US Biomedical Research
Basic, Translational, and Clinical Sciences

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The National Institutes of Health (NIH) is the world's largest biomedical research agency, with a 75-year record of responding to the nation's key medical challenges. Today, medical science is entering a revolutionary period marked by a shift in focus from acute to chronic diseases, rapidly escalating health care costs, a torrent of biological data generated by the sequencing of the human genome, and the development of advanced high-throughput technologies that allow for the study of vast molecular networks in health and disease. This unique period offers the unprecedented opportunity to identify individuals at risk of disease based on precise molecular knowledge, and the chance to intervene to preempt disease before it strikes. Conceptually, this represents the core scientific challenge of the coming century. The NIH is committed to the discoveries that will change the practice of medicine as we know it in order to meet this challenge. The NIH Roadmap constitutes an important vehicle for generating change—a most critical element of this plan is the reengineering of the national clinical research enterprise. This reinvention will call for the transformation of translational clinical science and for novel interdisciplinary approaches that will advance science and enhance the health of the nation.

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THE NATIONAL INSTITUTES OF Health (NIH), a component of the US Department of Health and Human Services, supports more biomedical research than any other single entity in the world and plays a key role in shaping future research directions and in advancing the health of the biomedical research enterprise. The scope, depth, and momentum of the NIH research portfolio provides me, as director of the agency, with a unique view of the ways in which science is poised to radically transform the practice of medicine. Perhaps the most compelling prospect is the potential to practice preemptive medicine—by making use of precise molecular knowledge to detect disease before symptoms are manifest, and intervening before disease can strike.

National Institutes of Health programs both stimulate and complement private-sector medical research and development. In fiscal year (FY) 2004, the $28 billion NIH budget comprised about one third of national biomedical research spending, with pharmaceutical and biotechnology industry support accounting for $49 billion in 2004[1] and other federal and private sector entities making up the remainder. The NIH spends approximately 36% of its budget on clinical research, while the remainder supports long-term investments in fundamental biomedical research. The NIH is often the only source of funds for those studies considered too risky or lacking sufficient financial incentives to attract private capital, in areas such as vaccine development, or in the staging of large population studies designed to identify optimal strategies for the prevention of high-prevalence disorders. The training of future scientists represents a core responsibility of the agency. Supporting research to address the special needs of vulnerable populations and to study rare diseases represents additional areas in which public investment is considered essential.

Managing a $28 billion budget and a research portfolio that integrates public health needs and optimizes scientific opportunities constitutes a complex task. In carrying out this challenging responsibility, the NIH seeks input annually from more than 30 000 scientists and members of the public who serve on NIH advisory bodies, review groups, and expert panels.

The NIH awards resources based on a highly competitive, 2-tiered review process that serves to ensure that only the best ideas and scientists receive taxpayer dollars. In FY 2004, more than 64 000 research, fellowship, and training applications went through this rigorous review process, representing an increase of almost 50% over FY 2001. More than 80% of NIH funding is targeted to extramural research, which involves more than 200 000 scientists and other research personnel affiliated with more than 3100 organizations nationally and internationally. The NIH In-

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tramural Research Program (IRP) is composed of approximately 1250 principal investigators and accounts for almost 10% of the NIH budget. The IRP sponsors research that would be exceedingly difficult to conduct elsewhere given its public health importance and its need for long-term support. The NIH Clinical Center, situated on the Bethesda, Md, campus, is the world's largest clinical research hospital complex and serves internationally as a model facility for translational research and training.[2] The NIH strives to channel as much of its budget as possible directly into research; as a result, only 3.7% of NIH's FY 2004 budget, for example, was used to cover administrative expenses.

NIH: The Crown Jewel of Biomedical Research

Given the collaborative nature of this issue of *JAMA* in conjunction with the Lasker Foundation, it is noteworthy to report that NIH-supported scientists have been recognized with a total of 114 Lasker Awards out of the 186 awarded in the past 4 decades. The cumulative achievements of NIH scientists are difficult to overstate. For example, since the 1970s, death rates from coronary heart disease and stroke have decreased substantially,[3,4] partly as the result of innovative NIH research that yielded drugs to control high blood pressure, medications to reduce blood cholesterol levels, and surgical interventions to enhance heart function (eg, angioplasty, coronary artery bypass grafting), and that identified behavioral risk factors (eg, smoking, diet, exercise) associated with morbidity and mortality.[5] The National Cancer Institute has overseen a paradigm shift in cancer therapy associated with a significant increase in survival rates for certain cancers and the emergence of rationally targeted therapies. Recent advances in distinguishing molecular features of certain lung and breast cancers have led to the identification of subgroups of patients more likely to benefit from specific chemotherapies. For example, new research revealed a powerful prognostic indicator for breast cancer recurrence in patients with estrogen receptor–positive, lymph node–negative cancer.[6]

Similarly, the breakthrough success of highly active antiretroviral therapies relied on the insights of a large cadre of NIH-supported scientists who determined how human immunodeficiency virus (HIV) infects cells, driven by technological advances in molecular biology such as polymerase chain reaction. The recognition by NIH-supported researchers and drug companies that a "cocktail" of inhibitors—namely a combination of drugs from at least 2 classes of inhibitors—was most efficacious in blocking HIV transformed AIDS in the United States from an acute to a chronic disease, thereby preventing hundreds of thousands of hospitalizations and numerous premature deaths.[7]

National Institutes of Health researchers have also pioneered powerful new research tools such as high-throughput DNA sequencing, protein identification, expression arrays, and imaging technologies. These tools have greatly accelerated the research process, spurred progress, and spawned new hypotheses and discoveries in all areas of biomedical research. Perhaps nowhere else have the technological advances in imaging and genotyping elicited more excitement than in mental and behavioral health, for which NIH-supported investigators have recently elucidated genes linked to schizophrenia, depression, bipolar disorder, and anxiety.[8] In combination with functional brain imaging, researchers can now evaluate the brain circuitry involved in thinking, affective expression, and a broad range of behaviors.[9]

The NIH research community rapidly incorporates basic research findings, such as the discovery of a new regulatory pathway involving interfering RNA (RNAi) that turns off or "silences" genes,[10] and transforms these insights into powerful new research tools and potential new treatment strategies. The RNAi mechanism has already shown promise in treating many disorders. It has been successfully used in rodent models to inactivate a harmful gene in the neurodegenerative disease spinocerebellar ataxia type 1[11] and has been used to silence specific genes responsible for proliferation of tumor cells.[12]

In addition, NIH has a legacy of cultivating state-of-the-art information technology for use by biomedical researchers and physicians worldwide. For example, few biomedical scientists would consider beginning a project without first consulting the suite of powerful informational research tools available through PubMed, a growing digital archive of peer-reviewed research articles and scientific databases developed by NIH's National Library of Medicine (TABLE). More than 670 million searches are conducted annually through this freely available service.[13] The Web-based ClinicalTrials.gov represents a landmark effort to provide information on NIH-funded clinical trials to patients and physicians across the country and the world.

The Changing Landscape of Health and Disease

In part because of research advances, the burden of disease is now shifting from more acute and lethal forms of disease to more long-term and debilitating chronic illness. Paradoxically, success in treating conditions like myocardial infarction and many infectious diseases is allowing people to live longer. In addition, advancing chronological age is associated with risks of additional long-term and chronic diseases, such as congestive heart failure, cancer, Alzheimer disease, Parkinson disease, and diabetes. More individuals are living with cancer, as new therapies transform some acutely fatal malignancies into chronic and manageable conditions. Furthermore, rapid changes in environment and lifestyle create a disequilibrium between an individual's genetic constitution and the ability to adapt to these changes. A dramatic recent example is reflected in the increased incidence of obesity, due in part to the greatly increased availabil-

Table. Sampling of National Institutes of Health Information Resources

Resource	Description	Web Site
PubMed/MEDLINE	References, including abstracts, from thousands of biomedical journals	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed
PubMed Central	Free digital archive of biomedical and life sciences journal literature	http://www.pubmedcentral.gov/
ClinicalTrials.gov	Patient studies for drugs and treatment	http://clinicaltrials.gov/
MedlinePlus	Health information for patients, families, and health care practitioners	http://medlineplus.gov/
TOXNET	Network of databases on toxicology, hazardous chemicals, and environmental health	http://toxnet.nlm.nih.gov/
Unified Medical Language System	Electronic "knowledge sources" and associated lexical programs including SNOMED CT	http://www.nlm.nih.gov/research/umls/umlsmain.html
National Center for Biotechnology Information	Databases and tools for data mining, including BLAST and the Molecular Modeling Database	http://www.ncbi.nih.gov/
GenBank	An annotated collection of all publicly available DNA sequences	http://www.ncbi.nlm.nih.gov/Genbank/GenbankSearch.html
Online Mendelian Inheritance in Man	Catalog of human genes and genetic disorders	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Cancer Genome Anatomy Project	Generates the information and technological tools needed to decipher the molecular anatomy of the cancer cell	http://www.ncbi.nlm.nih.gov/ncicgap/

ity of food and reduced opportunities for daily physical energy expenditure. In all, chronic conditions disproportionately affect the nation's older citizenry: currently, 13% of the US population is older than 65 years, a figure that is expected to increase to 20% in the next 25 years.[14]

Infectious diseases remain the leading cause of death worldwide. Due in part to the ease of global travel, new pathogens emerge and familiar ones frequently reemerge with new properties. In the United States, the West Nile and monkeypox viruses recently surfaced. In Asia, avian influenza jumped to humans, and a new infectious disease, severe acute respiratory syndrome (SARS), arose. As basic knowledge accumulates and research tools become more sophisticated, the capacity for rapid response to these challenges is improving and will continue to do so. Within weeks of the first SARS reports, NIH-funded researchers helped identify its coronavirus etiology and develop diagnostic tests.[15] An NIH-developed candidate vaccine is now in human clinical trials.[16] The new recombinant DNA approach to vaccine production also yielded a candidate vaccine against the avian influenza H5N1 virus. Preliminary data from an NIH-industry partnership indicate that the vaccine is safe and immunogenic, and analysis of the full cohort is under way (John Jay Treanor, MD, et al, unpublished data, March-July 2005).

The intentional release of anthrax in 2001 underscored the reality of a bioterrorism threat posed by category A agents, including smallpox, plague, tularemia, hemorrhagic fevers, and botulinum toxin. The NIH has responded swiftly to the threat, developing promising vaccine candidates for Ebola and smallpox, both currently in clinical trials.[17-20] Identification of the 3-dimensional structure of the anthrax toxin complex[21] is fueling the search for compounds capable of blocking the toxin's effects; the discovery of the key mechanism of Ebola virus cell entry[22,23] included experiments demonstrating that Ebola infection could be blocked in laboratory tests.[24] The NIH has moved to quickly implement new Project BioShield grants and contracts to support the development of new and improved medical products to identify and treat infection with category A agents.

Despite these signs of tremendous medical progress, minority racial and ethnic groups continue to sustain an unequal burden of serious illness, premature death, and disability in the United States, and the NIH must work hard to change this reality. American Indians and Alaska Natives are more than twice as likely to develop diabetes than adult non-Hispanic whites of similar age.[25] African Americans have the highest incidence and death rates from all cancers combined.[26] Under the umbrella of the NIH Strategic Plan to Reduce Health Disparities,[27] the NIH sponsors research on the biological, social, and environmental factors contributing to health disparities and investigates whether key treatments are as effective for disparity subgroups as they are for the general population.[28,29] Efforts to increase the number of minority scientists in biomedical research are a significant element of NIH's efforts in this area.

Major Trends in the Biomedical Sciences

The life sciences are now entering a revolutionary period. Major trends in science, society, and economic forces will usher in an era of exceptionally rapid change in the way biomedical research is conceived and performed. The rapidly escalating costs of health care characterized by the shift from acute to chronic conditions, aging of the popu-

lation, persistence of health disparities, and new public health challenges such as obesity and emerging infectious diseases call for the acceleration of our basic understanding of the complexity of biological systems and increase the need for more effective strategies for pursuing translational and clinical science. In this genomic age, the rapid development of genome-related technologies and the massive increase in research data have begun to enable multidimensional studies of complex but common diseases and are forcing scientists to reevaluate current strategies for staging biomedical research.

Using these advanced technologies, detailed mechanistic studies can now be performed not only on a single molecule but on the interactions of thousands of molecules,[30] and, at the same time, it is possible to attempt to identify critical nodes of function. Applied clinically, these approaches offer an unprecedented opportunity for development of new disease classifications based on genomic, proteomic, and metabolomic profiles. The reclassification of disease based on specific molecular signatures is likely to be one of the most original contributions to clinical science in the 21st century. This revolution in approach to disease, based on the identification of at-risk individuals, using knowledge of precise molecular interactions, has the potential to enable presymptomatic detection and, ultimately, prevention of disease. The prospect of being able to preempt disease by intervening before it strikes, rather than after it damages the human body, represents the core scientific challenge of the century and, for many, constitutes the optimal pathway for attaining singular gains in human health.

The current practice of medicine needs to change radically over the next few decades. This will require continuing focus on and investment in basic discoveries, given that many of the fundamental features of control and regulation of normal and disease states are not yet understood. Biological research data will need to encompass more quantitative, spatial, and temporal elements, in addition to variables at the molecular, cellular, tissue, and organ levels, if scientists are to understand the complex interactions that drive biological systems toward health or disease.

To move this new era forward, the NIH must explore a multiplicity of approaches designed to facilitate the ability of scientists to rapidly enter new fields of research. This entails encouraging unconventional forms of collaboration across disciplines and within and across scientific teams to include, to a far greater extent, the physical and quantitative sciences. Effective scientific teams of the future will require closer working relationships among basic, translational, and clinical scientists. Traditional disciplinary, departmental, and other artificial organizational barriers will have to be breeched in an era of scientific convergence in which basic life processes have been shown to be common across disease conditions, chronic multisystemic diseases are the norm rather than the exception, and research tactics and strategies have become very similar across diseases.

Response to a Changing World: the NIH Roadmap

The NIH is committed to funding the highest-quality science and preserving the extraordinarily productive intellectual engine of investigator-initiated research, introduced initially by Vannevar Bush.[31] At the same time, in the face of the rapidly evolving scientific landscape and challenging new public health concerns, the agency's institutes and centers also are working cooperatively to jointly pursue a new vision for biomedical and behavioral research. In 2003, the NIH embarked on an unprecedented, trans-NIH endeavor, the NIH Roadmap for Medical Research.[32,33] This effort grew out of extensive consultation with more than 300 nationally recognized leaders in academia, industry, government, and the public. As a conceptual framework, the Roadmap aims to identify and support cross-cutting research needs that are beyond the scope of any single NIH component and that would significantly enhance the individual mission of every institute and center. Current Roadmap initiatives aim to bolster the development and availability of modern scientific tools and information resources, foster novel methods of research collaboration, and markedly enhance the nation's clinical research enterprise.

To develop the preemptive, predictive medicine of the 21st century, capitalize on the sequencing of the human genome, and take full advantage of recent advances in molecular and cell biology, the research community will require wide access to technologies, databases, and other scientific resources that are more sensitive, more robust, and more easily adaptable to researchers' individual needs. Such capabilities will accelerate progress and catalyze the formulation of research hypotheses heretofore unattainable by NIH investigators. The NIH aims to develop resources for investigators by focusing on building blocks, biological pathways, and networks; molecular libraries and molecular imaging; structural biology; bioinformatics and computational biology; and nanomedicine. Specific programs and resources under the "New Pathways to Discovery" theme are described on the Roadmap Web site.[34]

The NIH Roadmap also aims to reconfigure the scientific workforce by encouraging novel forms of collaboration. The scale and complexity of today's biomedical research problems demand that scientists move beyond the confines of their individual disciplines and explore new organizational models for team science. Advances in molecular imaging, for example, require collaborations among diverse groups—radiologists, cell biologists, physicists, and computer programmers, among others. Although researchers within the life and physical sciences have traditionally had limited interaction, it is only by forging these critical connections that the current gaps in terminology, methods, and approach that so seriously impede

progress can be eliminated. On another front, the NIH is actively fostering a novel mechanism to support uniquely gifted individuals through the Director's Pioneer Award program. This program provides 5 years of support and the intellectual freedom for highly creative thinkers to pursue high-risk efforts with the potential to solve some of the most difficult problems in biomedical and behavioral research. While some of these efforts may fail, the potential for reward may be considerable. Specific programs and resources under the "Research Teams of the Future" theme are described on the Roadmap Web site.[35]

Clinical Research: A New Discipline

Reengineering the national clinical research enterprise represents the most challenging but critical element of the NIH Roadmap effort. Major concerns have been repeatedly expressed at the perceived loss of talent in translational and clinical sciences over the past 25 years. Leaders in basic science are concerned at the increasing difficulty of finding talented, high-quality scientific collaborators who understand human disease and can both translate and clinically apply insights from basic science. The opportunities have never been greater to use modern research methods such as genomics, proteomics, metabolomics, high-sensitivity biochemical methods, and other novel strategies to bring new insights to the study of human populations.

Unfortunately, the exploding clinical services demands and shrinking financial margins at academic health centers have limited protected research time and curtailed the mentoring of young investigators. Young faculty members interested in the clinical and translational sciences have difficulty finding a real intellectual home for their career aspirations. In the meantime, translational and clinical sciences have greatly increased in sophistication and complexity, such that the development of talent takes many years. Moreover, given the regulatory barriers, the difficulty in designing and executing high-quality translational and clinical research projects, and the long lead times required to generate significant results, these investigators face substantial barriers to promotion, tenure, and capacity to secure a viable career track.

Institutions need to be organized to provide access to multidisciplinary teams composed of MDs, PhDs, nurses, laboratory scientists, and pharmacologists, not only as a service but also as a crucible of talented faculty members and trainees dedicated to the growth of translational and clinical science as a new and emerging discipline. Over the years, the NIH has endeavored to address these perceived shortcomings with the development of loan repayment programs and a variety of training and career awards. However, rapid scientific developments in this arena suggest that the issue is more fundamental and requires a new vision to move the nation's clinical research enterprise forward.

Stimulated by Roadmap efforts, the NIH is taking bold steps to transform the academic standing of translational and clinical science as a discipline. The NIH recently introduced the Institutional Clinical and Translational Science Award, a program that aims to shape and catalyze the development of an intellectual academic home for clinical and translational sciences. This initiative will foster the development of programs that are uniquely and flexibly tailored to match the strengths of individual institutions and to ensure provision of integrated support for research design and methods; biostatistics; biomedical informatics; regulatory affairs; inpatient, ambulatory, and community research facilities; and core laboratories. Education cores will include integrated curricula, degree-granting programs, and support for faculty positions to ensure career development and progression.

In the context of the NIH Roadmap initiatives to "Re-engineer the Clinical Research Enterprise," the NIH aims to develop a national system of interconnected clinical research networks capable of more quickly and efficiently mounting large-scale clinical studies. As currently conceived, this system of networks will integrate and expand extant research networks using common or interoperable infrastructure, including harmonized informatics, governance, terminology, and training. Future efforts will help define exportable practices for use in NIH's National Electronic Clinical Trials and Research Network (NECTAR), which will provide software application tools and a national informatics backbone for support of the clinical research enterprise. Collectively, these efforts will hinge on widespread deployment of health information technology and maximal interoperability of health care information systems, a major initiative in development by the US Department of Health and Human Services.

To better evaluate the totality of disease risk and create the capacity to survey disease across diverse populations, the NIH seeks broader involvement of communities and community-based care settings in conjunction with academic health centers. The NIH is currently investigating the feasibility of creating a National Clinical Research Associates Program—a proposed cadre of 50 000 trained and certified community-based health care practitioners (eg, physicians, dentists, and nurses) who will participate in clinical studies, enroll and follow their own patients in research, and be among the first to integrate new research findings into routine health care delivery. This initiative will offer a more efficient means to accrue the large groups of well-characterized participants necessary to enhance current understanding of gene-environment interactions.

As part of Roadmap efforts to enhance clinical research, the NIH has integrated the strengths of modern measurement theory, embarking on the development of a validated, dynamic system to empirically measure self-reported health symptoms (eg, pain, fatigue) and health-related quality-of-life domains (eg, emotional distress, social well-being, physical function)

common to a variety of chronic diseases. When operational, the Patient-Reported Outcomes Measurement Information System (PROMIS) will deliver individually tailored health outcomes questionnaires, facilitate comparisons among research studies, and enhance measurement precision of treatment outcomes.

On another front, there is great need to harmonize the complex, often overlapping, and confusing profusion of regulatory and reporting requirements that affect clinical investigators. In partnership with other federal agencies, industry, and the public, the NIH is leading an effort to harmonize and simplify regulations that protect human research participants, with a critical eye toward sustaining the public's trust in clinical research. As a start, the NIH recently developed the Genetic Modification Clinical Research Information System, a Web-based adverse event reporting system that allows investigators to simultaneously report adverse events involving gene therapy to both the FDA and NIH.[36] Additional information about the initiatives under the "Re-engineering the Clinical Research Enterprise" theme is available on the Roadmap Web site.[37]

Strategic NIH Research Plans

As the world's largest biomedical research agency, to keep pace with the dramatic evolution taking place in today's health landscape, the NIH must engage in a more proactive and coordinated approach to its research activities. The NIH Roadmap, which serves an incubator function for enabling high-risk science, represents only one way to tackle major health challenges. In some cases, more targeted approaches are in order. For instance, the NIH has embarked on trans-NIH efforts to address specific yet highly multidimensional problems such as obesity and neurological diseases and new opportunities such as stem cell research, all of which involve the participation of multiple NIH institutes and centers.

The NIH leads the national research effort to combat obesity through the Strategic Plan for NIH Obesity Research, a plan that stimulates partnerships across federal agencies and disparate communities.[38] Reflecting the complexity of the obesity problem, this coordinated guide for obesity research activities links researchers with expertise in numerous disciplines—such as genetics, biochemistry, behavioral sciences, and environmental sciences—to perform basic, clinical, and population-based obesity research.

Progress in the neurosciences has revealed unforeseen connections among nervous system disorders and heralded therapeutic and prevention strategies potentially applicable to many problems. Fifteen NIH institutes and centers are currently engaged in the NIH Neuroscience Blueprint, which is focused on developing tools, resources, and training in the neurosciences.[39] In addition to establishing neuroscience core facility grants that promote interdisciplinary collaboration and cooperation among scientists, the Blueprint will create new interinstitute programs that provide interdisciplinary training in cross-cutting areas such as neuroimaging and computational neurobiology.

The NIH is establishing Centers of Excellence in Translational Human Stem Cell Research[40] to accelerate preclinical studies using human stem cells in animal models of disease. These centers will bring together basic stem cell biologists, researchers, and clinicians with disease-specific expertise; physicians and surgeons skilled in novel modes of cell delivery; and investigators experienced in developing and assessing animal models of human diseases. The NIH envisions that this investment will target critical gaps in research that currently delay the conversion of stem cell research discoveries into new therapies, with the goal of moving this emerging science toward the clinic.

NIH: the Engine for the Biomedical Future

It is evident that the US investment in biomedical research has dramatically improved health outcomes. The achievements of the past century were driven by both technological breakthroughs and fundamental insights into biological systems. Current basic research continues to blaze a pathway toward illuminating the almost unfathomable complexity shared by all life forms. Unraveling this complexity of interwoven pathways will herald a sea change in the practice of medicine. The integration of insights from imaging, together with molecular details—which may include a patient's genome, transcriptome, proteome, and/or metabolome—will revolutionize disease classification. This detailed knowledge of human biology, along with the ability to detect even small perturbations in biologic networks, will signal an era in which potential therapies can be rigorously tested and tailored to the unique individual.

Admittedly, the goal of learning how to preempt disease within the span of this century remains a major challenge. But gains in more precise diagnosis and targeted treatment will provide the necessary leverage and insight to make this challenge a reality. Biomedicine will successfully reach the finish line only by funding the best science, whether it is "big science," "discovery science," or the traditional hypothesis-driven research. Above all, the NIH recognizes that a diversity of experimental approaches is absolutely essential to moving ahead. Research questions and strategies must encompass a wide range of alternatives, and it is critical that researchers learn to work productively and collaboratively across traditional disciplinary boundaries. The NIH, along with medical scientists, must strive to reinvent the clinical research enterprise and continue to seek and sustain the public's trust, steadfast in the commitment to protecting and improving the health of every American.

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