

1 A Brief History of Translational Neuroscience

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SOME RECENT HISTORY

According to an Institute of Medicine (IoM) report released on July 17, 2003, translational research and interdisciplinary approaches to care must be more strongly supported by both academic health centers and federal funding agencies [1]. "Academic Health Centers: Leading Change in the 21st Century" strongly advocated increased attention to translational research. The report pointed out that, although "the various forms of research are interrelated, they are typically conducted by different scientists and funded separately." This approach will have to change, stated the IoM Committee on the Roles of Academic Health Centers in the twenty-first century. "Increased coordination and collaboration will be required to meet growing demands for rapid improvements in health care and for a greater focus on the types of research that answer questions about what does and does not work." Interestingly, the impression among congressional leaders has been that the justification for doubling the National Institutes of Health (NIH) budget was tied to increased support for translational and clinical research. Related to the need for translational research is a disturbing national trend showing that MDs holding R01 awards decreased from 20% in 1982 to only 4% in 2002. R01 awards are individual research grants to support a discrete projects and is the most common grant mechanism at the NIH. We researchers, both basic and clinical, stand to lose legislative and public support for research if the current trend continues.

Congressional leaders, policy-makers, and the public at large are increasingly concerned that the scientific discoveries of the past are failing to be translated into tangible benefits to public health. The response has been a series of initiatives making translational research a priority. However, two blocks to translational research have been identified, a lack of translation of basic science discoveries into clinical studies (T1) and

2 Translational Neuroscience

from clinical studies into medical practice (T2) [2,3]. The definitions of T1 and T2 research are actually that (a) T1 research addresses the translation of basic science breakthroughs into clinical trials, mainly on human subjects, while (b) T2 research attempts to implement those clinical trial findings into everyday clinical practice, thereby optimizing current treatments, for example, deciding between two equivalent therapies that may differ in cost-effectiveness, or developing novel therapies based on the results of well-drafted clinical trials. In fact, there has been a call to emphasize T1 and T2 research in proportion to its ability to improve health [4]. Additional blocks have been identified, blocks to T3 research foil attempts to move evidence-based guidelines into health practice, through delivery, dissemination, and diffusion of research, and blocks to T4 research impair the evaluation of the “real-world” health outcomes of a T1 application in practice. The latter require improved outreach programs, with considerable activity using telemedicine and other community-based research approaches.

Typical T1 blocks to translational research include lack of willing participants, regulatory burdens, fragmented infrastructure, incompatible databases, and lack of qualified investigators [3]. Among the T2 blocks to translational research are career disincentives, practice limitations, high research costs, and lack of funding [3]. These issues will be addressed throughout this book, but, before going further, a common misconception is that translational research must proceed on a linear basis. There is considerable precedent to suggest that the linear approach to translational research, that is, proceeding from basic research on animals to clinical studies on humans, followed by clinical trials, and then applied studies, is not necessarily optimal. The lack of translation from animal research to clinical trials, the so-called T1 obstacle, suggests that a bottleneck exists at the transition between the huge amount of knowledge from basic studies to the trickle of clinically oriented research at present. However, this linear concept has been questioned, and one of the leaders in suggesting that we should consider this process as cyclical is Bill Crowley at Massachusetts General Hospital in Boston, MA. He has developed convincing examples of bedside to bench research, in which it is the genetic testing of individuals with genetic disorders that can drive the design and development of animal models on which can be tested novel therapeutic avenues, which can then be carried back to the bedside [5]. A better model for the progression from basic to clinical research and back is thus a cyclical model in which research can begin at various points in the cycle (Figure 1.1). Given the fact that performing translational research is indeed open-ended, the NIH has been careful to leave definitions open to interpretation. This is a wise position, allowing the field to employ brainpower and imagination to forge the future of translational research. The lack of pigeon holing of the meaning of translational research should be viewed as an opportunity rather than a limitation.

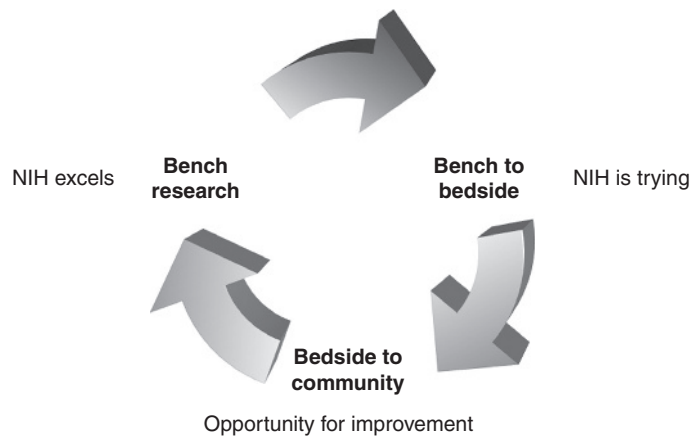


Figure 1.1 Circular model of translational research. Research can begin at any point in the cycle and inform researchers about the needs of the preceding and subsequent processes. For example, an agent that derived from animal studies and was tested at the bedside may work well in a clinical trial, but bedside to community “real-world” applications may find it less effective. This would require amending the basic research and “recycling” in order to make a more efficient treatment.

In September of 2003, Elias A. Zerhouni, MD, the then new Director of NIH, presented his “roadmap” for medical research. “The purpose is to identify major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone but that the agency as a whole must address to make the biggest impact on the progress of medical research.” In reengineering the clinical research enterprise, “the exciting basic science discoveries currently being made demand that clinical research continue and even expand.” “Translational research has proven to be a powerful process that primes the entire clinical research engine. Key to building a strong infrastructure will be to increase interactions between basic and clinical scientists, and ease the movement of powerful new tools from the laboratory into the clinic.”

FUNDING TRANSLATIONAL RESEARCH

Academic health centers have been very good at making enormous strides in basic scientific research. In the coming years, this is likely to continue, but they will also need to begin refining the evidence base for health care. The general framework is that of discovery, which relies on basic research, followed by testing and application, which rely on clinical research, and then evaluation, which relies on applied research. Results from applied research are presumed to feed information to the formulation of further discovery. In reality, the process should begin at any point in the cycle.

Academic health centers will begin to explore this cyclic continuum, with those that redesign and plan properly being more successful at garnering NIH, and public, support. A number of obstacles exist to the transition toward this continuum of research activities. First, there is a low supply of clinical researchers; second, there is a lack of institutional organization to support translational research; and third, there are inadequate funding levels to support such research. The first obstacle will be addressed in the next chapter on mentoring of clinician scientists and how to set up a career development program. The second obstacle will be addressed in the last chapter on how academic health centers can reshape themselves to not only meet the challenges of translational research, but also take advantage of the wide-open field of possibilities available for performing translational research.

LACK OF FUNDING

The third obstacle is being met on one front with the development of the Clinical Translational Science Award (CTSA) program under the National Center for Research Resources (NCRR). Even before the General Clinical Research Center (GCRC) program at NCRR was revamped into the CTSA, NIH-wide initiatives were implemented. You may recall that the GCRC program was intended as an institutional facility for inpatient and outpatient research. That model was critically flawed in terms of being unable to facilitate research for young investigators and failed to provide sufficient training to increase the pipeline of clinical scientists. These deficiencies have been addressed in the design of the CTSA program. But, even before these changes, there were concerns about the low funding levels of clinically oriented research. For example, in the review of NIH applications, informal surveys at NIH determined that those applications that used animals tended to score on average 10 percentile points better than those that used humans. That is, simply the fact that the “human subject” instead of the “animal research” box on the face of the application was checked meant that, on average, these applications were scored at a lower level of enthusiasm. Of course, research on human subjects is in many ways more difficult to control, and more fraught with variability and technological difficulties, so that it is not hard to understand this attitude. In response, the review criteria of standard research grant applications were changed at all levels and institutes at NIH. The following are now typical review criteria, with the phrases in bold being the new ones added to accommodate the new emphasis on clinically oriented research. “*Significance*: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge *or clinical practice* be advanced? What will be the effect of these studies on the concepts, methods, technologies, *treatments, services, or preventative interventions* that drive

this field? *Approach*: Are the conceptual or *clinical framework*, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? *Innovation*: Is the project original and innovative? *For example*: Does the project challenge existing paradigms or *clinical practice*; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area? *Investigators*: Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)? *Environment*: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or *subject populations*, or employ useful collaborative arrangements? Is there evidence of institutional support?"

Launched in 2006 and led by the NCRR, the CTSA program is working at institutional, regional, and national levels to create a discipline of clinical and translational science. Its primary mission is to more efficiently translate the rapidly evolving knowledge developed in basic biomedical research into treatments to improve human health. From 2006 to 2008, 38 academic health centers and research institutions in 23 states became part of the consortium. In 2010, the consortium consisted of 55 member institutions. When fully implemented, approximately 60 institutions will be linked in a way that is intended to energize the discipline of clinical and translational science with >\$500 million per year of NIH funding. Diversity in the size, scope, and geographic location of participating institutions has been mandated because such diversity is thought to strengthen the CTSA consortium and enhance its impact.

More recently, the NIH Scientific Management Review Board voted on December 7, 2010, to approve a recommendation to newly appointed NIH Director Francis Collins to create a new NIH center focused on translational medicine and therapeutics called the National Center for Advancing Translational Science (NCATS). The proposed center would house the currently NCRR-administered CTSA program along with the Cures Acceleration Network, Molecular Libraries Program, Therapeutics for Rare and Neglected Diseases, and Rapid Access to Interventional Development, as well as new NIH-FDA partnership activities.

These changes have generated considerable concern in the research community, and it is not yet clear whether congressional support will follow. For example, one of the mandates of NCATS will be the development of new drugs for therapeutic use. This is a response to the disturbing reduction in the pharmaceutical industry of spending on research and development, all in the face of a decline in the output of new drugs approved

by the Food and Drug Administration (FDA). While Dr. Collins has been predicting that gene sequencing will lead to a host of new treatments, investments in the billions of dollars by the drug industry have failed to yield new gene-related therapies. While the NIH has historically been very good at supporting basic research, many wonder how good it will be at drug development, which requires a different set of skills. On the plus side, it may turn out that such an effort may generate a new type of researcher who can perform in both academic and drug company settings. On the minus side, this is the first time in the 80-year history of the NIH that an institute will be dismantled and the parts scattered across the rest of NIH. Historically, orphan programs tend to be phased out of existence by the “host” institute. These concerns are likely to persist for years, but it is hoped that unbiased and independent assessment of the success of the NCATS will tell us if the investment is worthwhile.

There are additional concerns. For example, the creation of the several components of the NCATS will require most, if not all, of the funding accorded the NCRR in order to support these new directions. This means that cuts to other programs could ensue. Among the most controversial consequences of eliminating the NCRR is the future of such programs in the NCRR portfolio as the Research Centers for Minority Institutions that supports centers as the name implies, and the Institutional Development Award (IDeA) program that supports such statewide infrastructure development incentives as the IDeA Networks of Biomedical Research Excellence (INBRE) program, and the Centers of Biomedical Research Excellence (COBRE) program that underwrite the creation of thematic, multidisciplinary centers, all in states with historically low levels of Federal funding. These programs are intended to provide diversity and correct the geographical inequalities in research support. These fairly small programs produce a huge return on investment, and add to the economic impact of academic health centers in small and medium-sized communities, which is in the order of >\$3 billion for an average medical school [1]. The ramifications of this reorganization are likely to have considerable and lasting impact.

MAKING NIH FUNDING MORE EQUITABLE AND EFFICIENT

Most of the research in academic health centers in the United States is done under the auspices of the NIH. The NIH budget is currently around \$31 billion, which is about 0.27% of the Gross Domestic Product (GDP), and about one half of what most developed countries spend on research. It can be argued that we do not spend enough on research. On the other hand, the United States spends twice as much for health care per capita as other developed countries, yet lags behind other wealthy nations in such measures as infant mortality and life expectancy. This can be interpreted

to mean that the way we distribute our research dollar does not have sufficient impact on health care. Moreover, as mentioned in the preceding text, there is a regional inequality in the funding of biomedical research, being concentrated on the two coasts. The top 10 institutions are awarded about a third of all NIH extramural funding, while the next 40 institutions receive over one half of all the grant money. Institutions in states that account for over 20% of the population receive less than 10% of all awards. The NIH has instituted a number of measures to improve medical research. For example, during the Clinton administration, the NIH budget was doubled over a 10-year period. This had the effect of funding much new research and attracting three times the number of scientists into research, but it also made grants not twice, but three times more competitive. In the meantime, the disparity between the “haves” and the “have-nots” grew more severe. Such programs as INBRE and COBRE are essential to developing diversity in facilities throughout the country, increasing areas of research excellence, and serving the needs of all taxpayers. This is especially true when the issue is one of improving health for the public at large.

One massive cost that has not been addressed but could save millions of dollars is the establishment of a national indirect cost rate. Indirect costs are subsidies to the institution holding an NIH award for expenses incurred by the facilities related to the performance of the award such as heat and air, cleaning, purchasing, human resources, accounting, regulatory oversight, and so on. That is, an institution with a 50% indirect cost rate that is granted a \$1 million award will actually receive \$1.5 million, \$1 million in direct costs and \$0.5 million in indirect costs. Unfortunately, many institutions have negotiated rates as high as 100% or more. The same \$1 million award at one of those institutions would cost NIH \$2 million or more for performing the same research project. A national indirect cost rate of, say, 40% would be a good starting point toward saving millions of dollars that could be used to implement more fundable research grant applications.

HOW MUCH FUNDING IS NEEDED?

While the current level of funding at \$31 billion would seem impressive, lack of investment in research is much more expensive. The current NIH budget is divided into support for research grants (~85%) that includes backing for 50,000 awards and 325,000 scientists, support for the NIH intramural program (~10%), and pretty reasonable costs for administration (~5%). It is estimated that, for every dollar spent on research, it generates \$2.1 dollars to the local economy in terms of creation of jobs for highly skilled workers, faculty salaries, and so on [1]. A report by the Joint Economic Committee of the United States Senate in 2000, entitled “The Benefits of Medical Research and the Role of NIH,” estimated that publicly funded research in general generates high rates of return to the economy,

averaging 25–40% per year [6]. Compare this rate of return to the corporate model, where corporations often use an expected rate of return of 15% as the minimum for considering investments. “Despite the great success of medical advances in reducing health care costs for many diseases, there is concern that new medical technologies continue to drive health care spending upward. Certainly, NIH funding has created an increased *supply* of new technologies for diagnosis and treatment. However, the main reason that health care costs have risen quickly is the prevalence of third-party payers in the US health care system. Third-party payment in its current form artificially increases *demand* for health care by reducing incentives to use cost-saving technology” [6]. A more recent Wellcome Trust report from 2008 studied the economic benefits of the United Kingdom’s public and charitable investment in medical research [7]. The report concluded that the health and economic gains were equivalent to a 37% annual rate of return for mental health research *in perpetuity*. This analysis also found that the delay between research expenditures and health benefits was 17 years on average. They emphasized that shortening this time lag would improve the rate of return. Translational research is designed to accomplish just that. In the last chapter, we will discuss the benefits of translational research, and how academic health centers can reinvent themselves to regain the steadfast support of the public at large so necessary to the continued success of medical research.

There is also the danger of losing our leadership in biotechnology and medical research to countries that spend more of their GDP on biomedical research. This means that we need to fund research to the highest levels possible. What levels? When President Obama instituted the American Recovery and Reinvestment Act, an additional \$10 billion dollars was thrown into the health care research pot. NIH and other agencies responded quickly to issue imaginative and purposeful requests for applications (RFAs). Some programs with 30 or so awards to make expected to receive a few hundred applications. They received thousands. In one case, a program that was to fund 300–400 grants received over 23,000 applications. These data suggest that there are currently enough meritorious applications to accommodate a \$10 billion increase in the NIH budget. However, given the history of the doubling of the NIH budget in the 1990s, such increases should be implemented more gradually in order to account for the increased number of scientists and applicants. Unfortunately, only cuts to this budget are being contemplated, mortgaging our future further.

How does an agency review 23,000 applications instead of a few hundred? Usually, a review committee for individual investigator applications will convene 15–20 experts in the field, with each reviewing 5–6 applications, and most applications requiring three reviewers. Of the 60 or so applications considered by a committee, only a few will earn a fundable score. The review of thousands of applications would require thousands of reviewers. While many scientists consider performing NIH reviews to be a

duty as a researcher and faculty member, an equal number avoid the workload these reviews entail. Grant reviews are time consuming and difficult, requiring hours of reading per application on the part of the reviewer. The response of NIH to this complaint has been to reduce the length of the applications. Applications had a 25-page limit for many years, with about one half of the material representing experimental design and methods. Applications are now half that length. While this requires better writing on the part of the applicant, the brevity of the application places the applicant at a disadvantage since a reviewer can easily dismiss an application because it does not have enough “detail,” especially in the methods. This is used by some reviewers, whether justified or not, to triage applications, with little chance of appeal or recourse, generating uncertainty about the review process.

The NIH has also reduced the review committee meetings from 2 days to 1 day. This decreases the amount of time each application is discussed. During the review, applications that used to be discussed at length are now discussed for 15–20 minutes, depending on the degree of differing opinions by reviewers. In 90% of cases, all three reviewers are pretty much on the same page, and their scores reflect the consensus. The shortness of the review, however, makes it more difficult to determine if a reviewer is actually correct in the assessment, and there is little time for insisting that reviewers justify their opinions. This introduces additional uncertainty about the review process.

For years, the NIH review committees functioned under a scoring system that allowed reviewers to assign scores from 1.0 (best) to 5.0 (worst) with decimal places, that is, 1.1, 1.2, and so on. Most reviewers tended to use only one half of the range and score most grants between 1.0 and 2.5, that is, they had a range of 25 possible scores. Because of the number of highly meritorious grant applications, fundable scores tended to cluster between 1.0 and 1.6, or even lower. Awards were made using a percentile calculation across multiple review committees, and funding percentiles were at about 20 or less. As funding became more difficult due to flat budgets, especially during the GW Bush administration, purchasing power decreased due to inflation, and competition increased. Scores became even more compressed, between 1.1 and 1.3 or less, while funding levels decreased to 10 or even lower percentiles. NIH then decided to change the scoring method, introducing a 1–9 scoring range using only whole numbers. As expected, most reviewers use only one half of the range, that is, 1–5, so that now there is a range of five possible scores. Therefore, the discrimination between grant applications has decreased by 80%, adding further uncertainty to the review process. While NIH administrators may believe that reviewers will ultimately find a happy medium and use the whole 1–9 range, the fact is that this did not happen for years using the 1.0–5.0 range of scores. The current scoring system simply may not be discriminating between the best and the best of the best.

However, it should be noted that the peer review process at NIH has worked well for many years, excellent science is still supported, and most scientists do trust the system. The problems cited represent issues that undermine trust and do need remediation, but the process in general does work and it works well. How do you fix these (given the larger picture, minor) problems? First, reviewers need to justify their opinions better, making it imperative that the chair and other members of the committee question apparently unsubstantiated opinions. Second, the issue of lack of detail in methodology should be granted only partial weight, especially if the applicant has published previously using the methodology. Third, a wider range of scoring should be used, the current system will only lead to frustration and undermine the credibility of the review process. The key is to create confidence that the review process is fair, which it is in the vast majority of cases. It is the overcritical nature of many reviewers that undermines the process, with less thought given to the implications and potential benefits of the research. Any application can be nit-picked to death, so that it is incumbent on administrators, chairs, and members of review panels to determine when this is happening and put a stop to it.

Funding for translational research needs to be unbiased and sufficiently critical to ensure its validity, but without retreating into the overused excuse that experiments on humans cannot be as well controlled as those on animals. The experience of the reviewers in this field will be critical in ensuring accurate reviews. In addition, RFAs and program announcements for funding should be less restrictive, allowing for circular models of translational research to be applied. Reviewers with “big picture,” rather than “nit-picking,” attitudes will be sorely needed. Knowledge of the great number of options available for performing translational research, some of which will be discussed in the following chapters, will be essential in determining which science should be funded.

MEDICAL RESEARCH FUNDING IN EUROPE

The level of Federal funding in Europe is <15% than that of the United States, although there are almost as many scientists [8]. While the NIH budget was being doubled, increases in Europe amounted to <25%. Much of the funding in Europe is dedicated to applied research, while most of the funding in the United States is dedicated to basic research. European research and development accounts for ~1.9% of the GDP in the larger countries, and much less in smaller, newer members of the European Union (EU) [8]. Most research in Europe is carried out in state universities, which are mainly supported by national and local governments. However, new initiatives are driving research in new directions. More attention is being paid to research by such entities as the Wellcome Trust Foundation in the United Kingdom, and declarations proposing an increase in the national

investment for research to approach 3% of the GDP have been issued. In addition, the formation of a European Research Council (ERC) has been proposed, but current economic forces make it unlikely at this time.

Only ~€5 billion of the ~€50 billion research and development budget of the EU is dedicated to basic research [6]. Initiatives for translational research have yet to be implemented and funding allocated for such avenues. Funding from the EU as well as member nations need to be committed to an entity such as the ERC. Hopefully, the ERC can avoid some of the problems in the US funding mechanisms, keeping in mind that, despite the criticisms leveled at some of the mechanics, the fact is that the peer review system at NIH is an excellent example of fair and equitable scientific peer review. As in the United States, Europe faces an aging population, increasing rates of obesity, diabetes, mental health disorders and neurodegenerative diseases, rising allergic disease rates, and the daunting tasks of addressing cancer and cardiac disease. There is little doubt that scientific excellence and creativity are alive and well in Europe, witness the growing number of Lasker Award and Nobel Prize winners from the EU.

Initiatives for translational research in Europe lag behind those being implemented in the United States, mainly because of the lower level of support for basic research. However, Europe has a considerable base of clinical trials (mostly initiated from the United States), with a clinical trials network, the European Clinical Trials Network, and a new oversight agency similar to the FDA named the European Medicine Agency. Therefore, the transition to translational research should not be too difficult, given appropriate increases in support for medical research.

Specifically in the United Kingdom, the scientific research that is funded by the government is regulated by the Research Councils. Two research councils fund neuroscience research: the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). Recent important changes in the grants schemes offered by the Wellcome Trust, one of the major funding sources for biomedical research in the United Kingdom, have produced an overload of applications to the MRC (and possibly the BBSRC). This has decreased the funding levels in the MRC to one of the lowest levels in recent times. This situation has been aggravated by recent funding cuts. In this scenario, one of the predictions is that attention will now shift to the funding opportunities from charities supporting research oriented to cure or advance the knowledge of specific neurological diseases. This may increase the awareness in the basic science community to produce research with more translational possibilities.

However, it is clear that there is insufficient pressure from the MRC to fund translational neuroscience, even though the MRC is committed to fund research with potential clinical applications. As with NIH, all grant proposals submitted to the MRC are required to identify the public and economic benefits as well as the specific potential for any given proposal to advance the medical knowledge and to provide therapeutic possibilities.

Although this has become mandatory in every application, many of these are without a clear strategic plan of how could this be achieved.

On the other hand, in the United Kingdom (as in the United States), some basic scientists consider that the funding opportunities for pure basic research are increasingly more restricted. Most of the funding needs to be justified in terms of immediate or medium-term benefits for the society. Thus, the lack of clear funding channels for distinct research purposes produces ambiguity in the scientific community with regard to the most appropriate sources of funding for distinct research programs. Separate funding channels for distinct types of research, from basic to translational to implementation in the community, may help to shape the priorities for each funding body and unclog those opportunities where translational neuroscience could most benefit.

Other efforts have been initiated during the education and training of new generations of medical doctors. Some UK universities encourage medical trainees to enroll in a laboratory and carry out a project for a variable period of time, usually no less than 3 months. This allows future generations to obtain first-hand experience at the bench and appreciate how basic science is carried out, closing the gap between basic science and clinical professionals.

In conclusion, there is room for improvement in the support of translational research in Europe. There is no systematic endeavor to bring together basic and clinical scientists, and this ends up being a matter of personal choice for each scientist rather than a program strategy. More efforts are needed to support that part of the scientific community that is able to translate basic research findings into therapeutic benefits, as is encouraged by privately funded organizations and universities across Europe.

It should be noted that Asian countries are investing in research and development at higher levels. While the GDP in China has doubled in the last 10 years, its investment in research is increasing dramatically to about one-third of the levels in the United States. As their GDP grows, so should their investment in research and development. However, it is unclear how much is devoted to basic research, since target areas, like stem cell research, are being funded disproportionately, and most funding is still for applied programs.

Despite the mostly negative news on the research enterprise, we know that the current downturn is tied to the economy worldwide. This downturn will doubtless be followed by an upturn, with a reestablishment of effective funding levels. The scientific community can hasten the return of solid support from funding agencies and governments at large if they help justify their efforts, and if they draft research that addresses the needs of the public health. A simple way to accomplish that is to place a premium on translational research. The perception is that for too long funding has been directed at curiosity-driven research, with less attention paid to the pipeline of new treatments and cures. We know that basic scientific research,

especially brain research, is absolutely essential to the understanding of brain processes, and, therefore, necessary for the development of those cures. However, there is plenty of room for translational research that addresses immediate health care concerns. The more the funding agencies, governments, and the public at large are informed about these efforts, the faster proper support for all research efforts will return.

The next chapter will discuss T1 and T2 blocks to translational research and how these can be overcome through a mentoring and career development program, while the following chapter will describe how infrastructure, in the form of core facilities that meet translational research goals, can be developed. Following several chapters describing examples of translational research, the final chapter will discuss how basic science and clinical departments can develop novel interactions to optimize translational research. Such reorganization could take advantage of the new funding avenues available, all in order to help improve the health of the public, while maintaining preeminence in biomedical research in both the United States and Europe.

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