retreats, joint seminars, etc.) that bring clinicians and laboratory scientists together and foster appreciation of each other's work should be strongly encouraged.

Remove the physical barriers blocking collaboration

The physical structure of the AMC should evolve so that it is more conducive to collaboration. This is not always easy, but opportunities to restructure space should not be squandered. Opportunities may arise with the construction of new buildings. Interdepartmental programs and centers should be created and supported, so that scientists working on similar areas can collaborate and have the spontaneous interaction and mutual insights conducive to collaboration. The AMC will need to protect such programs and centers from incursion by traditional departments.

Provide support for regulatory compliance

Even though clear guidelines for protection and ethical treatment of patients need to be maintained, it is essential to preserve the opportunities for translational and clinical research. IRBs need to alter their procedure so that they evaluate the benefits as well as the risks of research. To do so will require additional resources, e.g., for obtaining outside expert consultation. Second, the growing regulatory burden should not fall solely on investigators. The AMCs should provide effective clinical trials offices to aid investigators with compliance. Financial conflict of interest should, whenever possible, be addressed by disclosure and (when warranted) by monitoring. Prohibition of participation in research should be the act of last resort if we are to encourage discoverers (and holders of intellectual property) to participate in developing and applying their ideas. This would be especially relevant when clinicians, through participation with basic investigators, become coinventors.

Provide administrative facilitation for translational research

Administrative facilitation is needed to implement all of the solutions proposed above. Starting at the top, the

AMC should have leadership positions to galvanize the cause of translational research and spearhead solutions to problems that arise. These individuals can be housed in the medical school, in the hospital, or both. On a day-to-day level, researchers need clerical support as well as administrative resources to submit grants and administer funding for laboratories and programs once the grants have been awarded. Such support may need to come from individual centers or, more generally, from an AMC-wide office established specifically to facilitate translational research. This will be necessary because it is likely that departmental offices with limited resources will not facilitate interdepartmental programs at the expense of traditional department-based efforts.

CONCLUSIONS

Translational research is the mechanism for harnessing advances in science to the improvement of clinical care. Successful translation requires an interactive interplay between the laboratory and the clinic. AMCs are the natural home for translational research, because they incorporate faculty with clinical and laboratory-based skills. The principal components of AMCs have much to gain from performing translational research. However, success in this endeavor has been elusive. Our analyses lead us to conclude there are multiple impediments to translational research at AMCs, including the obvious ones such as inadequate financial support and limited numbers of physician-scientists, as well as less obvious ones such as the barriers that traditional academic culture and AMC structure place on collaborative research across disciplines. These barriers can and must be overcome. FJ

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