

## EDITORIAL

### Lost in Translation—Basic Science in the Era of Translational Research<sup>∇</sup>

**The concept of translational research, which aims to facilitate the application of basic scientific discoveries in clinical and community settings, is currently in vogue. While there are powerful forces driving this trend, support for translational research must be accompanied by a robust investment in basic science, which provides the essential raw material for translation and continues to represent humanity's best hope to meet a wide range of public health challenges.**

“Poetry is what gets lost in translation.”  
 —Robert Frost

No, we're not talking about ribosomes. Translational research is defined as “the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease” (<http://grants1.nih.gov/grants/guide/pa-files/PAR-02-138.html>), sometimes abbreviated as “from bench to bedside” (<http://www.nihroadmap.nih.gov>). Although there is no universal agreement on what the word “translational” really means (16), there is no denying that translational research is the buzzword of the moment. In 2006, the NIH launched a Clinical and Translational Science Awards consortium of nearly 50 centers throughout the country, with a committed investment of \$500 million annually by 2012 (1; <http://www.ctsaweb.org>). In 2009, the American Association for the Advancement of Science announced the publication of a new journal, *Science Translational Medicine*.

There are obvious reasons for the new emphasis on translational research. One is political. With ever-present political pressure on NIH administrators to demonstrate the tangible public benefit from the billions of dollars invested in scientific research, translational research is an easy sell—the testing of new treatments, vaccines, and diagnostic tests. Another is to fill a genuine need. A number of factors have combined to impede the flow of information between basic science and clinical medicine, perhaps most notably a lack of sufficient resources to support early-stage investigation and the challenges involved in organizing clinical trials. The new focus on translational research aims to remove these obstacles and facilitate and expedite the practical application of scientific discoveries. A third reason is an increasing impatience with the pace with which basic scientific discovery has resulted in new products and cures. Although translation of the molecular biology revolution into genetically modified crops, recombinant drugs, molecular forensics, and nascent gene therapy within a mere generation has been rapid by historical standards, the age of instant communication and fast-forward remote control buttons has created even greater expectations. For feared diseases such as cancer, AIDS, and Alzheimer's disease, progress toward prevention or cure has not been as rapid as many would like. Hence, some of the impetus toward translational research comes from an impatient public speaking through its political leaders, who are the ultimate source of support for most scientific investigation through federally supported research. Finally, there is in some scientific fields, such as immunology, an increased awareness that observations from animal models do not always precisely extrapolate to humans. For this reason,

more translational research in humans is believed to be essential, despite the complexities and logistical hurdles posed by such research.

In a different era, Vannevar Bush argued strenuously to President Truman that the federal government should invest in basic science. He presciently observed the following:

“Discoveries pertinent to medical progress have often come from remote and unexpected sources and it is certain that this will be true in the future. It is wholly probable that progress in the treatment of . . . refractory diseases will be made as a result of fundamental discoveries in subjects unrelated to those diseases, and perhaps entirely unexpected by the investigator. . . . Basic research is the pacemaker of technological progress. . . . New products and new processes do not appear full-grown. They are founded on new principles and new conceptions, which in turn are painstakingly developed by research in the purest realms of science” (2).

In Bush's view, basic research would be performed by academia, and applied research would be performed largely by industry and government facilities (11). The conceptual dichotomy of basic and applied research has proven to be an enduring one. The late Daniel Koshland viewed basic and applied science as “revolutionary” and “evolutionary,” respectively, summarizing the difference thus:

“Basic research is the type that is not always practical but often leads to great discoveries. Applied research refines these discoveries into useful products” (8).

And so basic research discoveries, such as semiconductors and the structure of DNA, have revolutionized electronics and biology, making possible the laptop computer on which this essay was composed and the molecular research to which so many of us have devoted our careers.

The consensus forged after the Second World War that basic and applied research were the domains of academia and industry, respectively, began to fade to in the 1980s when the Bayh-Dole act allowed universities to patent knowledge obtained with federal funding. Universities ascertained that certain discoveries were enormously lucrative, and academic scientists began to emerge in a new role: that of the discoverer-entrepreneur. Within a decade, all major universities developed offices specializing in intellectual property to promote the protection and commercialization of scientific discoveries. Whatever the merits of this approach, one outcome was the blurring of the intellectual boundaries between academia and industry. Hence, scientists that formerly worked solely on basic biological mechanisms found greater freedom to develop their research along more practical lines, with the encouragement of their institutions. Furthermore, universities learned that it was much easier to connect with the public as well as with potential benefactors by highlighting their translational advances rather

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than their basic science discoveries. Translational research generated revenue, brought publicity, and enhanced public relations. In the evolving zeitgeist, academia is no longer viewed as an impartial champion for basic research.

Recently we considered the definition of “importance” in science and concluded that this quality is a function of four parameters: size, practicality, integration, and newness (3). From this perspective, basic and translational science differ primarily in integration and practicality, respectively. The importance of basic science derives from its contribution to knowledge deeper within the tree of information and, consequently, its greater potential for integration with other facts. In contrast, the importance of translational science lies in its practicality. Hence, we do not view basic and translational science as one being more important than the other but rather as complementary areas of human endeavor, with the important distinction that basic science findings often precede advances in translational science. We also note that observations in translational or applied science can generate new questions for fundamental research, as illustrated from the fact that vaccination preceded the field of immunology. Hence, the epistemological flow is bidirectional, and investments in both types of science are needed. As we scan a recent issue of *Infection and Immunity*, we see a stimulating mix of basic research, such as a novel mechanism by which diverse bacterial toxins stimulate expression of a host transcription factor (6), and applied or translational research, such as the improved immunogenicity of an anthrax vaccine following the addition of a heterologous helper T-cell epitope (12)—which seems just as it should be.

If the current emphasis on translational research leads to more scientific applications that benefit human society, that will be all for the better. However, it will be critical not to allow our impatience for translational applications to skew resources and researchers away from the open-ended exploration of the natural world that has provided the foundation for so many translational successes and remains as essential as ever. In other eras, generations elapsed between the discoveries of electricity and the light bulb or the laws of thermodynamics and the internal combustion engine. In our own less patient times, we note that retroviruses were discovered long before they were associated with human disease and that the dizzyingly rapid development of effective antiretroviral therapy against HIV was possible only because basic science had already provided the framework for rapid diagnosis and drug development. One might argue that the absence of an effective vaccine against HIV despite considerable efforts at translating what we currently know reflects an inadequate basic knowledge of immunology as it relates to retroviruses.

Writing in *Newsweek*, Fareed Zakaria recently expressed concern that America may have lost its innovative edge (17). He noted that the rest of the world is rapidly catching up and that bright young foreign scientists are no longer flocking to the United States as they once did. Citing the robust federal funding of basic science that began in the 1950s, he observed the following:

“Government funding of basic research has been astonishingly productive. Over the past 5 decades it has led to the development of the Internet, lasers, global positioning satellites, magnetic resonance imaging, DNA sequencing, and hundreds of other technologies.”

Whatever the need for further investment in translation, one must acknowledge that basic research has served us extremely well.

It is somewhat discomfiting that every grant application to

the NIH must now be evaluated on its practical merits, as if an obvious practical application is an essential requirement of all research (<http://enhancing-peer-review.nih.gov>). It is difficult to imagine how one might have justified the practical applications of basic research into the DNA polymerase of *Thermus aquaticus*, a thermophilic microbe with no medical or agricultural consequences, without the 20/20 hindsight provided by the development of the PCR. Similarly, how would one justify the practical applications of fungal metabolism research that led to the discovery of statins, without the hindsight that these molecules can lower cholesterol? Of course, all basic scientists have become proficient at writing justifications that “X will lead to improved strategies to prevent or treat. . .” in the introductions to their grant applications, but the words can sometimes feel disingenuous. Furthermore, such efforts neglect the marvelous “childish curiosity” of unfettered exploration that led to such unanticipated discoveries as antibiotics and statins (15). While one can be confident that increased scientific knowledge can lead to improvements for society, it is impossible to accurately predict from whence key breakthroughs will come. As Harold Varmus insightfully noted:

“Just investing in clinical trials and things that are very disease-specific would be a huge mistake. . . . Look at what pride people take now in advances made in diabetes and cancer research and infectious disease research. Almost all of it is based on recombinant DNA technology, genomics and protein chemistry. These are methods that grew out of basic science that was funded for years and years in a noncategorical way. Even if you move a little closer to the disease borders, you find that *predictability is not the mantle under which we fund this stuff*” (emphasis added) (4).

The scientific community must educate politicians and the public about how science really works, emphasize the complementary relationship between basic and applied research, and advocate more stable and sustained support of the nation’s scientific enterprise. Our goal in this commentary is not to pit translational versus basic research but rather to draw renewed attention to the tenuous present condition of basic research, which will continue to be the engine driving humanity’s hopes for curing disease, increasing productivity, eliminating poverty, developing renewable sources of energy, sustaining agriculture, and ameliorating climate change, to mention only a few current challenges. In the current enthusiasm for translational research, we must not forget that basic science is under threat. Medically related basic science research is particularly vulnerable because the NIH is the only source of support for much of this work, whereas applied research may be supported by a mixture of government, commercial, and private foundational sources. Moreover, over the past 2 decades industry has replaced the federal government as the leading source of support for research and development (Fig. 1). Funding trends have shown flat federal support for basic science for more than 5 years (7) (Fig. 2A). The success rate for individual investigator-initiated R01 applications has fallen sharply (9), as the proportion of federal awards and funding devoted to R01 projects has steadily declined over the past decade (Fig. 2B). Translators need something to translate. The time is ripe for a massive new national investment in science that includes basic research. Until the pendulum swings and basic science reemerges as a national priority, basic scientists will have to be imaginative in promoting the potential translational applications of their research, develop new methods to “humanize” their work (10), integrate their basic studies as components of larger translational programs, and hope that study sections will continue to

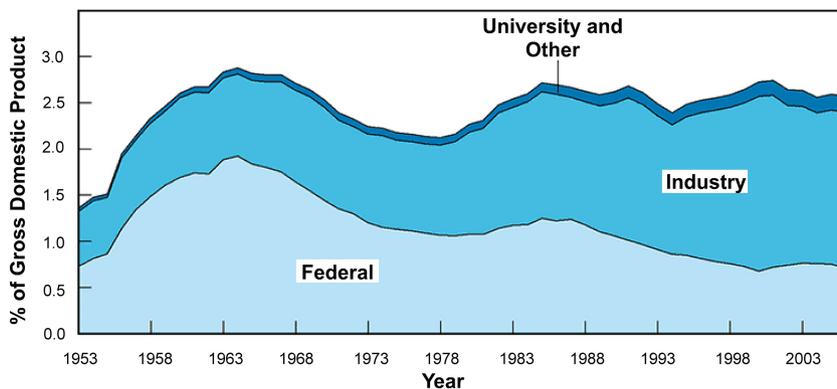


FIG. 1. U.S. research and development spending as a percentage of the Gross Domestic Product, 1953 to 2006. Reprinted from the Congressional Budget Office website (<http://www.cbo.gov/ftpdocs/91xx/doc9135/AppendixA.4.1.shtml>).

support good science even when it is not immediately apparent what the practical applications will be.

History has taught us that the path from basic discoveries to scientific and technological applications is seldom a straight line. Marie Curie described how her discovery of radium, which presaged the therapeutic use of radioisotopes, was purely serendipitous:

“When radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it” (5).

More recently, we have seen studies of insect embryogenesis

lead to a revolution in innate immunity (14), resulting in innumerable applications in drug and vaccine development. In her Nobel banquet speech, Christiane Nüsslein-Vollhard recalled her discovery of the Toll gene in *Drosophila*:

“We started out in our research with a deep interest in understanding the origin and development of pattern during embryogenesis. None of us expected that our work would be so successful or that our findings would ever have relevance to medicine” ([http://nobelprize.org/nobel\\_prizes/medicine/laureates/1995/nusslein-vollhard-speech.html](http://nobelprize.org/nobel_prizes/medicine/laureates/1995/nusslein-vollhard-speech.html)).

And when American Society for Microbiology member Carol Greider learned earlier this year that she had been

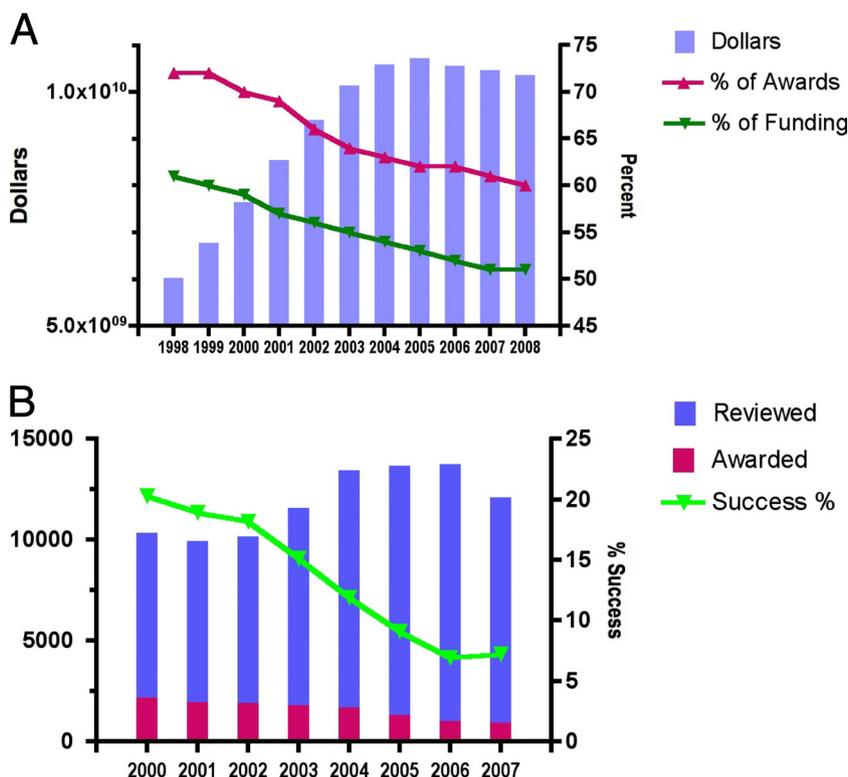


FIG. 2. (A) R01-equivalent grants as a percentage of all research grants and research funding. The graph was created from data available in the National Institutes of Health data book (<http://www.report.nih.gov/nihdatabook/Charts/SlideGen.aspx?chartId=32&catId=2> and <http://www.report.nih.gov/nihdatabook/Charts/SlideGen.aspx?chartId=33&catId=2>). (B) Outcome of new unsolicited R01-equivalent research grant applications. The graph was created from data reported in reference 9.

awarded the Nobel Prize for her groundbreaking work on telomeres, which may lead to advances in the treatment of cancer or the amelioration of aging, she emphasized the following:

“We didn’t know at the time that there were any particular disease implications. We were just interested in the fundamental questions. . . [this] is really a tribute to curiosity-driven basic science” (13).

Her words require no translation.

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#### Ferric C. Fang

*Editor in Chief, Infection and Immunity*

*Department of Microbiology*

*University of Washington School of Medicine, Seattle, Washington*

#### Arturo Casadevall

*Editor in Chief, mBio*

*Departments of Microbiology & Immunology and Medicine*

*Albert Einstein College of Medicine, Bronx, New York*

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*Editor: R. P. Morrison*