National Institutes of Health

Annual Performance Plan & Report

Government Performance and Results Act

- Initial FY 2005 Annual Performance Plan
- Final FY 2004 Annual Performance Plan
- FY 2003 Annual Performance Report

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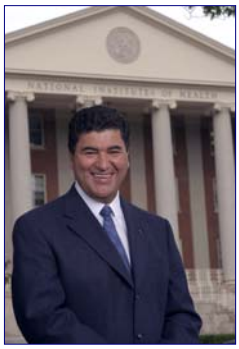
I. FROM THE DIRECTOR



In accordance with the Government Performance and Results Act (GPRA) of 1993, I am pleased to present the National Institutes of Health (NIH) Annual Performance Plans for FYs 2004 and 2005 and the Annual Performance Report for FY 2003. The report has more outcome goals and efficiency goals in all functional areas of our research program. The extensive narrative herein is evidence that performance is a high priority for the NIH and that the continued tracking of our goals and targets is an essential component of agency management.

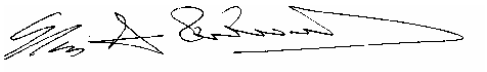
One of the agencies of the U.S. Department of Health and Human Services, the NIH is one of the world's foremost centers for the conduct and support of medical research.

The value of the Nation's investment in the NIH is easily appreciated when put in the perspective of the dramatic reductions in mortality and suffering in which NIH discoveries played a major role. These include:

- A 61 percent reduction in age-adjusted cardiovascular mortality rates since 1968
- A 61 percent reduction in age-adjusted stroke mortality rates since 1972
- A 70 percent reduction in annual deaths among people with acquired immune deficiency syndrome (AIDS) since 1995
- A reduction in transmission of blood transfusion-related diseases, such as infection with hepatitis types B and C viruses and human immunodeficiency virus (HIV), making the U.S. blood supply the safest in the world
- A decline in the age-adjusted rates of death for all cancers (from about 215 to 203 deaths per 100,000 in 1998) since 1992

Today, the NIH continues to meet its mission to uncover new knowledge that will lead to better health for everyone. For example, working with an international consortium, NIH-funded research resulted in the completion of the sequencing of the human genome – an accomplishment which will allow scientists to tackle disease at the most fundamental level. NIH funded scientists also decoded the DNA sequence of the anthrax microbe *Bacillus anthracis*, unveiling details of genetic information that will be invaluable in providing targets for the development of a new drug against this dangerous pathogen.

In the spirit of transparency and accountability, I look forward to reporting on our scientific research outcomes, our efforts to communicate and transfer results, our capacity building and research resources, our plans for strategic management of human capital, and our innovations in program oversight and improvement – all described in this Annual Performance Plan/Report for FY 2003, 2004 and 2005.



Elias A. Zerhouni, M.D.
Director, National Institutes of Health

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II. EXECUTIVE SUMMARY

II.A. MISSION STATEMENT

The NIH mission is to uncover new knowledge that will lead to better health for everyone.

The National Institutes of Health (NIH) undertakes activities and strategies in pursuit of the NIH research mission. NIH probes the unknown to gain new knowledge; communicates and transfers new knowledge to the public and health care providers; trains new investigators; and manages and supports the people, systems, and facilities necessary to carry out this work. All these activities are integral elements of the research enterprise that is striving to improve the prevention, diagnosis, and treatment of diseases and disabilities.

II.B. OVERVIEW OF PLAN AND PERFORMANCE REPORT

II.B.1. Summary of Measures

From FY 2002 to FY 2003, there is a 10 percent decrease in goals and a 44 percent reduction in targets. Of the FY 2003 goals, 78 percent are outcome goals, and 33 percent were efficient; 83 percent of targets were met. No goals were reported as unmet.

PROGRAM PERFORMANCE REPORT SUMMARY								
Fiscal Year	Goals				Targets			
	Total	Outcome	Output	Efficiency	Total	Results Reported	Met	Extended
1999	46	NA	NA	NA	86	86	80	1
2000	44	NA	NA	NA	88	88	78	3
2001	36	NA	NA	NA	90	90	83	2
2002	40	NA	NA	NA	80	79	65	12
2003	36	28	8	12	45	47[1]	39	8
2004	41	30	11	12	51	Performance results will be reported in February 2005.		
2005	39	29	10	12	50	Performance results will be reported in February 2006.		

NA = Not applicable

[1] Two additional targets were extended from FY 2002.

II.B.2. Overview of Performance Successes, Challenges, and Goals in Development

II.B.2.a. Performance Successes

The following are examples some of the most significant FY 2003 performance successes related to NIH GPRA performance goals, sorted by goal categories or functional areas:

Scientific Research Outcomes

- *Creation of a Haplotype Map (HapMap) Across all Human Chromosomes.* Building on the success of sequencing the entire human genome, NIH has begun development of the HapMap. The goal of the HapMap is to pinpoint sites of individual genetic variation across all human chromosomes. These sites, known as single nucleotide polymorphisms or SNPs, represent differences of one letter in a DNA sequence. A pattern of SNPs in a particular region is a haplotype, and cataloging of haplotype regions and the SNPs that tag them yields the HapMap. The value of the HapMap is that will allow scientists to study how genetic variation influences not only the development of common diseases (i.e., diabetes) but also its role in individual susceptibility to drugs, infections, and environmental factors. NIH has taken the lead in this international effort, in which samples from four populations around the world have been collected and are now being analyzed.

- *Expanding the Range of Methodology To Discover New Therapeutics.* As the Nation encounters an increasing diversity of infections that withstand traditional drugs, there is an urgent need to advance drug discovery. NIH has accelerated this effort by funding additional Centers for Excellence for Chemical Methods and Library Development. The goal of these Centers is to utilize a new and powerful strategy that can quickly generate unique chemical compounds ("chemical libraries"). These libraries, the methodology used to generate them, and the biological screening that will be performed will be shared among scientists. This collaborative process will serve to fast-track compounds into the drug development pipeline with potential for becoming new and desperately needed therapeutics for disease and disorders and that can improve the health of the U.S. population.

- *Genetic Link to Depression Discovered.* NIH-funded researchers, studying conduct disorder and depression in young adults, found a link between a specific gene and the development of depression. This clear interaction between genetic vulnerability and environmental events holds great promise for developing treatments that can manipulate the gene's activity and behavioral interventions that decrease the environmental influence. This finding also will have major impact on research in other psychiatric diseases and the search for their causes. Additionally, it may help researchers provide better treatment therapies for persons with depression.

- *Genomic Sequencing Exceeded.* NIH researchers were able to exceed the planned number of genomic sequencing, largely due to gaining a more efficient sequencing process. Ten bacterial pathogen and three protozoan sequences were completed. Additionally, NIH supported 36 large-scale DNA sequencing genome projects for microbial pathogens and invertebrate vectors of infectious diseases.

Communication and Transfer of Results

- *Communication to Reduce the Risk of Sudden Infant Death Syndrome (SIDS).* The national "Back to Sleep" public health education campaign is making strides in promoting back sleeping as the safest sleep position for infants younger than 1 year of age to reduce the incidence of SIDS. However, despite the overall success of the campaign, African American infants still sleep on their stomachs more often (68%) than white infants (51%). One of the ways NIH is working to reduce this disparity is through "Partnerships for Reducing the Risk of SIDS in African American Communities." NIH worked with the Alpha Kappa Alpha Sorority, Inc., the National Coalition of 100 Black Women, and the Women in the NAACP to sponsor summits in three regions of the United States that have both high rates of SIDS and large African American populations: Tuskegee, Alabama; Los Angeles, California; and Detroit, Michigan.

Capacity Building and Research Resources

- *Advent of Electronic Progress Reporting.* Developing the capability for end-to-end electronic research administration is a central goal of the NIH electronic research administration (eRA) system, NIH's infrastructure for conducting interactive electronic transactions for the receipt and review of applications and the monitoring and administration of NIH grant awards to biomedical investigators worldwide. Electronic reporting is now available to the original 65 institutions (as well as 80 additional FDP-participating institutions) participating in the Federal Demonstration Partnership.

Strategic Management of Human Capital

- *Ensuring That NIH Commercial Functions Are Efficient and Cost-Effective–NIH Wins Two MEOs.* In FY 2003, NIH conducted competitive sourcing reviews in the functional areas of extramural administrative support services and real-property management as required by Office of Management and Budget circular A-76. The purpose of these reviews was to determine whether NIH activities identified as commercial services can meet or beat the market competition. For both functions, the employee-developed "most efficient organization" (MEO) bids prevailed, and the services will continue to be handled by NIH employees. NIH has already carried out preplanning for FY 2004 reviews and has identified 10 functional areas for competition.

Program Oversight and Improvement

- *Improved Accountability for Organizational Performance Results.* To meet the Department-wide objective of results-oriented management, NIH implemented results-oriented performance plans for managers and supervisors. This achievement moves NIH closer to its goal of improving accountability for organizational performance results by (1) ensuring that all Institute activities flow from, and are aligned with, NIH and Department management objectives, and (2) promoting leadership accountability for results.

II.B.2.b. Performance Challenges

Programmatic

Over the past 5 years, stellar scientific advances have resulted and helped to revolutionize basic and clinical research. Along with the stunning achievement by NIH-supported scientists of sequencing the human genome, there have been dramatic advances in research technologies, ranging from large-scale DNA arrays to molecular imaging. Enhanced understanding of communication within the human body and of the regulation of activities within and among cells also is radically altering approaches to longstanding questions.

This burgeoning scientific opportunity stands side by side with a shifting and growing range of public health challenges. Chronic diseases have replaced acute conditions as the Nation's leading health concerns and are now responsible for more than 70 percent of all deaths. At the same time, dire new threats continue to emerge, such as bioterrorism. The AIDS pandemic continues to ravage developing nations and some of the most vulnerable members of the U.S. population, while new diseases, such as severe acute respiratory syndrome (SARS) and a new pox virus, continue to arise.

Improving the NIH GPRA Plan/Report

Integrating Budget and Performance. Using FY 2002 and FY 2003 funding to date, Institutes and Centers developed budget projections based on committed levels for continuation projects, both extramural and intramural. In addition, by working closely with scientific program staff, IC budget staff identified planned Requests for Applications, Requests for Proposals, and Program Announcements. Costs of these initiatives were also included in total estimates for each program goal. Estimates also included the number and amount of investigator-initiated grants likely to be relevant to achieving each program goal, based on historical trends. The full cost devoted to each identified segment is included in the Program Performance Tables on pages 18-39.

Reporting on Scientific Research Outcome Goals. The use of representative scientific research outcome goals with prospective reporting is the new GPRA approach for NIH. The inclusion of implementation strategy

samples and representative annual targets is NIH's approach to blend prospective reporting with the uncertainty of science discovery.

II.B.2.c. GPRA Goals in Development

Specifically, NIH is working on the definition of goals addressed in consolidation/restructuring. In response to government-wide efforts to look to consolidation and restructuring as ways of providing more responsive, flexible, and efficient administrative services, in April 2003 the NIH Director formed an Administrative Restructuring Advisory Committee (ARAC). Drawing on input from the ARAC, the NIH leadership prepared a restructuring/consolidation plan, which is under consideration by the Department. A version of that plan will be the basis for a future GPRA goal.

II.B.3. Significant Events

The three examples below illustrate how NIH builds on the science base and monitors and responds to public health needs. NIH actions related to these "events" (e.g., rapid action in response to an unanticipated incident such as exposure to anthrax, development of a trans-agency initiative to address a growing public health epidemic like obesity, or disseminating science-based information to address a chronic health problem such as hypertension) clearly demonstrate the Agency's performance in putting science to work for the public. The ability to respond quickly to acute and chronic health problems, including initiation of the next generation of research based on the current knowledge base, exemplifies the performance of the NIH research program.

The guideposts for NIH priority setting are public heath needs and scientific opportunity. As illustrated below, when "events" reshape need or opportunity, NIH plans, programs, and performance are significantly affected.

II.B.3.a. Biodefense

In September and October 2001 a terrorist deliberately exposed U.S. citizens to *Bacillus anthracis,* the microbe that causes potentially fatal inhalation anthrax. By January 2003 NIH had published two plans addressing the Nation's biodefense needs. The President proposed and Congress allocated a massive funding increase for biodefense research. The February 2002 *Strategic Plan for Biodefense Research* was not the first NIH biodefense research plan, but the events of fall 2001 dramatically reshaped NIH biodefense research.

II.B.3.b. Obesity

Obesity cuts 6 to 7 years from the lifespan—comparable to the effects of smoking—and costs an estimated $117 billion annually. NIH has established the National Task Force on Prevention and Treatment of Obesity to maximize trans-NIH collaboration; capitalize on the expertise of many NIH components in developing research initiatives to understand the genetic, behavioral, and environmental causes of obesity; and test new prevention and treatment strategies.

II.B.3.c. Prehypertension, Hypertension, and Stroke

NIH administers and coordinates the National High Blood Pressure Education Program (NHBPEP), a cooperative effort among professional and voluntary health agencies, State health departments, and many community groups. The lifetime risk of developing hypertension is much greater than once thought. NIH released findings from several studies related to this issue to address public health concerns. NIH is advancing prevention efforts and first-line treatments for prehypertension, hypertension, and strokes and is launching several activities to help the public and health care providers more effectively understand, prevent, and treat these conditions.

II.B.4. Major Changes in the Structure of the Plan

NIH has significantly restructured this latest NIH GPRA Plan/Report from the FY 2004 submission. This restructuring constitutes the second phase of a process that began with the February 2003 shift from Research goals that were comprehensive and qualitative to Scientific Research Outcome goals that are representative and specific. In this FY 2005 GPRA Plan/Report, NIH prepared a more streamlined document. NIH has achieved this by (1) including fewer measures, (2) making goals more outcome oriented, (3) increasing linkage to administration plans and initiatives, and (4) reporting full cost.

From FY 2002 to FY 2003, there is a 10 percent decrease in goals, a 44 percent reduction in targets, and 78 percent are outcome goals.

NIH also reorganized this Plan/Report to present activities as the one program that NIH conducts and supports—Research—undertaken in pursuit of the NIH mission. Under that program, NIH has five categories of performance goals that will be referred to as functional areas around which the Plan/Report is organized. These areas support the achievement of the research program they are as follows:

- Scientific Research Outcomes
- Communication and Transfer of Results
- Capacity Building and Research Resources
- Strategic Management of Human Capital
- Program Oversight and Improvement

II.C. CONTACT PERSON

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This document is for administrative use only and will not be published or posted on the World Wide Web. However, previous performance plans and reports are available at http://www1.od.nih.gov/osp/ospp/gpra/gpra_nih.htm.

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III. TABLE OF CONTENTS

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IV. PERFORMANCE PLAN AND REPORT

IV.A. INTRODUCTION

IV.A.1. NIH Mission, Functional Areas, and Description of the Agency

The NIH mission is to uncover new knowledge that will lead to better health for everyone.

Pursuing the NIH mission involves a wide range of activities to conduct & support research. These activities have been grouped under the following five functional areas with the purpose highlighted:

- *Scientific Research Outcomes*
  - Increase understanding of normal and abnormal biological functions and human behavior
  - Expand the generation of new scientific knowledge of innovative or improved prevention, diagnosis, and treatment of disease and disabilities

- *Communication and Transfer of Results*
  - Ensure that advances from science are shared for public benefit

- *Capacity Building and Research Resources*
  - Nurture a highly trained, multidisciplinary, and diverse talent base for the Nation's biomedical research enterprise
  - Maximize the ability of scientists to ask and answer questions through support for information technology, networks, and other infrastructure and resources
  - Enable highly effective research administration and agency management through information technology

- *Strategic Management of Human Capital*
  - Foster a highly skilled and diverse workforce focused on program goals
  - Enhance the work environment to support the effectiveness of personnel

- *Program Oversight and Improvement*
  - Promote program effectiveness and compliance with relevant laws and regulations

The NIH research mission is pursued by an array of individual Institutes and Centers (ICs), which work individually and collectively in partnership with an extensive extramural research community.

Institutes and Centers. NIH is composed of 27 ICs, whose research activities extend from basic research that explores the fundamental workings of biological systems and behavior, to studies that examine disease and treatments in clinical settings, to prevention, and to population-based analyses of health status and needs (a brief mission statement for each IC appears in Appendix 6). The Office of the Director, NIH, provides leadership, oversight, and coordination for the enterprise.

The ICs are the NIH "visible" to most Americans. Some of the ICs focus on diseases (e.g., cancer, diabetes); others concentrate on organ systems (e.g., heart, eye, kidney), whereas others focus on a stage of life (e.g., children, the aging population). Yet, no less essential to the Nation's health are NIH ICs that address overarching scientific needs and opportunities, including deciphering the human genome, understanding cellular and tissue biology and physiology, and developing the array of technologies dictated by the needs of cutting-edge research. All are scientific innovations that lead to discovery, move research findings into clinical practice, and lead to improvements in the quality of medical care. Most ICs support research and training through extramural activities and also conduct "in-house" science and training through intramural activities.

The Extramural Community. The extramural community is composed of non-Federal scientists at universities, medical centers, hospitals, and research institutions throughout the country and abroad. With NIH support, these investigators and their institutions conduct the lion's share of the research that uncovers new knowledge leading to improvements in the prevention, detection, diagnosis, and treatment of disease and disability. In tandem with the conduct of research, the extramural community contributes to training the next generation of researchers, enhancing the skills and abilities of established investigators, and renewing the infrastructure for NIH-sponsored research.

More than $8 out of every $10 appropriated to NIH flows out to the scientific community at large. The extramural research community numbers more than 212,000 scientists and research personnel affiliated with approximately 2,800 organizations, including universities, medical schools, hospitals, and other research facilities located in all 50 States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and points abroad.

NIH's Intramural Laboratories. A much smaller fraction of NIH funds, slightly less than 10 percent of the budget, supports a core program of basic and clinical research activities administered and staffed by NIH physicians and scientists. Approximately 1,250 principal investigators lead intramural research projects. This in-house, or intramural, research program includes the NIH Clinical Center and other resources that provide scientific, clinical, and educational benefits to citizens of the United States and the world.

Balanced Portfolio of Goals. This continuum of science discovery affirms the need for a balanced portfolio of goals, such that high-risk/ambitious goals as well as low-risk/probable goals and all those in between are included. NIH, with its vast investment in scientific research, articulates its portfolio in this way, using a framework that incorporates goals according to risk and time to achievement.

IV.A.2. Summary of Measures

From FY 2002 to FY 2003, there is a 10 percent decrease in goals and a 44 percent reduction in targets. Of the FY 2003 goals, 78 percent are outcome goals, and 33 percent were efficient; 83 percent of targets were met. No goals were reported as unmet.

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[1] Two additional targets were extended from FY 2002.

IV.A.2.a. Efficiency Measures

NIH has efficiency goals in all functional areas of the research program. The complex nature of biomedical research presents unique challenges that must be addressed in measuring efficiencies. First, the NIH enterprise is comprised of multiple scientific disciplines, which means that multiple variables apply to the overall research effort. Second, although the deliverables may be defined upfront, they may change due to serendipitous findings or due to the elimination of what heretofore was considered as fact. Third, the deliverables deal with the unknown, i.e., a patient's response to a trial vaccine, and the time and cost parameters are uncertain. Fourth, although the cost may create the appearance of a low yield ratio, the results are still valuable with long-term benefits.

Consider the emergence of severe acute respiratory syndrome (SARS) infections in 2003, which turned into an international crisis. Scientists around the world responded by determining the causative agent - a novel coronavirus – and made available genetic sequence data for further study. NIH spurred further research by purchasing SARS DNA microarrays and making them available (at no cost) to qualified investigators. These arrays consisted of a reference strain of the SARS coronavirus embedded in a quartz chip. Having a single lot of a reference DNA provided a baseline with which scientists could make comparisons with additional viral strains as they were discovered. Further, a family tree of the SARS coronaviruses could be constructed using the reference strain as the starting point. Without such a reference, laboratories would have had to develop their own individual baselines and comparisons would have to await agreement among multiple laboratories as to which strain to use. Thus, while NIH assisted the world's public health system to successfully stop SARS transmission last year, this efficiency was difficult to quantify.

NIH has developed a time-risk-cost continuum to address efficiency measures. NIH views efficiency as an overlay of baseline performance. It assesses the level of performance in comparison to baseline, and how the performance was achieved; however, it does not set the baseline. Using the concepts of time, costs, and deliverables within a scientific environment, efficiency can be viewed as (1) achieving annual implementation and improvement strategies, finding the hypothesized discovery(ies), and/or discovering other relevant findings before the projected time; (2) increasing the number of hypothesized or , serendipitous, research discoveries, products, and/or processes within the projected time (and eliminating or changing hypotheses based on findings); (3) completing annual strategies and/or making discoveries and/or other relevant discoveries under the projected budget; and (4) being necessary for the next generation of scientific discovery to be efficient.

Assessing efficiency in a scientific environment requires factoring in additional dynamics, including (1) the difficulty of the endeavor and (2) the effectiveness of the outcome. Difficulty measures the *level of risk* in achieving the outcome (uncertainty regarding the path to discovery and the likelihood of success) and the *scope* of discovery needed to achieve a particular goal (the range, depth, and uniqueness of the scientific questions entailed in the discovery). Effectiveness measures the extent to which the discovery accomplishes the intended result, e.g., for a new drug: Does it treat almost all cases of the disease for which it was developed? Is the level of side effects low? Is the cost reasonable?

NIH gathers information related to the efficiency, difficulty, and effectiveness of its research activities, and the systems for collecting and recording such information undergo continual improvement. To improve those systems and thus the Agency's ability to measure efficiency, difficulty, and effectiveness, NIH will further develop its administrative data collection systems, including the criteria for what data are collected and the mechanisms and algorithms for efficiency analysis and reporting.

Using the approach above, the 33 percent efficiency reported for FY 2003 Performance was determined by retrospective assessments. Efficiency was defined as having more product/outcome than expected and/or achieving the end result with less money or less time. It is symbolized with a superscript "e" in the Performance Table.

IV.A.3. Narrative Description of Layout of Plan/Report

Every activity at NIH is carried out in support of NIH's single mission: *To uncover new knowledge that will lead to better health for everyone.* Thus, this Plan/Report is structured to reflect a single program—Research—for the purpose of planning and performance assessment. Under that program, NIH carries out activities in five functional areas to accomplish its mission. This Plan/Report is organized around these five functional areas and relevant performance goals:

GOALS BY FUNCTIONAL AREA SUMMARY TABLE			
	FY03	**FY04**	**FY05**
Scientific Research Outcomes	27	28	27
Communication and Transfer of Results	1	4	4
Capacity Building and Research Resources	2	4	3
Strategic Management of Human Capital	3	2	2
Program Oversight and Improvement	3	3	3
Totals	36	41	39

This Plan/Report will first describe the research program, followed by the required Program Performance Table. Next, NIH presents the five functional area sections of the Plan/Report. Each section begins with text that introduces the functional area, followed by the FY 2003, FY 2004 and FY 2005 performance goals addressing that functional area. Each goal begins with a goal statement followed by background text to put the goal in context. Baselines and implementation strategies are presented to demonstrate the building blocks of science. A table that presents the targets NIH uses to measure performance on the goal follows. Finally, if the goal pertains to FY 2003, a performance summary is provided with the target achievements and advances on implementation strategies, and when applicable, efficiency is included.

An overview of each of the five functional area sections appears below.

- *Scientific Research Outcomes.* NIH research encompasses the support and conduct of investigations across the full range of the health research continuum, including basic research, which may be disease oriented or related to the development and application of breakthrough technologies; observational and population-based research; behavioral research; applied research; prevention research; health services research; translational research; and clinical research. Clinical research includes research to understand both normal health and disease states, move laboratory findings into clinical interventions, and assess new treatments or compare different treatment strategies and approaches.

- *Communication and Transfer of Results.* The new knowledge resulting from NIH research activities cannot benefit human health unless it is disseminated. Thus, a core NIH function is to facilitate the communication of research findings—both in the United States and abroad—to clinicians, public health systems, voluntary health organizations, and the public at large. Scientific knowledge is the bedrock of evidence-based prevention and treatment programs. The diversity of the U.S. population means that effective communication requires varied approaches. Equally important is transferring knowledge to the private sector to be used in the development of interventions, behavioral strategies, drugs, biomedical technologies, and devices that benefit health.

- *Capacity Building and Research Resources.* The productivity of the research enterprise depends in large measure on the strength of the talent pool and on the technological and other research resources available for use in investigations. Support for pre-doctoral and postdoctoral research training replenishes and revitalizes the talent pool with new highly trained investigators. Support for career development hones and expands the skills of those already performing research. In building capacity in the talent pool through training and career development, NIH particularly strives to augment the ranks of clinical researchers, enhance diversity, ensure well-trained foreign collaborators, and facilitate aptitude for multidisciplinary teamwork. Capacity building also encompasses improving and maintaining the Nation's biomedical research infrastructure. Also

fundamental to the productivity of the research enterprise are the availability and accessibility of essential research tools, cutting-edge technologies, animal models, reagents, and databases and other information repositories. This is because research resources reset the boundaries for what questions can be investigated. Within research resources, information technology requires special note. New technologies to share, transfer, and mine vast amounts of complex data electronically are revolutionizing the conduct of science and the management, administration, and support of the research enterprise.

- *Strategic Management of Human Capital.* NIH recognizes human capital as one of the most important resources of the organization. A qualified workforce, working in an environment that utilizes their strengths, fosters the effective and efficient implementation of the NIH research program. NIH aims in this area include delayering, competitive sourcing, and developing a plan for strategic recruitment and retention as well as continuity and leadership succession.

- *Program Oversight and Improvement.* Ensuring that NIH activities and strategies are carried out effectively and in compliance with all applicable laws and regulations requires careful oversight and thoughtful improvement in procedures, policies, and systems. Management systems need to be continually reviewed and updated to keep pace with advances in public administration, and mechanisms to ensure proper stewardship must evolve with the development of new requirements and rising thresholds for accountability. Meeting these challenges is a priority for NIH.

IV.A.4. Highlights of the NIH Contribution to Administration Initiatives

Highlighted below are a few of the significant FY 2003 performance results associated with NIH GPRA goals that relate to the President's Management Agenda, the DHHS Strategic Plan for FYs 2003-2008, and *Healthy People 2010*. The performance results listed below are a limited representation of NIH contributions to Administration initiatives. Within GPRA, and more significantly, beyond progress reported under GPRA goals, many more NIH activities address and help realize Administration initiatives. In the Program Performance Tables (see IV.B.2.a. on page 18), the reference field for each goal shows the link to the President's Management Agenda (), the DHHS Strategic Plan for FYs 2003-2008 (SP), and/or *Healthy People 2010* (HP). However, the presentation below, organized by each Administration initiative, provides a more direct perspective on the NIH contributions to those initiatives.

IV.A.4.a. President's Management Agenda (PMA)

Strategic Management of Human Capital

- *Delayered organizational units* (Strategic Management of Human Capital Goal (IV.B.2.b.4.a.). By the close of FY 2003, NIH completed delayering for each identified organizational unit.

- *Developed an initial strategic workforce plan* (Strategic Management of Human Capital Goal IV.B.2.b.4.c.). NIH has developed an initial strategic workforce plan as a first step toward a comprehensive plan for strategic management of human capital.

- *Created a leadership succession plan* (Strategic Management of Human Capital Goal IV.B.2.b.4.b.). The framework for a sustainable succession plan was built by coordinating existing programs and integrating concepts for needed new elements of succession planning.

Competitive Sourcing

- *Completed competitive sourcing competitions in accordance with OMB Circular A-76* (Strategic Management of Human Capital Goal IV.B.2.b.4.d.). In FY 2003, NIH preplanning identified two potential functional areas for review. These were deemed appropriate for competitive sourcing review and were reviewed. Also, transition plans were developed for empoyers affected by the reviews.

Improved Financial Management

- *NIH is poised to launch the first two modules of the NIH Business System* (Capacity Building and Research Resources Goal IV.B.2.b.3.b.). Implementation of the NIH Business System will allow for greater integration of administrative processes with the financial system and encompass new financial systems to comply with all applicable accounting requirements and standards.

Expanded Electronic Government

- *Electronic progress reporting in pilot-testing* (Capacity Building and Research Resources, Goal IV.B.2.b.3.d.). Developing the capability for end-to-end electronic research administration is a central goal of the NIH electronic research administration (eRA) system. eRA is NIH's infrastructure for conducting interactive electronic transactions for the receipt and review of applications and the monitoring and administration of NIH grant awards to biomedical investigators worldwide. After a setback when preliminary pilot-testing determined that an early prototype for electronic progress reporting was inadequate, NIH developed a more effective infrastructure; now, all 65 institutions participating in the Federal Demonstration Partnership are pilot-testing the system. In FY 2004, availability of electronic progress reporting will be expanded to all grantee institutions.

- *Implementation of the Enterprise Human Resources and Payroll system* (Capacity Building and Research Resources Goal IV.B.2.b.3.b.). NIH successfully implemented the Enterprise Human Resources and Payroll System (EHRP) in FY 2002. The EHRP is a Web-based system that feeds data to the Department's current Central Pay System. DHHS Personnel Offices will use the EHRP to process personnel action requests (e.g., promotions, reassignments) and employee benefits such as life and health insurance.

Budget and Performance Integration

- Using FY 2002 and FY 2003 funding to date, Institutes and Centers developed budget projections based on committed levels for continuation projects, both extramural and intramural. In addition, by working closely with scientific program staff, IC budget identified planned Requests for Applications, Requests for Proposals, and Program Announcements. Costs of these initiatives were also included in total estimates for each program goal. Estimates also included the number and amount of investigator-initiated grants likely to be relevant to achieving each program goal, based on historical trends. The full cost devoted to each identified segment is included in the Program Performance Tables on pages 18-39.

IV.A.4.b. DHHS Strategic Plan for FYs 2003-2008

The goals identified within the NIH Annual Performance Plan and Report enhance the fulfillment of goals within the DHHS Strategic Plan. The text below indicates selected goals of the DHHS Strategic Plan, and a brief description of how NIH goals are associated with them.

1. Reduce major threats to the health and well-being of Americans: 1.1 Chronic Diseases.

- *New Drugs Protect Nerve Cells in Parkinson Mice* (Scientific Research Outcomes Goal IV.B.2.b.1.-5.d.). Two experimental drugs appear to prevent Parkinson's disease-like brain damage and motor dysfunction in mice, according to investigators at the Gerontology Research Center. The finding identifies a new approach for slowing or halting the progression of Parkinson's disease that may one day help treat people who have it. In the study, dopamine-producing nerve cells in mice treated with pifithrin-alpha (PFTalpha), an experimental cancer treatment, and Z-1-117, a modified version of PFT-alpha, were more resistant to being killed by environmental toxins and pesticides such as MPTP, iron, and rotenone. These toxins are suspected of increasing the risk of Parkinson's disease in humans and can induce symptoms of the disease in rats and mice. The drugs also helped preserve motor function in mice exposed to these compounds. The investigators suspect the drugs work because they block the action of p53, a protein that may promote the death of dopamine-producing nerve cells.

2. Enhance the ability of the Nation's health care system to effectively respond to bioterrorism and other public health challenges.

- *Anthrax DNA Decoded* (Scientific Research Outcomes Goal IV.B.2.b.1.-8.a.). The sequence of the DNA of the deadly anthrax microbe *Bacillus anthracis* has been fully mapped by NIH-supported researchers. Remarkably, its DNA structure differs very slightly from that of its close relative, the common soil bacterium. In the more than 5,000 genes analyzed, researchers found only about 150 significant differences. But those genetic differences are enough to confer on *B. anthracis* its disease-causing properties. Researchers also found a number of genes that play a crucial role in the bacterium's ability to enter its host's cells. For example, *B. anthracis* has the capacity to scavenge iron—present in the majority of host organisms—to enhance its survival in its host. This information is valuable in providing new targets for drug development.

- *Potential Bioterrorism Agent Unmasked* (Scientific Research Outcomes Goal IV.B.2.b.1.-8.a.). Collaborative research, funded by NIH and the Defense Advanced Research Projects Agency, has deciphered the genetic blueprint of the bacterium *Coxiella burnetii*, the agent that causes a debilitating flu-like illness in humans called Q fever. *C. burnetii* is a potential bioterrorist threat because early diagnosis of the disease is difficult, and the microbe is a sturdy organism that can be aerosolized. Knowing the genetic signature of Q fever will allow scientists to find new targets for drugs, vaccines, and diagnostics.

4. Enhance the capacity and productivity of the Nation's health science research enterprise.

- *Human Genome Sequencing Finished.* In April 2003, the International Human Genome Sequencing Consortium announced the successful completion of the Human Genome Project more than 2 years ahead of schedule.[1] The sequencing of the human genome, which contains 3 billion DNA letters, now is essentially complete. As characterized by Eric Lander, Ph.D., Director of the Whitehead-MIT Center for Genome Research, the Human Genome Project transformed biology into an information science, able to take comprehensive global views of biological systems; with knowledge of all the components of the cells, scientists can tackle biological problems at their most fundamental levels. The accomplishment also represents a major boon to the growing field of comparative genomics in which researchers are attempting to learn more about human genetic makeup and function by comparing human genomic sequence to that of other organisms, such as the mouse, the rat, and even the fruit fly.

- *Protein Universe Mapped* (Scientific Research Outcomes Goal IV.B.2.b.1.-2.c.). The billions of proteins that make up life on Earth are almost as numerous as the stars in the heavens, and mapping them is almost as difficult. In a step toward charting the protein structure universe, scientists created a map of the protein shapes that nature repeats over and over again to construct the billions of complex proteins that make up life. The three-dimensional map shows similarities and differences among the protein shapes, letting scientists visualize the organization of all protein structures—the many possible twists, turns, and shapes—and see evolutionary changes that may have occurred over time.

7. Improve the stability and healthy development of our Nation's children and youth.

- *Summits Feature SIDS Risk Reduction* (Communication and Transfer of Results Goal IV.B.2.b.2.a.). The national "Back to Sleep" public health education campaign is having tremendous success in promoting back sleeping as the safest sleep position for infants younger than 1 year of age to reduce the incidence of sudden infant death syndrome (SIDS). Since the launch of the campaign, the SIDS rate has dropped significantly. However, despite the overall success of the campaign, African American infants are placed on their stomachs to sleep more often (68%) than white infants (51%). One of the ways NIH is working to reduce this disparity is by working with the "Partnerships for Reducing the Risk of SIDS in African American Communities." The partnership is a project with the Alpha Kappa Alpha Sorority, Inc., the National Coalition of 100 Black Women, and the Women in the NAACP. The leaders of these three organizations committed to hosting three summits featuring NIH SIDS risk reduction campaign information and materials. The NIH staff worked on a

[1] This research outcome was forecast in the FY 2003-2004 NIH GPRA Plan/Report—that the sequencing of the human genome would be essentially complete in April 2003.

one-to-one basis with the leaders of the three organizations to develop and support a strategic and operational plan for conducting the three summit meetings. The summits were held in three regions of the United States that have both high rates of SIDS and large African American populations: Tuskegee, Alabama; Los Angeles, California; and Detroit, Michigan. The fervor generated among the partners and participants at the summits demonstrated the power of fusing public, private, and volunteer organizations.

8. Achieve excellence in management practices (also see PMA above).

8.1. Create a unified DHHS committed to functioning as one Department.

- *Consolidated human resource management functions* (Strategic Management of Human Capital Goal IV.B.2.b.4.a.). NIH has consolidated its human resource management functions to serve as one of four DHHS human resources service delivery sites.

- *Implemented performance contracts* (Program Oversight and Improvement Goal IV.B.2.b.5.c.). The new DHHS performance contracts initially applied only to the Senior Executive Service. NIH has now "cascading" the new performance contract to all NIH supervisors and managers in two-grade interval professional positions, that is, those with two-grade promotion patterns (e.g., GS-9 to GS-11).

- *Initiated development of the NIH Business System (NBS)* (Capacity Building and Research Resources Goal IV.B.2.b.3.b.). Implementation of the NBS will allow greater integration of administrative processes with the financial system and encompass new financial systems to comply with all applicable accounting requirements and standards. The NBS serves as a proof of concept for and a major element of the DHHS Unified Financial Management System. As both systems mature, the NBS will merge into the single financial management system envisioned by DHHS.

8.2. Improve the strategic management of human capital (see PMA above).

8.3. Enhance the efficiency and effectiveness of competitive sourcing (see PMA above).

8.4. Improve financial performance (see PMA above).

8.5. Enhance the use of information technology (see PMA, on e-government, above).

8.6. Achieve integration of budget and performance information (see PMA above).

8.7. Reduce regulatory burden.

- *Made significant progress in shortening the application-to-award cycle* (Program Oversight and Improvement). NIH successfully shortened the time between grant submission and receipt of funds or notification by establishing the process of expedited en bloc Council concurrence. By the end of FY 2001, 13 Institutes were employing the process, thus making or providing notification of awards to the most meritorious grant applications in approximately 6 to 8 months from application receipt. Additional Institutes were expected to begin using the expedited process within the next year.

- *Streamlined administrative processes associated with non-competing applications* (Capacity Building and Research Resources Goal IV.B.2.b.3.d.). NIH worked with the extramural community to simplify the administrative processes required of grantees and identified ways to reduce the number of steps and information required for non-competing continuation awards. The streamlined non-competing award process has been integrated into the new electronic progress reporting system that is being pilot-tested with the 65 Federal Demonstration Partnership institutions under the NIH electronic research administration system. Continual efforts to simplify administrative processes have become an integral part of the electronic research administration effort. An operational practice now firmly established at NIH ensures that before any process is redesigned and made electronic, the NIH technical staff, the NIH policy staff, and

the affected community are brought together to collaborate on the most appropriate ways to streamline the processes and requirements.

IV.A.4.c. Healthy People 2010

13. HIV

- *Groundwork Laid for Potential New Class of Anti-HIV Drugs* (Scientific Research Outcomes Goal IV.B.2.b.1.-5.a.). Researchers funded in part by NIH have laid the groundwork for development of a potential new class of drugs—so-called assembly inhibitors—to treat people with HIV/AIDS. Although the current combination of reverse transcriptase inhibitors and protease inhibitors used against HIV can effectively lower a patient's viral load, lack of compliance and interactions with other drugs or diet can weaken the effect of these drug "cocktails," allowing resistant strains of HIV to emerge. Adding a new class of anti-HIV drugs such as assembly inhibitors to the mix may help solve this problem. The recently identified compounds bind to HIV-1 capsid proteins and prevent these molecular building blocks from assembling into the HIV capsid, a cone-shaped inner structure of the virus that houses viral ribonucleic acid (RNA), enzymes, and other key viral components. Although the compounds do not stop new viruses from assembling, they cause viruses to form with defective capsids, and these abnormal viruses cannot infect new cells.

14. Immunization and Infectious Diseases

- *Making Headway on Antibiotic Resistance* (Scientific Research Outcomes Goal IV.B.2.b.1.-3.b.). Understanding how bacteria develop drug resistance is crucial to controlling infectious diseases, which cost several million lives each year. In a recent tuberculosis study, NIH-funded researchers pinpointed a specific gene called DnaE2, which allows the tuberculosis bacterium (MTb) to mutate its DNA and, as a result, develop resistance to commonly used antibiotics. The role of Dna2E was further illuminated in mouse studies: Mice infected by the bacterium lacking the Dna2E gene did not develop resistance and responded to common antibiotics. On the other hand, mice infected with the normal strain of MTb died quickly, even when treated with common antibiotics. In another NIH-supported study, researchers found the source for the resistance of the malaria-causing parasite *Plasmodium falciparum* against the antimalaria drug chloroquine—a single gene mutation. Interestingly, the presence of this mutated gene, pfcrt, also makes *P. falciparum* more susceptible to two other antimalarial drugs, artemisinin and quinine. Overall, these discoveries for tuberculosis and malaria give scientists new ways to identify and attack the parasite's most vulnerable points.

- *Parasite, Mosquito Genomes Complete Malaria Picture* (Scientific Research Outcomes Goal IV.B.2.b.1.-8.a.). Genome sequences of *P. falciparum*, the most lethal malaria-causing parasite, and *Anopheles gambiae*, a mosquito that transmits the parasite to humans, were completed in October 2002. The sequencing of both *P. falciparum* and its insect vector heralds a new era in the fight against malaria. When joined with information about the human genome, a much fuller understanding of this disease and its transmission is now possible.

18. Mental Health and Mental Disorders

- *Lithium Shows Promise Against Alzheimer's in Mouse Model* (Scientific Research Outcomes Goal IV.B.2.b.1.-3.a.). In the May 22, 2003, issue of *Nature*, NIH-funded scientists reported that, in studies with cells and mice, by blocking the enzyme glycogen synthase kinase-3 alpha, lithium stems the accumulation of beta amyloid, which forms Alzheimer's plaques. Inhibiting the enzyme also blocks formation of neurofibrillary tangles by the tau protein. This science advance relates to the GPRA goal to identify at least one clinical intervention that will delay the progression of, delay the onset of, or prevent Alzheimer's disease.

19. Nutrition and Overweight

- *Drug Targets Brain Circuits That Drive Appetite and Body Weight* (Scientific Research Outcomes Goal IV.B.2.b.1.-2.b.). Research conducted in animals has revealed that the appetite-suppressant drug D-fenfluramine (D-FEN) activates brain pathways that regulate food intake and body weight. The NIH-funded study suggests that drugs targeting central nervous system pathways affecting appetite, obesity, and anorexia may lead to selective, effective treatments for weight control. The work gives a mechanistic explanation of how drugs like D-FEN may inhibit food intake. Investigating the neurobiology of drug-caused anorexia may lead to the development of new drugs with fewer side effects to prevent and treat obesity.

IV.B. Discussion and Performance Analysis

IV.B.1. Program Description and Context

IV.B.1.a. Legislative Intent

The mission of the National Institutes of Health (NIH)—*to uncover new knowledge that will lead to better health for everyone*—–derives from Section 301 of the Public Health Service Act, which reads, in part:

> *The Secretary shall conduct… cooperate with, and render assistance to...scientific institutions, and scientists in the conduct...of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man...*

NIH authority to "make grants-in-aid" and to "make available research facilities" is contained in Section 301. Under Title IV of the Act, specific provision is made for some individual Institutes and Centers, authorities of the NIH Director, National Research Service Awards, and other activities.

IV.B.1.b. Resources

The FY 2005 NIH budget request provides funding to support each of the core NIH programs. The following table provides a 3-year summary of funding (in millions) for NIH.[1]

	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
	Amount	Amount	Amount
NIH Budget Authority	$27,173	$28,028	$28,757
NIH Full Cost of Program	$27,173	$28,028	$28,757

The FY 2004 Final Conference and the FY 2005 Estimate are detailed by budget mechanism in the NIH Overview to the FY2005 President's Budget. The NIH Budget Mechanism table for FY 2003 is provided below.

NIH BUDGET MECHANISM	FY 2003 ENACTED (COMPARABLE)[2] (DOLLARS IN MILLIONS)
Research Project Grants	$14,242
Research Centers	2,425
Other Research	1,587
Research Training	712
Research and Development Contracts	2,399
Intramural Research	2,547
Research Management and Support	920
Cancer Prevention and Control	531
Construction	495
Library of Medicine	298
Office of the Director	286
Buildings and Facilities	646
VA/HUD Superfund	84
All Mechanisms	$27,173

Budget–GPRA Integration

Medical research funded by NIH is conducted by extramural as well as intramural scientists. The majority of funds appropriated to NIH flows to the extramural scientific community at large—of which the lion's share supports individual scientists who are located at universities, hospitals, and other research facilities in the United States and points abroad. The extramural research community is funded through a variety of mechanisms of support including grants, cooperative agreements, and contracts. A smaller fraction of NIH funds supports research that is conducted by NIH's own physicians and scientists—the intramural research program.

[1] As noted above in Section IV.A.3., Narrative Description of Layout of Plan/Report, every activity at NIH is carried out in support of the NIH mission: *To uncover new knowledge that will lead to better health for everyone.* Thus, this Plan/Report is structured to reflect a single program—Research—for the purpose of planning and performance assessment.

[2] Includes Superfund and transfer from the White House Office of National Drug Control Policy; includes type 1 diabetes.

The major funding instruments used by NIH to fund extramural research are financial assistance award grants, cooperative agreement grants, and acquisition awards or contracts. Grants are the most common funding mechanism. All grants are identified as either competing (for NIH support) or non- competing continuations (receiving support previously committed during the competing grant cycle). A research project grant (RPG) provides a commitment of support for an average of four years of funding. Thus, after the competing year, the grantee receives non-competing continuations each year for the specified length of the grant (subject to the availability of funds and satisfactory progress as documented to the NIH each year). Nearly three-quarters of funding allocated to RPGs supports non-competing continuations. Using FY 2003 funding, Institutes and Centers developed budget projections based on committed levels for continuation projects, both extramural and intramural. By working closely with scientific program staff, IC budget identified planned Requests for Applications, Requests for Proposals, and Program Announcements. Costs of these initiatives were also included in total estimates for each program goal. Estimates also included the number and amount of investigator-initiated grants likely to be relevant to achieving each program goal, based on historical trends.

NIH does not have an account or collection of accounts dedicated to program management. To allocate costs for program management, we selected the Research Management and Support (RMS) line item from the NIH mechanism display and Office of the Director Operations, a line item in the appropriation for the Office of the Director. Although these lines support some activities in addition to program management, they represent the majority of NIH program management activities. These totals were reduced by the direct costs of the performance goals that are funded through RMS or OD operations. This calculated level for Program Management was allocated across GPRA goals and the unsampled program on a pro-rata basis. The funding amounts devoted to each goal are included in the Program Performance Tables on pages 18-39.

NIH has one program-Research. Five functional areas categorize research and research-related support activities into similar clusters to provide a framework for presenting the entire portfolio. NIH utilizes a representative sampling approach to report on program performance progress. NIH has selected representative goals as proxies for performance of the larger research portfolio for each of the functional areas. Both performance goals and budget for these goals are representative.

To reflect the representative nature of performance in the GPRA plan and report, NIH has added a budget line titled “Unsampled Balance.” This approach will report 100% of NIH’s budget in the plan. It assumes that NIH is maintaining customary assessments and will continue reporting on the representative goals as proxies for the entire portfolio. Therefore, additional representative sampling is not needed.

NIH strives to achieve effective and efficient management of the research portfolio as stewards of public health. Routine assessments are conducted to improve proficiency, to modernize processes and to sustain quality management. Some of these results are reported through other venues, such as the FMFIA and CJ, while others are used for internal management. These usual and customary assessments, as well as improvement strategies, are assumed under this label.

IV.B.1.c. Core NIH Activities and Operational Strategies

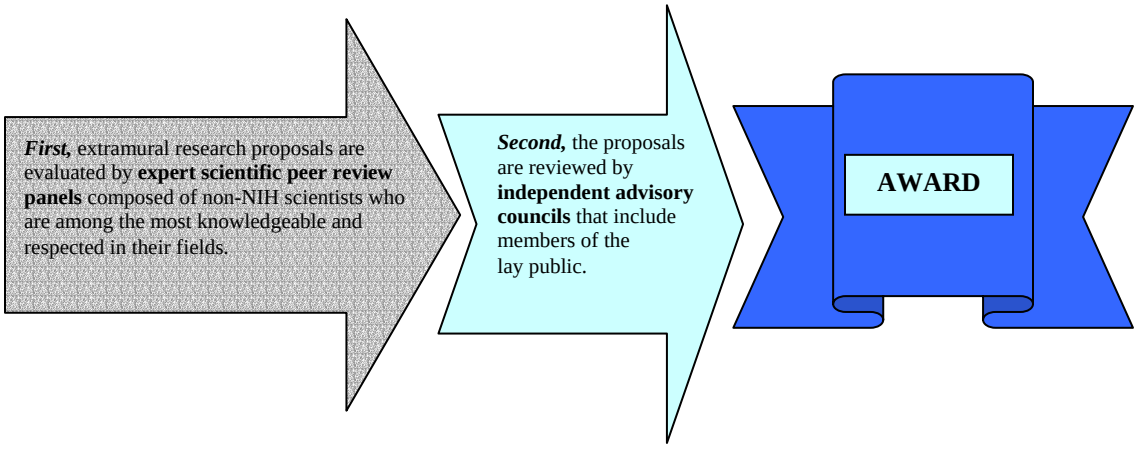
Sustained and diligent Federal stewardship is the touchstone for the activities carried out by each IC as it pursues the NIH mission. The strategies used to achieve that stewardship, and thus guide the utilization of resources for program purposes, are described below. These strategies ensure the relevance, quality, and performance of NIH programs.

- *Provide scientific leadership and establish research priorities*. Establishing research priorities is essential to ensure that science meets national public health needs and efficiently uses limited resources. In general, NIH sponsors research that addresses burden of illness—ways to prevent, treat, and cure disease and minimize pain and suffering. But addressing burden alone is not enough; there must also be some real opportunity for success.

How do we identify areas of increased scientific opportunity? New knowledge comes from the pursuit of answers to gaps in knowledge. The rate-limiting step in the generation of new knowledge is not the number of experiments conducted, but rather the number of new hypotheses or questions. When an arena of research is enjoying an exponential increase in the number of new questions, it is, indeed, an area of scientific opportunity. New questions emerge as a result of several converging factors, including the creativity of individual investigators, the emergence of new methods and tools that allow previously unanswered questions to be addressed, and what is already known about a problem. It is imperative that NIH capitalize on such areas of scientific opportunity.

NIH uses a multilevel system to establish and review research priorities. The NIH Director, in collaboration with IC Directors and their respective advisory councils and boards and the biomedical research community, guides the priority-setting process. Additional input is sought from the administration, including DHHS, and from Congress and the public. NIH considers the research priorities identified through this process and makes resource allocation decisions intended to ensure that NIH commits Federal resources to projects and programs that are relevant and are most likely to achieve the greatest yield from the Nation's medical research investment. In short, understanding burden of illness, identifying knowledge gaps, and deciding how to best capitalize on scientific opportunities are the primary drivers in the allocation of resources.

- *Fund the best extramural research and training*. NIH funds are awarded through a highly competitive process to the most promising and productive scientists as illustrated below.



This two-tiered independent review system is critical to ensuring that the best proposals are funded from the approximately 44,000 research and training applications NIH receives each year.

- *Conduct leading-edge research in NIH laboratories*. NIH also ensures that the research conducted in its own (intramural) laboratories is of the highest caliber. Each Institute and Center maintains a board of scientific counselors, composed of external experts, that reviews the intramural programs and makes recommendations to the Institute Director. The intramural program enables scientists to apply the results of laboratory research to patient care and to seek answers in the laboratory to questions that arise in the clinical setting. This national resource permits NIH to respond rapidly to critical health problems and emergencies and take advantage of emerging opportunities.

- *Collaborate and coordinate with others*. NIH collaborates and coordinates on an ongoing basis with other Federal agencies and research organizations where research interests intersect and when joint efforts will enhance the individual activities of each entity. Medical research benefits from multiple perspectives being brought to bear on a particular problem. Collaborative efforts bring diverse domains of expertise together and

can facilitate a more rapid response to emerging opportunities. In addition, collaborative efforts work to produce the best possible science while making the most economical use of the resources available.

These collaborative endeavors frequently involve NIH's sister agencies in DHHS, including the U.S. Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality. Nonetheless, the full scope of NIH's collaborative activities, both in the past and those contemplated for the future, is far wider. NIH partners include many other Federal agencies, government bodies, nongovernmental organizations, and industry. Details on NIH partnerships and collaborations with other DHHS agencies are provided in Appendix 3.

- *Support a Balanced Portfolio of Goals.* The continuum of scientific discovery affirms the need for a balanced portfolio with high-risk/ ambitious goals as well as low-risk/probable goals and all those in between. NIH recognizes that all of its goals involve some degree of uncertainty because of the risk inherent in the nature of scientific discovery. Also, NIH promotes ambitious goals because they hold promise to address a critical need and improve the health of the Nation. Goals that are ambitious and/or involve risk will by necessity be difficult, since the pathway to discovery may not be linear and the building blocks needed to make a scientific breakthrough still have to be determined. Through utilizing goals that span the range of the continuum, NIH is making progress toward its mission of uncovering new knowledge leading to better health for everyone.

IV.B.1.d. Programmatic Challenges

Over the past 5 years, stellar scientific advances have helped revolutionize basic and clinical research. Along with the stunning achievement by NIH-supported scientists of sequencing the human genome, stand dramatic advances in research technologies, ranging from large-scale DNA arrays to molecular imaging. Enhanced understanding of communication within the human body and the regulation of activities within and among cells also are radically altering approaches to longstanding questions.

This burgeoning scientific opportunity stands side by side with a shifting and growing range of public health challenges. Chronic diseases have replaced acute conditions as the Nation's leading health concerns and now are responsible for more than 70 percent of all deaths. At the same time, dire new threats continue to emerge, such as the threat of bioterrorism. The AIDS pandemic continues to ravage developing nations and some of the most vulnerable members of the U.S. population; moreover, diseases such as SARS, and now a new pox virus, continue to arise. Finally, incidents of morbidity, such as cancer and physical disability, will be increasing, in part because of the longer life expectancy of the U.S. population. These and other health problems typically associated with an aging population will draw on NIH resources more and more as it faces this societal change.

IV.B.1.e. Significant Events

The three examples described below illustrate how NIH builds on the science base and monitors and responds to public health needs. NIH actions related to these "events"—rapid action in response to an unanticipated incident such as exposure to anthrax, development of a trans-agency initiative to address a growing public health epidemic like obesity, and dissemination of science-based information to address a chronic health problem such as hypertension—clearly demonstrate the Agency's performance in putting science to work for the public. The ability to respond quickly to acute and chronic health problems, including initiation of the next generation of research based on the current knowledge base, exemplifies the performance of the NIH research program.

As is often stated, the guideposts for NIH priority setting are public heath needs and scientific opportunity. As illustrated below, when events reshape need or opportunity, NIH plans, programs, and performance are significantly affected.

Biodefense
In September and October 2001, a terrorist deliberately exposed U.S. citizens to *Bacillus anthracis*—the microbe that causes potentially fatal inhalation anthrax. By February 2002 NIH had published the *Strategic Plan for Biodefense Research* and the *Biodefense Research Agenda for CDC Category A Agents*. Category A agents have created the most concern because they can cause high death rates or serious illness, spread relatively easily, trigger panic, and require special steps for public health preparedness. The *Biodefense Research Agenda for Category B & C Priority Pathogens* followed in January 2003.

In the wake of the anthrax mail attacks and cognizant of the promise inherent in NIH's ambitious activities and plans addressing biodefense, the President proposed and the Congress allocated a massive funding increase for biodefense research—from $291.1 million in FY 2002 to $1,745.8 million in FY 2003. The February 2002 *Strategic Plan for Biodefense Research* was not the first NIH biodefense research plan, but the events of fall 2001 certainly had a dramatic affect in reshaping NIH biodefense research.

Obesity
Recent findings revealed that obesity cuts 6 to 7 years off of life—comparable to the effects of smoking—and costs this country an estimated $117 billion annually in health care-related expenditures. People who are overweight are more likely to develop health problems such as heart disease, stroke, diabetes, certain types of cancer, gout (joint pain caused by excess uric acid), and gallbladder disease. Being overweight can also cause problems such as sleep apnea (interrupted breathing during sleep) and osteoarthritis (wearing away of the joints). The more overweight a person is, the more health problems he or she can expect to have. Many overweight people have difficulty reaching their healthy body weight. Studies show that health can be improved by losing 10 to 20 pounds; yet, it is often very difficult even for many people who are motivated and committed to a weight-loss program.

NIH has made tremendous progress recently in understanding the biologic basis of obesity, including the discovery of new hormones, ghrelin and PYY, that control appetite. These hormones are produced by the stomach and small intestine, and each signals the brain to either increase or decrease appetite. Blood levels of ghrelin peak just before meals, and peaks are significantly higher among obese individuals who have lost weight by dieting, perhaps explaining why sustaining weight loss is so difficult. Blocking the action of ghrelin is thus a potentially attractive target for drug development and obesity management. NIH is making similar advances in understanding how the body decides whether and where to metabolize or store fat. The discovery of hormones such as leptin and adiponectin, which are secreted by fat, has shown that fat signals to brain, liver, and muscle regulate fuel metabolism and the response to insulin. Such discoveries help explain how obesity leads to insulin resistance and type 2 diabetes and may offer new ways of treating or preventing obesity-associated disorders.

Given the severity of heart disease, type 2 diabetes, and other obesity-associated health problems, along with new scientific opportunities from discoveries such as those described above, NIH established the National Task Force on Prevention and Treatment of Obesity to facilitate progress in obesity research. The task force seeks to maximize collaboration across NIH and capitalize on the expertise of many NIH components in developing research initiatives in a variety of areas, such as understanding the genetic, behavioral, and environmental causes of obesity and testing new prevention and treatment strategies, with the goal of improving human health.

Prehypertension, Hypertension, and Stroke
The National High Blood Pressure Education Program (NHBPEP) is a cooperative effort among professional and voluntary health agencies, State health departments, and many community groups. The NHBPEP is administered and coordinated by NIH. As a result of publication of many new studies; the need for new, clear, and concise guidelines useful for clinicians; and the need to simplify the classification of blood pressure, the NHBPEP Coordinating Committee reviewed these findings, which are presented in the *Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) Express. The JNC 7 Express Report* (May 2003) focuses on practical applications of the new evidence, including a revised

treatment algorithm, drug tables, and convenient references. It was developed for the health care worker who needs to keep abreast of standards of treatment and incorporates the latest evidence into daily practice.

Findings presented in *The JNC 7 Express Report* include a new prehypertension level that covers about 22 percent of American adults—about 45 million persons. The new report changes the former blood pressure definitions to (1) normal, less than 120/less than 80 millimeters of mercury (mm Hg); (2) prehypertension, 120-139/80-89 mm Hg; (3) stage 1 hypertension, 140-159/90-99 mm Hg; and (4) stage 2 hypertension, $\geq$ 160/ $\geq$ 100 mm Hg.

The lifetime risk of developing hypertension is much greater than once thought. Recent developments show that damage to arteries begins at fairly low blood pressure levels—those formerly considered normal and optimal. Studies show that the risk of death from heart disease and stroke begins to rise at blood pressures as low as 115/75 mm Hg and that it doubles for each 20/10 mm Hg increase. High blood pressure is the chief risk factor for stroke and heart failure and also can lead to kidney damage. It affects about 50 million Americans—one in four adults. Treatment seeks to lower blood pressure to less than 140 mm Hg systolic and less than 90 mm Hg diastolic for most persons with hypertension (less than 130 systolic and less than 80 diastolic for those with diabetes and chronic kidney disease). Unless preventive steps are taken, stiffness and other damage to arteries worsen with age and make high blood pressure more difficult to treat. The new prehypertension category reflects this risk and should prompt people to take preventive action early to reduce their risk of stroke.

NIH released findings from several studies related to this issue to address public health concerns. The ALLHAT (Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial) compared expensive new drugs (e.g., calcium-channel blockers, angiotensin-converting-enzyme inhibitors, and alpha blockers) with a diuretic—one of a class of blood pressure-lowering drugs that has been used for many years and can be had for mere pennies a day. It found that the diuretic did as well or better than newer agents in preventing the complications of hypertension. Results of another study, called PREMIER, underscores the importance of lifestyle changes as a first-line weapon in the fight against high blood pressure, the first time a host of behavioral steps to prevent or control high blood pressure have been put together in one intervention to help Americans reduce their blood pressure and thus lower their risk for heart disease and stroke. Recommended lifestyle steps to prevent or control hypertension are to lose weight if overweight, follow a heart-healthy eating plan such as DASH (Dietary Approaches to Stop Hypertension) (including reducing salt and other forms of sodium), increase physical activity, limit consumption of alcoholic beverages, and quit smoking.

Looking at the results of previous trials of ticlopidine, a type of clot inhibitor, investigators believed there was a strong possibility that this agent would be safer and more effective than aspirin in African Americans with a history of stroke. The results from the African American Antiplatelet Stroke Prevention Study (AAASPS), a large multi-center trial of 1,809 African American stroke patients, demonstrated that aspirin is as effective as ticlopidine in preventing a second stroke in this population. For those who can tolerate it, aspirin is readily available, inexpensive, and easy to administer. Ticlopidine, on the other hand, is more expensive and more difficult to use and has the potential for serious side effects. This is an important finding, since African Americans are at about twice the risk of experiencing a stroke or dying from a stroke, compared with whites, and have a higher prevalence of stroke and cardiovascular disease risk factors such as hypertension, diabetes mellitus, obesity, and cigarette smoking.

NIH plays a critical leadership role in advancing prevention efforts and first-line treatments for prehypertension, hypertension, and stroke. NIH is launching several activities to help the public better understand and health care providers to more effectively prevent and treat these conditions. NIH will continue to transfer research-based information to health care professionals, industry, and the public—information critical to improved public health.

IV.B.1.f. Program Assessment Rating Tool (PART) Assessments

The NIH AIDS research program received a final score of 83 in the 2005 PART. NIH reviewed and is implementing recommendations from the PART process. However, this form does not provide an appropriate format to report improvements in areas that did not receive perfect scores.

The AIDS research program received a score of 100 percent on two out of the four PART sections—the ones on Program Purpose and Design and Program Management. The PART process provided the NIH AIDS research program with an opportunity to highlight its unique strategic planning and budget development process that was established 10 years ago, as well as its extensive coding system to track expenditures for all AIDS research projects. The PART helped identify an opportunity to further refine and improve that process by also linking it to the recommendations of scientific program evaluations. In its development of the annual comprehensive budget for AIDS research, the Office of AIDS Research will now also require that Institutes and Centers submit reports from any extramural program evaluations or recommendations of changes in the intramural program as a result of reviews by boards of scientific counselors conducted in the past year. In addition, Institutes and Centers will be required to provide information about grant turnover in extramural programs. Through the PART process, the AIDS research program extended the date of the GPRA goal for the development of an AIDS vaccine from 2007 to 2010 to more realistically reflect the state of the science in this complex area of research.

The human and economic toll of the AIDS pandemic is profound and thus requires a unique response that is complex, comprehensive, multidisciplinary, and global. NIH demonstrated through PART its fundamental and unprecedented role in this response. NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated opportunistic infections and malignancies that will lead to a better understanding of the basic biology of HIV, the development of effective therapies to treat it, and the design of better interventions to prevent new infections. This diverse AIDS research portfolio demands scientific coordination and management of research funds to enhance collaboration, minimize duplication, and ensure that research dollars are invested in the highest priority areas of scientific opportunity. The FY2005 budget will allow the program to support critical research initiatives to address the AIDS epidemic in the United States as well as overseas, particularly in developing nations.

IV.B.1.g. Contact Person

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This document is for administrative use only and will not be published or posted on the World Wide Web. However, previous performance plans and reports are available now at http://www1.od.nih.gov/osp/ospp/gpra/gpra_nih.htm.

IV.B.2. Performance Analysis

IV.B.2.a. Program Performance Tables

Comprehensive summary tables covering all the FY 2004 and 2005 goals and targets in NIH's Research Program follow. These tables provide updated information on the status of all of the program's performance targets. The targets included on the following pages represent the first phase of implementing budget and performance intergration. The identified targets are subject to change. More extensive information on each goal, including a chart summarizing the performance results for each target, can be found at the referenced page number (i.e., "D–#). Outcome, output, and efficiency goals are noted in the reference column of the chart where appropriate.

Program Performance Tables: FY 2004 and 2005 Goals

SCIENTIFIC RESEARCH OUTCOMES

SRO-1a	By 2005, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.	REFERENCE[1]
		SP–1.4, 4.1, HP–26, D–44, Outcome, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Prepare clinical protocol for testing rimonabant in humans.	1. Two drugs have been approved for use in the US to treat alcohol addiction, with limited effectiveness	1. (MET) Rimonabant has been shown to reduce ethanol intake in rodent models of voluntary ethanol drinking.
FY 2004 1. Complete a toxicologic evaluation on antalarmin.	1. Antalarmin and rimonabant show promise in nonhuman animal models as excellent candidates for Phase I clinical trials	1. Performance results will be reported in February 2005.
FY 2005 1. Test antalarmin for relapse prevention in alcoholics.	1. Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking	1. Performance results will be reported in February 2006.

SRO-1b	By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	REFERENCE[1]
		SP–4.1, 6.2, HP–28, D–47, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Design and test a device (diaphragm) that responds to sound based on the ears of the parasitic fly *Ormia ochracea.*	1. Small insect model system exists and has hyperacute sound localization	1. (MET) NIH scientists successfully completed design and testing of a novel microphone diaphragm that responds to sound and is based on the ears of the parasitic fly *Ormia ochraca*.
FY 2004 1. Design and test the electronic circuitry to create a sound output from the diaphragm.	1. Sound-responsive diaphragm based on an insect model system is available	1. Performance results will be reported in February 2005.
FY 2005 1. Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid.	1. Diaphragm and electronic circuitry combination responds to and processes sound	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$8	$9	$9

SRO-2a	By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.	REFERENCE[1] SP–4.1, HP–5, D–49, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Recruit 12 participants for a Phase I trial to evaluate the safety of anti-CD52 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. First trial of anti-CD52 to promote tolerance	1. (EXT) Protocol to begin Phase I trial to evaluate anti-CD52 antibody is pending approval by participating sites. Target completion is expected in February 2004. Performance results will be reported in February 2005.
FY 2004 1. Recruit 8-12 participants for a Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. First trial of anti-CD3 to promote tolerance	1. Performance results will be reported in February 2005.
FY 2005 1. Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation.	1. An international multi-center trial of islet transplantation using the Edmonton protocol in patients with type 1 diabetes met the target enrollment of 36 subjects	1. Performance results will be reported in February 2006.

SRO-2b	By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.	REFERENCE[1] SP–4.1, HP–19, D–52, Outcome, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Identify two new drug targets that can be used in screens for potentially therapeutic compounds in drug discovery projects or that could be evaluated for use as therapeutic agents for weight control.	1. No highly effective drug therapies exist for overweight or obesity. Potential drug targets need to be identified	1. (MET) Three molecules can be characterized and screened as targets for therapeutic compounds or evaluated as potential therapeutic agents for weight control.
FY 2004 1. Develop and launch at least two studies to test the effects of worksite interventions on weight control.	1. No programs for weight control at the worksite have been examined in studies with valid designs to clearly evaluate if they are effective	1. Performance results will be reported in February 2005.
FY 2005 1. Enroll and randomize 60 children with hyperinsulinimia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.	1. No clinical trials have demonstrated efficacy of any medication for overweight during childhood. Pilot data suggest metformin may be of benefit for those children with hyperinsulinemia	1. Performance results will be reported in February 2006.

SRO-2c	By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	REFERENCE[1] SP–4.1, D–56, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Develop software for making comparative alignments of protein domains according to structure and molecular evolutionary classification, and which provides functions for domain family updates.	1. 256 domain families curated; software to align domains by structure and class unavailable	1. (MET) Software was released which improved structure-based alignments of proteins and classification of protein domain families based on molecular evolution; software was used to annotate over 500 protein domain families.
FY 2004 1. Obtain annotation for a total of 1,500 protein domain families in the conserved domain database using two advanced classification methods: (1) structure-based alignment and (2) molecular evolutionary classification. Cover 35% of sequences in PubMed (the National Library of Medicine's database of biomedical research literature), extended to 70% by adding first-generation alignments.	1. 800 domain families curated; 25% coverage of PubMed sequences	1. Performance results will be reported in February 2005.
FY 2005 1. Obtain annotation for a total of 2,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 45% of PubMed sequences, extended to 75% by adding first-generation alignments.	1. 1,500 protein domain families curated; 35% coverage of PubMed sequences	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$35	$40	$45

SRO-3a	By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease.	REFERENCE[1] SP–4.1, 6.2, HP–18 D–59, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Initiate a double-blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether it can slow the rate of progression of AD.	1. Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of AD	1. (MET) CLASP study was enacted to further investigate the role that cholesterol has in the pathogenesis of Alzheimer's Disease.
FY 2004 1. Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	1. Estimated 30 compounds are presently or will soon be tested in human AD clinical trials but additional targets are needed	1. Performance results will be reported in February 2005.
FY 2005 1. Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment and AD, and use as potential surrogate markers for drug development and clinical trials.	1. Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression	1. Performance results will be reported in February 2006.

SRO-3b	By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.	REFERENCE[1]
		SP–2.1, 4.1, HP–14, 24, D–62, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Identify one molecule with a common role in bacterial and viral infections that may serve as a target for broad-spectrum antimicrobial drug development.	1. None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule with a common role in both bacteria and viruses	1. (MET) Two different molecules with a common role in different classes of microbes were identified.
FY 2004 1. Identify one molecule or mechanism that is shared by a class or across different classes of microbes that may serve as a target for broad-spectrum antimicrobial drug development.	1. None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes	1. Performance results will be reported in February 2005.
FY 2005 1. Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad-spectrum antimicrobial drug development.	1. None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes	1. Performance results will be reported in February 2006.

SRO-3c	By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.[2]	REFERENCE[1]
		SP–4.1, D–66, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Implement at least five research projects directed at developing integrated technologies for the efficient and simultaneous detection of key molecules in human saliva.	1. No integrated technologies to quickly and efficiently measure multiple substances in saliva	1. (MET) Seven research projects implemented to develop technology aimed at human salivary diagnostics.
FY 2004 1. Implement research projects directed at identifying and cataloging saliva proteomes. Identification of salivary proteomes will help scientists detect changes in saliva that are associated with specific diseases or conditions.	1. Technology available to help identify salivary proteomes	1. Performance results will be reported in February 2005.
FY 2005 1. Develop electronic microfluidic assay systems (e.g., microchip-based systems that are replacing large and costly instruments) that can quantify C-reactive protein (a biomarker for cardiovascular disease) in saliva.	1. Systems to quantify C-reactive protein in saliva have not yet been developed	1. Performance results will be reported in February 2006.

SRO-3d	By 2010, develop an HIV/AIDS vaccine.	REFERENCE[1]
		SP–1.2, 4.1, HP–13, D–68, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Design and develop new or improved vaccine strategies and delivery/production technologies.	1. Existing DNA and viral-vector vaccines strategies require further evaluation	1. (MET) Four newly identified vaccine strategies increased scientific knowledge of how AIDS causes disease and the immune response to it.
FY 2004 1. Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	1. HIV Vaccine Trials Network currently supports clinical trials at 12 international sites	1. Performance results will be reported in February 2005.
FY 2005 1. Initiate four new Phase I or II trials of new or improved concepts and designs and expand capacity to conduct clinical trials in three international sites.	1. NIH has conducted 68 phase I and phase II HIV vaccine trials to date	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$1,168	$1,356	$1,438

SRO-4a	By 2004, develop two new animal models to use in research on at least one agent of bioterror.	REFERENCE[1]
		SP–2.1, 4.1, HP–14, D–73, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Conduct validation studies of new monkey models of smallpox by employing them in testing of new smallpox vaccines and therapies.	1. Previous non-human primate models of smallpox/orthopox diseases inadequately modeled the progression of human smallpox disease	1. (MET) Human variola and models were tested for protection against disease when administered Modified Ankara (MVA) or Dryvax smallpox vaccines.
FY 2004 1. Expand by 25% the animal model resources available for use by the research community and for licensing products under the FDA Animal Efficacy Rule.	1. 8 animal models available	1. Performance results will be reported in February 2005.

SRO-4b	By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD), based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.	REFERENCE[1]
		SP–4.1, HP–8, D–77, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Establish a mouse model repository at a Morris K. Udall Center of Excellence for Parkinson's Disease Research to house PD genetic models and make them available to the PD research community.	1. No repository with this specific housing and distribution capacity exists for PD research	1. (MET) Mouse model repository to house PD genetic models established.
FY 2004 1. Determine if slowing the metabolism of rotenone through cytochrome P-450 inhibition facilitates creation of a mouse model for PD.	1. Cytochrome P-450 accelerates rotenone metabolism in mice so that the PD phenotype cannot be shown	1. Performance results will be reported in February 2005.
FY 2005 1. Combine the mouse model with at least one genetic model of PD and assess its interaction with rotenone.	1. A rotenone mouse model is not yet available	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$20	$14	$14

SRO-5a	By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens.	REFERENCE[1] SP–4.1, HP–13, D–81, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Increase the ability of resource-poor countries to conduct clinical trials for the treatment and prevention of HIV disease by providing training and capacity building at 4 sites.	1. 12 AACTG sites and 10 PACTG sites	1. (MET) Sites in resource-poor countries are better able to conduct HIV clinical trials as a result of training.
FY 2004 1. Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	1. 23 approved antiretroviral drugs exist for HIV infection treatment	1. Performance results will be reported in February 2005.
FY 2005 1. Initiate clinical trials of new anti-HIV drugs and/or anti-HIV multidrug regimens in U.S. and international clinical trial sites.	1. Clinical trials for the next generation of fusion inhibitors and lead compounds representing integrase inhibitors are being completed	1. Performance results will be reported in February 2006.

SRO-5b	By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).	REFERENCE[1] SP–4.1, HP–12, D–85, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Complete the training of personnel involved in conducting the trial, including sonographers and those operating the Interactive Voice Response System.	1. Standard operating procedures are being completed but training not yet done	1. (EXT) Training incomplete for sonographers involved in conducting the trial. Performance results will be reported in February 2005.
FY 2004 1. Launch patient enrollment in at least 10 of the 20 planned sites.	1. Protocol for patient enrollment established	1. Performance results will be reported in February 2005.
FY 2005 1. Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	1. One ancillary study approved to assess the effect of statins on blood cells	1. Performance results will be reported in February 2006.

SRO-5c	By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.	REFERENCE[1]
		SP–4.1, D–87, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	1. Prior to FY 2003, only two centers existed	1. (MET) Two additional Centers of Excellence for Chemical Methods and Library Development were established at Harvard Medical School and the University of Kansas.
FY 2004 1. Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through the funded Centers. Ensure that inventories of libraries and methods are established so that the successful results of this work can be readily accessible to the scientific community for dry development.	1. High throughput methods for making chemical libraries for drug development are limited	1. Performance results will be reported in February 2005.
FY 2005 1. Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	1. CMLD centers are currently being established; screening of their libraries has not yet begun	1. Performance results will be reported in February 2006.

SRO-5d	By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.	REFERENCE[1]
		SP–4.1, HP–26, 18, D–89, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	1. None of the NCDDG Programs focus on mood disorders and nicotine addiction	1. (MET) Three grants modeled on the National Cooperative Drug Discovery Group (NCDDG) Program were awarded for development/testing of new medications/treatments for mental disorders and nicotine addiction. Prior to these awards, the NCDDG did not address these conditions.
FY 2004 1. Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	1. 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened	1. Performance results will be reported in February 2005.
FY 2005 1. Create a publicly available collection of 750 bioactive compounds, with defined activity in the nervous system, from industry, academia, and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	1. Known bioactive compounds require further evaluation of activity and improved availability	1. Performance results will be reported in February 2006.

SRO-5e	By 2008 develop and test two new evidence-based treatment approaches for drug abuse in community settings.	REFERENCE[1]
		SP—3.4; HP—26, 27; D–93, Outcome.

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004 1. Adapt two treatment approaches from small-scale research settings to community-based settings for the purpose of bringing research-based treatments to communities.	1. No randomized clinical trials have delivered BSFT and Seeking Safety to these specialized populations	1. Performance results will be reported in February 2005.
FY 2005 1. Build capacity for targeted treatments by training 90 treatment providers to: (a) participate in clinical trials to promote treatment fidelity; and (b) deliver evidenced-based behavioral treatment to target populations in community settings.	1. Less than 25 treatment providers have been trained to deliver BSFT and Seeking Safety to these specialized populations in randomized clinical trials in community settings	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$1,030	$1,084	$1,115

SRO-6a	By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.	REFERENCE[1]
		SP–4.1, 6.2, HP–28, D–95, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Expand the genomic resources available to vision researchers through NEIBank and related trans-NIH activities.	1. 31,000 human gene sequences; 12,000 unique human eye-expressed genes	1. (MET) Genomic resources expanded to include 30% more human gene sequences, 8% more unique human eye-expressed genes, and new DNA sequence data and clones.
FY 2004 1. Reach consensus on a descriptive manual with standards that can be used to describe the diverse retinal phenotypes found in macular degeneration.	1. No consensus descriptions on AMD phenotypes exist	1. Performance results will be reported in February 2005.
FY 2005 1. Collect and make available to investigators genetic material and information from over 4,000 well-characterized patients with either AMD or glaucoma.	1. DNA specimens from large numbers of well-characterized AMD or glaucoma patients are not available	1. Performance results will be reported in February 2006.

SRO-6b	By 2011, assess the efficacy of at least three new treatment strategies to reduce cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease.	REFERENCE[1] SP–4.1, HP–4, 5, 12, D–98, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	1. No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	1. (MET) Effects of intensive versus conventional glycemic control were assessed in EDIC study participants. Finding suggests that aggressive management of blood glucose levels can produce short- and long-term benefits.
FY 2004 1. Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects of intensive versus conventional interventions on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	1. Look AHEAD had recruited about half (2,500) of its patients	1. Performance results will be reported in February 2005.
FY 2005 1. Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	1. ACCORD had recruited 1,184 participants in a Vanguard phase	1. Performance results will be reported in February 2006.

SRO-6c	By 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	REFERENCE[1] SP–1.1, 4.1, HP–8, D–101, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	1. Intramural databases and commercial software to build ProtoCEBS available	1. (MET) ProtoCEBS launched, tested, and implemented.
FY 2004 1. Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields and by creating a data portal that will load toxicology data.	1. CEBS object model to capture molecular expression data (only) designed but not tested	1. Performance results will be reported in February 2005.
FY 2005 1. Create and provide public access to a global molecular expression and toxicology/pathology database of environmental chemicals and drugs (CEBS) featuring simple query download capability.	1. CEBS version 1.0 launched in August 2003 contains only microarray data	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$85	$89	$92

SRO-7a	By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical drug interactions.	REFERENCE[1] SP–4.1, 5.1, D–106, Outcome, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Identify results of studies on three botanicals that show inhibition/induction of enzymes that metabolize drugs.	1. Some characterization of St. John's wort; very little known about other botanicals	1. (MET) Effects were observed on selected botanical extracts on the inhibition or induction of selected enzymes that metabolize drugs.
FY 2004 1. Identify results of studies on three additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	1. St. John's wort better characterized. Good characterization of ginkgo, garlic, saw palmetto, 2 species of ginseng, and PC-SPES	1. Performance results will be reported in February 2005.
FY 2005 1. Identify results of studies on four additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	1. Characterization of additional botanicals from FY 2004	1. Performance results will be reported in February 2006.

SRO-7b	By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.	REFERENCE[1] SP–4.1, HP–3, D–108, Outcome, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Establish intramural and extramural collaborations to select and employ substrate nanotechnology fabrication techniques to enable high-throughput and highly reliable/reproducible proteomic analyses.	1. Lack of relevant collaborations	1. (MET) Collaborations established and work progressing on employing nanotechnology techniques to enable high-throughput proteomic analyses relevant to early detection of cancer.
FY 2004 1. Establish a core laboratory at NIH to bring together extramural and intramural fabrication technologies with the capability to derive targets, identify the most promising applications for combined functionalized nanoparticles, and steward therapeutic nanotechnologies through validation.	1. No current core laboratory with needed capacity	1. Performance results will be reported in February 2005.
FY 2005 1. Integrate nanosensors and nanoparticles into a platform technology for development in applied research settings.	1. Existing nanosensors and nanoparticles not integrated into a common platform	1. Performance results will be reported in February 2006.

SRO-7c	By 2005, create the next-generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.	REFERENCE[1]
		SP–4.1, D–112, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. For existing blood samples from U.S. residents of Western and northern European ancestry, obtain additional consent from the donors for this new use and begin genotyping 300,000 single nucleotide polymorphisms (SNPs, sites in the human genome where individuals differ by a single letter) in those samples.	1. 90 existing samples, none of which included the necessary consent for genotyping	1. (MET) All needed consents obtained and genotyping performed on 132,000 SNPs.
FY 2004 1. Collect samples from populations in Japan, China, and Nigeria; and complete collection of additional 3 million SNPs and release in public databases.	1. 2.4 million SNPs in database	1. Performance results will be reported in February 2005.
FY 2005 1. Develop a first-pass draft HapMap containing 600,000 SNPs.	1. 2.4 million SNPs in database but none of the samples genotyped to produce any part of the HapMap	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$40	$25	$22

SRO-8a	By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.	REFERENCE[1]
		SP–1.2, 2.1, 4.1, HP–14, 24, 25, D–116, Outcome, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Complete the genomic sequences of at least five bacteria and two protozoa that cause infectious disease.	1. Genome sequences for 29 bacterial pathogens, 1 protozoan parasite, and 1 insect completed	1. (MET): Genomic sequences were identified for 8 bacterial pathogens and 3 protozoans.
FY 2004 1. Complete the genomic sequences of at least three fungal pathogens, five bacterial pathogens, and two protozoa that cause infectious disease.	1. Genome sequences for 39 bacterial pathogens, 4 protozoan parasites, and 1 insect completed	1. Performance results will be reported in February 2005.
FY 2005 1. Complete the genomic sequences of at least two fungal pathogens, five bacterial pathogens, and four protozoa that cause infectious disease.	1. Genome sequences for 44 bacterial pathogens, 6 protozoan parasites, 3 fungi, and 1 insect completed	1. Performance results will be reported in February 2006.

SRO-8b	By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.	REFERENCE[1] SP–4.1,6.2, HP–2, D–120, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Characterize effects of the bone protein thrombospondin-2 on the generation of bone-forming cells from precursor cells in the bone marrow and identify regions of the thrombospondin-2 molecule that are required for the effects.	1. Information on the role of thrombospondin-2 in bone generation is incomplete	1. (MET) Thrombospondin-2 promotes bone formation in the early stage of cell differentiation; functional elements at one end of molecule responsible for this effect.
FY 2004 1. Identify biochemical pathways in bone-forming cells that are responsible for extended survival of cells on interaction with the bone protein osteonectin.	1. Biochemical pathways that mediate cell survival are unknown	1. Performance results will be reported in February 2005.
FY 2005 1. Identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation. Generate a genetically altered mouse strain in which a fluorescent protein is produced under the control of the same genetic elements that control the production of thrombospondin-2.	1. Information incomplete on where thrombospondin-2 is produced; mouse model can provide this data	1. Performance results will be reported in February 2006.

SRO-8c	By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, nonredundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.	REFERENCE[1] SP–4.1, D–123, Outcome, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Make the RefSeq Collection database available for downloading to enable commercial or academic groups to perform exhaustive analyses across the entire RefSeq Collection data set.	1. At the end of FY02, the RefSeq collection included 446,000 proteins and was not available for FTP	1. (MET) The RefSeq collection was made available on a regular release cycle to scientists at commercial and academic sites for downloading and analysis of the entire data set.
FY 2004 1. Develop the infrastructure to support wider access to the RefSeq Collection via the Internet to provide users with a centralized set of annotated sequence information.	1. RefSeq collection includes sequence data from 2124 species; only a limited database is available	1. Performance results will be reported in February 2005.
FY 2005 1. Expand the project to include outside groups to increase the amount of sequence and functional information in the database. Collaborations will provide additional reference sequence records, whole-genome annotation, functional annotation of multigene families, and expert review of single genes.	1. About 40 collaborations in place for obtaining annotated RefSeq records and other functional data	1. Performance results will be reported in February 2006.

SRO-8d	By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.	REFERENCE[1] SP–4.3, D–126, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Develop a data collection and management system to allow for the retrieval of potential target indicators to evaluate the impact of the IDeA/Centers of Biomedical Research Excellence (COBRE) Program.	1. Indicators from previous evaluations and pre-COBRE analysis and previous evaluations	1. (MET) Data collection and management system in place for retrieval of potential target indicators related to evaluating impact of IDeA/Centers of Biomedical Research Excellence Program.
FY 2004 Assessment Methodology for IDeA Program (Step 1): • Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact. • Develop a data collection system for BRIN.	• Data collection and management system to evaluate impact of IDeA/COBRE in place • Indicators from IDeA/COBRE evaluation design	1. Performance results will be reported in February 2005.
FY 2005 Assessment Methodology for IDeA Program (Step 2): • Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact. • Assess results of COBRE evaluation design study.	• Data collection and management system to evaluate impact of IDeA/BRIN in place • COBRE evaluation design completed but not evaluated	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$290	$375	$388

SRO-9a	By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United States by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).	REFERENCE[1] SP–4.1, 6.2, HP–18, D–129, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Identify at least one biological (e.g., gene-environment) interaction that has high probability of contributing to depression.	1. Known that stress linked to depression but interaction not known	1. (MET) A link was made between a specific gene-environment interaction (5-HTT and high stress) and vulnerability to depression.
FY 2004 1. Determine whether vascular changes related to aging contribute to depression.	1. Subcortical lesions, common in elderly with depression and in vascular disease, are being studied as potential cause of depression	1. Performance results will be reported in February 2005.
FY 2005 1. Determine at least four characteristics that help identify subgroups of people with depression who respond differentially to existing treatments.	1. To be determined	1. Performance results will be reported in February 2006.

SRO-9b	By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.	REFERENCE[1]	
		SP–1.1, 3.4, 4.1, 4.4, HP–7, 12, D–133, Outcome, Efficiency	
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**	
FY 2003 1. Establish a 5-year program to create 12 to 14 Partnership Centers to Reduce Health Disparities that will focus on influential factors that reduce health disparities.	1. Piloted programs to build nursing center research capacity focused on health disparities	1. (MET) Seventeen Nursing Partnership Centers established to reduce health disparities, including stroke, which link research-experienced nursing schools with minority-serving nursing schools across the nation.	
FY 2004 1. Establish a minority-focused, acute stroke research and care center to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and quality of care within the specific racial/ethnic communities being served by the care center.	1. Acute stroke center exists but is not focused on stroke disparities or in a minority community	1. Performance results will be reported in February 2005.	
FY 2005 1. Establish the infrastructure for a Stroke Prevention and Intervention Research Program at a minority institution.	1. Minority institution research /training programs exist but not on stroke prevention/intervention	1. Performance results will be reported in February 2006.	
FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$60	$61	$59

[1] SP–# Indicates the DHHS Strategic Plan goal to which each GPRA goal pertains.
HP–# Indicates the Focus Area of *Healthy People 2010* to which each goal pertains.
D–# Indicates the page in this report at which details on the goal can be found.

COMMUNICATION AND TRANSFER OF RESULTS

CTR-a	By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).	REFERENCE[1]: SP–3.4, 7, HP–11, 16, D–139, Outcome, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. In collaboration with African American organizations, community health and other local officials, and faith-based organizations, conduct regional summit meetings to train and motivate individuals who will implement SIDS risk reduction activities in their communities.	1. No regional summit meetings were held prior to 2003	1. (MET) Over 1,000 participants were trained and motivated to reduce SIDS in African American communities during 3 regional U.S. summits.
FY 2004 1. Conduct 250 interviews among the approximately 1,500 participants who attended the three summit meetings held in 2003 to determine that each summit resulted in a minimum of 50 outreach activities.	1. No interviews have been conducted for this purpose	1. Performance results will be reported in February 2005.
FY 2005 1. Continue to extend "Back to Sleep" campaign messages to African American populations through community-based collaborations/partnerships by involving a minimum of six national organizations in SIDS training and educational activities.	1. Three participating national organizations	1. Performance results will be reported in February 2006.

CTR-b	Increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the campaign, "Know Stroke. Know the Signs. Act in Time."	REFERENCE[1]: SP–1.1, 4.4, HP–11, 12, D–142, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Work with partners in five communities each with at least 15 percent African American population to extend the "Know Stroke" campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 "Know Stroke" community education kits and 100,000 "Know Stroke" brochures (25,000 will be distributed to African American audiences).	1. National partnerships developed; no current comprehensive local partnerships	1. Performance results will be reported in February 2005.
FY 2005 1. Extend the outreach program to an additional five communities nationwide, arming community leaders with tools and information to distribute an additional 5,000 "Know Stroke" community education kits (1,000 will be through African American partners).	1. Partnerships developed in FY 2004 target.	1. Performance results will be reported in February 2006.

CTR-c	Through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.	REFERENCE[1]: SP–4.4, D–144 Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	1. No known needs assessment studies exist for developing technology TA program	1. Performance results will be reported in February 2005.
FY 2005 1. Based upon the result of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	1. No personnel	1. Performance results will be reported in February 2006.
2. Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside.	2. Limited access to targeted training in developing countries	2. Performance results will be reported in February 2006.

CTR-d	**Increase the percentage of Small Business Innovative Research (SBIR) Program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.**	**REFERENCE[1]**
		SP–4.4, D–146, Outcome

FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Implement the trans-NIH Commercialization Assistance Program (CAP) based on the recent CAP pilot.	1. CAP Pilot completed	1. Performance results will be reported in February 2005.
2. Initiate pilots for additional programs of technical assistance services.	2. 1 pilot to date	2. Performance results will be reported in February 2005.
FY 2005 1. Achieve higher than baseline indication of progress toward solution of technical problems or commercialization for participants in CAP pilot.	1. 50 participants	1. Performance results will be reported in February 2006.
2. Increase by 5 percent the SBIR awardees who successfully identify appropriate resources and partners through the programs of technical assistance services.	2. 50 awardees	2. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$1	$5	$7

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CAPACITY BUILDING AND RESEARCH RESOURCES

CBRR-a	Recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, career development awards, and student loan repayment programs.	REFERENCE[1]: SP–4.3, D–152, Output

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004		
1. Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	1. NRSA Group: 7,125 Comparison Group A: 9,985 Comparison Group B: 9,229	1. Performance results will be reported in February 2005.
2. Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	2. Applied for but did not receive= 174 recipients; 929 trainees Received last year of training support 10 years before: 324 recipients; 808 trainees	2. Performance results will be reported in February 2005.
3. Ensure that there is multidisciplinary training on at least 10% of all training grants as evidenced by trainees reporting different Field of Training codes.	3. 486 multidisciplinary grants	3. Performance results will be reported in February 2005.
4. Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.	4. 120 K23 awards for FY03-FY06 50 K24 awards for FY03-FY06 50 K30 awards for FY03-FY06	4. Performance results will be reported in February 2005.
5. Increase by 1% over baseline the number of research training and career development positions occupied by individuals from underrepresented racial and ethnic groups.	5. White= 9,957; Asian: 1,862 African American= 1,112 American Indian= 106 Pacific Islander=52	5. Performance results will be reported in February 2005.
6. Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. Applications received= 1,881 Contracts awarded= 1,193	6. Performance results will be reported in February 2005.
FY 2005		
1. Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	1. NRSA Group: 7,125 Comparison Group A: 9,985 Comparison Group B: 9,229	1. Performance results will be reported in February 2006.
2. Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	2. Applied for but did not receive= 174 recipients; 929 trainees Received last year of training support 10 years before: 324 recipients; 808 trainees	2. Performance results will be reported in February 2006.
3. Ensure that there is multidisciplinary training on at least 10% of all training grants as evidenced by trainees reporting different Field of Training codes.	3. 486 multidisciplinary grants	3. Performance results will be reported in February 2006.
4. Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.	4. 120 K23 awards for FY03-FY06 50 K24 awards for FY03-FY06 50 K30 awards for FY03-FY06	4. Performance results will be reported in February 2006.
5. Increase by 1% over baseline the number of research training and career development positions occupied by individuals from underrepresented racial and ethnic groups.	5. White= 9,957; Asian: 1,862 African American= 1,112 American Indian= 106 Pacific Islander=52	5. Performance results will be reported in February 2006.
6. Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. Applications received= 1,881 Contracts awarded= 1,193	6. Performance results will be reported in February 2006.

CBRR-b	Promote data sharing and provide information in real time by implementing the NIH Business System.	REFERENCE[1]: SP–8.5, D–155, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Deploy the general ledger/budgeting module.	1. NBS without general ledger/budget module	1. (MET) General ledger/budgeting module deployed.
2. Deploy the property module.	2. NBS without property module	2. (EXT) Further analysis of the system is needed. Extended to February 2005. Performance results will be reported in February 2006.
3. Deploy the travel module.	3. NBS without travel module	3. (MET) Travel module deployed.
FY 2004 1. Deploy the property and contracts/acquisition/accounts payable/supply modules.	1. NBS without contracts/acquisition/accounts payable/supply modules	1. Performance results will be reported in February 2006.
FY 2005 *See FY 2003 target #2 and FY 2004 target #1 which have been extended to FY 2005.*		
3. Deploy the service and supply fund activities module.	3. NBS without service and supply fund activities module (Target extended to FY 2006)	3. Performance results will be reported in February 2007.

CBRR-c	Streamline business processes and automate data movement by implementing the Clinical Research Information System (CRIS).	REFERENCE[1]: SP–8.5, D–158, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Implement a core hospital system, including scheduling and resource utilization modules and pharmacy management system.	1. 28 year old legacy system	1. Performance results will be reported in February 2005.
FY 2005 1. Implement a surgery and anesthesia management system.	1. No current system exists	1. Performance results will be reported in February 2006.
2. Implement a clinical data warehouse.	2. No trans-NIH clinical data warehouse currently exists	2. Performance results will be reported in February 2006.

CBRR-d	Provide greater functionality and more streamlined processes in grants administration by continuing to develop NIH electronic research administration (eRA).	REFERENCE[1]: SP–8.5, D–160, Output, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Implement electronic progress reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership.	1. No institutions using electronic reporting	1. (MET) Electronic reporting available to the 65 FDP participating institutions.
2. Expand availability of electronic reporting to all grantee institutions.	2. 145 FDP institutions given access to electronic reporting	2. (EXT) Volume testing needed. Extended to third quarter February 2004. Performance results will be reported February 2005.
FY 2004 1. Pilot-test eXtensible Markup Language (XML) transmission between extramural community and NIH.	1. Need for system to conform with OMB/Federal Enterprise Architecture	1. Performance results will be reported in February 2005.
2. Begin pilot-testing of progress reporting for multi-project mechanisms.	2. 14 simple competing grant applications received	2. (EXT) XML development needed. Performance results will be reported in February 2005.
FY 2005 1. Complete migration of existing client/server applications to Web-based technology.	1. Migration plan developed	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 03	FY 04	FY 05
	$1,383	$1,442	$1,499

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

SMHC-a	**Implement governmentwide initiative on delayering management levels and streamlining organizations.**	**REFERENCE[1]**
		SP–8.2, D–164, Output, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Complete delayering for each organizational unit identified.	1. Six units identified	1. (MET) Delayering completed for the identified NIH organizational units.

SMHC-b	**Identify and develop potential successors for critical leadership positions by (1) developing and implementing an NIH-wide succession planning process that assesses the gaps between senior leadership needs and talent available; (2) identifying leadership competencies that will be critical to the mission of NIH now and in the future; and (3) providing developmental opportunities that will prepare potential successors to meet the demands required of senior leadership positions.**	**REFERENCE[1]**
		SP–8.2, D–166, Output

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Conduct a study and report on average age, years of service, and retirement eligibility. Assess future potential impact.	1. NIH Workforce Plan, June 2001	1. (EXT) Administrative restructuring initiatives and need for comprehensive web-based tool delayed study commencement. Performance results will be reported in February 2006.
2. Conduct a study and report on current state. Assess strengths, weaknesses, and needs for changes in current practices.	2. NIH Workforce Plan, June 2001	2. (MET) Succession Planning Report issued on current state of workforce strengths, weaknesses, and opportunities.
3. Establish a steering committee.	3. Administrative Restructuring Advisory Committee	3. (MET) NIH Steering Committee established.
4. Identify industry best practices. Develop a succession planning process to meet the needs of NIH.	4. Study questions identified	4. (EXT) Discussion with intramural research leaders identified gaps in original planned study, which led to study redesign and renegotiation with contractor. Performance results will be reported in February 2005.
5. Conduct study to identify competencies needed by NIH leaders who will drive future development efforts.	5. Workgroup established to study competencies	5. (EXT) NIH co-chairs departmental workgroup for the study; progress is dependent on time frames agreed upon by all HHS OPDIVs. Performance results will be reported in February 2005.

SMHC-c	Improve the strategic management of NIH human resources by developing a comprehensive human capital plan based on the Agency's programmatic objectives and projected future needs.	REFERENCE[1] SP–8.2,*D–169, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Considering the scientific agenda, applicable DHHS management initiatives, and future workforce trends, project the NIH human capital needs for the next 3 to 5 years.	1. NIH Strategic Workforce Plan of August, 2002	1. Performance results will be reported in February 2005.
2. Using the standards for success outlined in the Office of Personnel Management's Human Capital Assessment and Accountability Framework (i.e., the Framework), assess where NIH strengths and weaknesses exist regarding management of human capital.	2. Federal Human Capital Survey, 2002	2. Performance results will be reported in February 2005.
FY 2005 1. Implement succession planning and leadership development processes for critical positions.	1. Succession Planning Report and Planning Proposal, November 2002	1. Performance results will be reported in February 2006.
2. Revise the NIH strategic workforce plan to include new projections regarding human capital requirements and expand it to include an associated system of human capital management accountability.	2. NIH Strategic Workforce Plan of August, 2002; OPM Human Capital Standards; the Framework	2. Performance results will be reported in February 2006.
SMHC-d	**Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the Agency's commercial inventory.**	**REFERENCE[1]** SP–8.3, D–172, Output; Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Identify annually commercial activities for competitive sourcing comparison.	1. Preplanning initiated for identifying functional areas	1. (MET) Extramural Administrative Support Services and Real Property Management groups identified for competitive sourcing comparison.
2. Complete negotiated competitive sourcing reviews annually.	2. Functional areas identified as appropriate for review	2. (MET) Competitive sourcing reviews completed for Extramural Administrative Support Services and Real Property Management groups.
FY 2004 1. Identify annually commercial activities for competitive sourcing comparison.	1. Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2005.
2. Complete negotiated competitive sourcing reviews annually.	2. Functional areas identified as appropriate for review	2. Performance results will be reported in February 2005.
3. Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. Transition plans for employees	3. Performance results will be reported in February 2005.
FY 2005 1. Identify annually commercial activities for competitive sourcing comparison.	1. Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2006.
2. Complete negotiated competitive sourcing reviews annually.	2. Functional areas identified as appropriate for review	2. Performance results will be reported in February 2006.
3. Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. Transition plans for employees	3. Performance results will be reported in February 2006.

FULL COST (dollars in millions) **excludes SMHC-a and SMHC-d.*	FY 03	FY 04	FY 05
	$5	$13	$13

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D-#: Indicates the page in this report at which details on the goal can be found.

PROGRAM OVERSIGHT AND IMPROVEMENT

POI-a	Ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing an Earned Value Analysis and Management System.	REFERENCE[1] SP–8, D–175, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Evaluate and assess existing project management systems and implement them into a proof-of-concept version of the NIH EVAMS.	1. Policies and procedures in place to identify data needed for evaluation	1. Performance results will be reported in February 2005.
FY 2005 1. Implement a revised project management system that incorporates earned value analysis and management.	1. EVAMS proof-of-concept version	1. Performance results will be reported in February 2006.

POI-b	Expand the use of Performance-Based Contracting (PBC).	REFERENCE[1] SP–8, D–177, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	1. For FY 2002, $207 million projected for contracted work with requirements tied to performance	1. (MET) Over $226 million of NIH-eligible service contracting dollars were allocated to PBC contracts.
FY 2004 1. Obligate 40% of eligible service contracting dollars through PBC.	1. Percentage of a contract that must be performance-based meets FAR minimum requirements	1. Performance results will be reported in February 2005.
FY 2005 1. Obligate 50% of eligible service contracting dollars through PBC.	1. 40% of eligible service contracting dollars were PBC in 2004	1. Performance results will be reported in February 2006.

POI-c	Improve accountability for organizational performance results and support for the President's Management Agenda by linking the employee performance management plans/contracts to NIH's program and management priorities.	REFERENCE[1] SP–8.1, D–179, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Incorporate outputs and outcome methodology in managers' and supervisors' performance plans.	1. Measurable outputs and outcomes placed in executive plans (completion of Phase I, FY 2002)	1. (MET) Measurable outputs and outcomes placed in managers' and supervisors' performance plans.

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[2] The nearly tenfold increase in the dollar volume of the performance target in FY 2002 is primarily due to a single, large, performance-based contract awarded in FY 2000.[1]

POI-d	Ensure proper stewardship of public funding for research.	REFERENCE[1]	
		SP–8, D–181, Output	
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**	
FY 2003 1. Conduct five proactive compliance site visits.	1. Criteria in place for selecting institutions for site visits	1. (MET) Five proactive compliance site visits conducted.	
2. Perform a risk assessment and develop a plan for reviews of compliance with grant-related policies.	2. Framework for risk assessment in place	2. (MET) Initial risk assessment of 35 grants administration policies performed; ten policies selected for compliance review.	
3. Provide Internet-accessible resource information and/or tools for implementing institutional compliance programs.	3. Web site in place for grants compliance and oversight under the Office of Extramural Research	3. (MET) Internet-accessible resource information posted on enhancing institutional compliance programs.	
FY 2004 1. Begin internal compliance reviews.	1. Ten policies selected for compliance reviews	1. Performance results will be reported in February 2005.	
FY 2005 1. Implement recommendations from the internal compliance reviews held in 2004.	1. Recommendations developed from ten compliance reviews	1. Performance results will be reported in February 2006.	
FULL COST (dollars in millions) *excludes POI-c	FY 03	FY 04	FY 05
	$3	$2	$3

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[2] The nearly tenfold increase in the dollar volume of the performance target in FY 2002 is primarily due to a single, large, performance-based contract awarded in FY 2000.[1]

IV.B.2.b. Narratives

IV.B.2.b.1. Scientific Research Outcomes

NIH conducts and sponsors investigations in this country and abroad across the full range of the health research continuum, including basic research, which may be disease oriented or lead to the development and application of breakthrough technologies, observational and population-based research, behavioral research, prevention research, health services research, translational research, and clinical research. Clinical research includes research to understand both normal health and disease states, move laboratory findings into clinical interventions, and assess new treatments or compare different treatment approaches.

Each NIH Institute and Center (IC) maintains an extensive portfolio of research activities in its area of focus. In addition to providing grant support to the extramural research community through a competitive proposal process, most of the ICs also conduct their own research in NIH's intramural laboratories. Each year, NIH supports approximately 50,000 awards made to the most promising and productive scientists at universities and research centers throughout the country and, where special opportunities exist, to scientists abroad.[1]

The vastness of the NIH portfolio presents a challenge in terms of articulation of goals. NIH has selected 28 specific, representative research goals, as proxies for performance on the larger, research portfolio. The goals were selected based on the following criteria:

- **Representative.** The goals are a sampling of NIH aims that, as a set, represent the NIH mission. NIH has abandoned the previous approach of goals that, collectively, embody the NIH mission comprehensively.
- **Meaningful.** The goals must be credible to the research community, as well as to the public and NIH stakeholders.
- **Specific.** Goals should be as specific to a disease or definable problem as possible, with reference to a metric and/or a date for progress/completion, as appropriate.
- **Objective.** Objective goals are self-measuring; that is, they permit a comparison between the actual achievement level and that targeted by the performance goal.
- **Reportable.** Goals must lend themselves to *annual* reporting. Reports of incremental progress are fine.
- **Not obviously attainable.** The goal must be recognized as an outcome that *could* be achieved in the future, but may not be reachable for any number of reasons.

Central to this approach is a framework that characterizes goals on the basis of risk (i.e., likelihood of attaining the goal) and time. One way of visualizing this framework is to use a three-by-three matrix (see page 43). Following presentation of the goals in the matrix format, the goals are presented with accompanying background information. Baseline information provides the current state of the field upon which the goal was developed. The implementation strategies provide the key building blocks of science for a three year range. These strategies will be adjusted from year to year to adapt to scientific discoveries and advancements that facilitate progress toward the goal. Since scientific discovery is complex, the annual target selected represents only one critical step in the process of achieving the final outcome.

The matrix of goals selected by NIH reflects the challenges of complex biological systems. They range across a continuum of low to medium to high risk, and they have a corresponding timeline for achievement (i.e., 1-3 years, 4-6 years, and 7-10 years, respectively). For example, the NIH portfolio includes high-risk goals that reflect the start of a scientific journey, which often means that the knowledge is limited and pathways to success are primarily unknown. Achievement of a high-risk goal in the early stages cannot be guaranteed. In contrast, NIH low-risk goals usually have a long history associated with the scientific effort, and the knowledge base has known parameters. With low-risk goals, only a few steps remain to translate the knowledge into an application that could

[1] Includes all research, training, fellowship, R&D contracts, and SBIR/STTR.

lead to improved public health. NIH also utilizes performance goals that span the middle of the continuum. For the latter, a foundation of knowledge has been set but not extensively developed. Yet the goal is pursued because achievement is deemed probable. The elements used to determine the level of risk/ambition/difficulty include predictability of outcomes, absence of clear pathways, delivery time, and needed resources.

This continuum of scientific discovery affirms the need for a balanced portfolio with high-risk/ambitious goals as well as low-risk/probable goals and all those in between. NIH recognizes that all of its goals involve some degree of uncertainty because of the risk factor inherent in the nature of scientific discovery. NIH promotes ambitious goals because they hold promise to address a critical need and improve the health of the Nation. Goals that are ambitious and/or involve risk will by nature be difficult: The pathway to discovery may not be linear, and the building blocks needed to make a scientific breakthrough still have to be determined. Through utilizing goals that span the range of the continuum, NIH is making progress toward its mission of uncovering new knowledge leading to better health for everyone.

NIH's scientific research outcome goals in the matrix represent NIH as a whole. Almost all of the goals involve the scientific and/or financial contributions of more than one IC; most goals involve several ICs. This representative approach enables an approximate performance assessment of NIH's vast and complex research program. In laying the groundwork for reporting on prospectively defined targets, NIH presents linkages among inputs, processes, outputs, and outcomes in science as unique and nonlinear in the sense that:

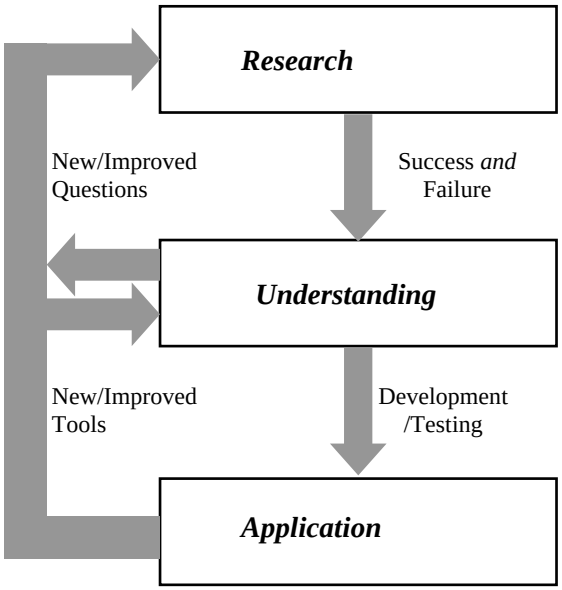
- Outcomes are challenging to foresee with a high degree of accuracy, but can be captured in many cases with milestones of progress toward the end goal.

- The full value of any given research finding can be visible at the time of discovery, and often reaches a state of fruition after many years or in combination with other advances.

- Although outcomes may encompass the proposed hypothesis, unplanned results such as serendipitous discoveries and findings that narrow the avenue of the research focus (elimination discoveries) can be just as significant.

- NIH supports the discovery of scientific knowledge; knowing that the downstream impact of basic research usually is dependent on substantial further development of new knowledge by private industry, other public sector researchers, and economic factors.

Each of these factors will need to be considered in interpreting research performance reports.



The typically circuitous course of progress in science is depicted above. The graphic illustrates that gaps in scientific knowledge drive the development of hypotheses for research studies. Yet, the findings from those studies may unveil roadblocks that will further narrow or redirect the research efforts. Often considerable time will pass before a new approach to the problem (a new scientific opportunity) emerges. In addition, findings that did not validate a specific hypothesis may be used in other research efforts leading to new scientific knowledge. Thus, each NIH research result has merit and may prove critical in the realm of scientific discoveries.

Research is an inherently collaborative endeavor and partnerships are crucial to achieving scientific research outcome goals. The role of the extramural research community (the scientists at universities and hospitals across the country and even around the world) as NIH's partner in research is well known. However, of increasing importance are partnerships with private companies, not-for-profit institutions, non-governmental organizations, and state and foreign governments. Joint research and training activities and other exchanges with such groups leverage NIH resources. Moreover, such partnerships facilitate valuable information feedback loops that identify emerging needs, suggest important new research questions, and otherwise inform priority setting. Partnerships also provide access to populations that are key in advancing knowledge.

All scientific research carried out through NIH support is subjected to a rigorous and consistently applied review process. For example, the Extramural Program, which oversees the largest category of NIH-funded research, utilizes two levels of peer review. The first level consists of chartered scientific groups composed of experts in particular scientific disciplines. The second level is the National Advisory Boards of the various Institutes. For the Intramural Program, an outside Board of Scientific Counselors participates in evaluating entire laboratory programs. The latter occurs once every 4 years, which allows ongoing assessments of all intramural labs and the accomplishments of the scientists who contribute to them. It is through this well-honed system of peer review that NIH can maintain its focus on supporting research of the highest possible quality.

NIH GPRA Scientific Research Outcomes Goals Matrix

RISK	1-3 YEARS	4-6 YEARS	7-10 YEARS
HIGH	**1a** By 2005, conduct medications development using animal models and begin conducting Phase I and II trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin. **1b** By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	**2a** By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1diabetes in human clinical studies. **2b** By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. **2c** By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	**3a** By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD). **3b** By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. **3c** By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease. **3d** By 2010, develop an HIV/AIDS vaccine.
MEDIUM	**4a** By 2004, develop two new animal models to use in research on at least one agent of bioterror. **4b** By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD) based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.	**5a** By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens. **5b** By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus). **5c** By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs. **5d** By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools. **5e** By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings.	**6a** By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans. **6b** By 2011, assess the efficacy of at least three new treatment strategies to reduce cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease. **6c** By 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.
LOW	**7a** By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical-drug interactions. **7b** By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. **7c** By 2005, create the next generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.	**8a** By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases. **8b** By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals. **8c** By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, nonredundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms. **8d** By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.	**9a** By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United States by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes). **9b** By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.

GOAL 1a) BY 2005, CONDUCT MEDICATIONS DEVELOPMENT USING OF ANIMAL MODELS AND BEGIN CONDUCTING PHASE I AND II HUMAN TRIALS OF TWO POTENTIAL TREATMENTS FOR ALCOHOLISM: THE CANNABINOID ANTAGONIST RIMONABANT AND THE CORTICOTROPIN-RELEASING HORMONE ANTAGONIST ANTALARMIN.

BACKGROUND

Prevalence/Incidence

The 2002 World Health Organization report lists alcohol as the third leading risk factor for preventable, premature death in developed countries, after tobacco and hypertension.[1] In the United States, alcohol is the third leading root cause of death not attributable strictly to genetic factors, after tobacco and diet/activity patterns.[2] Almost 14 million American adults are alcoholic (physically dependent on alcohol) or abuse alcohol (dysfunctional, but not dependent).[3] Children also are at risk. Almost 30 percent of 9th to 12th graders report having had five or more drinks, in a row, at least one day of the previous month.[4]

Disease Burden

Alcohol use disorders cost U.S. society almost $185 billion each year through injury, lost wages, property damage, death, and other factors.[5] Unlike other drugs of abuse, alcohol can have toxic effects on any organ in the body. Heavy alcohol use can cause brain damage, contributes to cardiovascular disease, and is a leading cause of liver cirrhosis and pancreatitis.[6] Alcohol also is linked to some kinds of cancer.

Rationale

Alcoholism is a chronic disease subject to relapse; sustaining abstinence is the goal of treatment. However, current medications work for some people but not others. Different factors contribute to abusive drinking and to subtypes of alcoholism. Some alcoholics have a genetic predisposition that affects specific brain systems, such as those regulating stress or rewarding sensations, resulting in molecular and cellular variations. Others are vulnerable to environmental stimuli. Developing more widely effective medications requires (1) understanding the different biological and environmental variations that underlie alcoholism and targeting them and (2) the availability of a wide array of candidate medications for testing. Animal models enabling the testing of compounds in different biological and environmental scenarios are making this goal possible.

Two recently identified classes of compounds with treatment potential are antalarmin and rimonabant. By blocking a brain cell receptor (CRH1) for a hormone that elicits anxiety in response to stress, antalarmin reduced drinking in monkeys going through alcohol withdrawal. Rimonabant blocks another receptor (CB1) that otherwise would stimulate biological pathways in specific areas of the brain that result in rewarding sensations. In mice, this medication reduced drinking by young animals. Researchers must continue to cast a wide net to identify compounds with therapeutic potential for the different subtypes of alcoholism. This involves identifying molecular targets and new and existing compounds that act on them, conducting

[1] World Health Organization. *The World Health Report 2002: Reducing Risks, Promoting Healthy Life.* October 30, 2002. 250 pp. http://www.who.int/whr/en/.
[2] McGinnis JM, Foege WH. Actual causes of death in the United States. JAMA. 1993 Nov 10;270(18):2207-12.
[3] Grant BF et al. Prevalence of DSM-IV alcohol abuse and dependence. United States, 1992. Epidemiologic Bulletin No.35. Alcohol Health Res World 1994;18(3):243-8.
[4] Centers for Disease Control and Prevention. Youth 2001. http://www.cdc.gov/nccdphp/dash/yrbs/2001/youth01online.htm; Youth Risk Behavior Survey, CD-ROM Youth '99, and Youth Risk Behavior Survey, CD-ROM Youth '97.
[5] Harwood HJ, Fountain G, Livermore G. *The Economic Costs of Alcohol and Drug Abuse in the United States,* 1992. NIH Publication No. 98-4327, September 1998; updated October 1999.
[6] Smart RG, Mann RE. Alcohol and the epidemiology of liver cirrhosis. Alcohol Health Res World. 1991;16(3):217-22.

screenings that predict the utility of these compounds, and confirming their utility with animal and human studies.

PLANNED IMPLEMENTATION STRATEGIES

Three strategies have been identified. First, NIH plans to prepare a clinical protocol to test rimonabant for its ability to reduce ethanol drinking and obtain approval to proceed. Such testing should lead to enhanced techniques for treating alcoholism. Second, NIH plans to contract for toxicology studies of antalarmin with the purpose of getting an IND from FDA. This toxicologic evaluation should be completed by the end of FY 2004. Third, NIH plans to design a protocol for testing antalarmin in alcoholics for relapse prevention and reduced ethanol drinking.

BASELINE(S)

- Currently, two drugs have been approved for use in the United States to treat alcohol addiction: disulfiram, an emetic, and naltrexone, an opiate antagonist. Both show limited effectiveness. Phase III clinical trials are currently under way for acamprosate, which acts on the NMDA system and decreases alcohol craving.

- Another 15 classes of drugs have been identified as being in the preclinical phase of development. Antalarmin and rimonabant have shown promise in nonhuman animal models as excellent candidates to proceed to Phase I clinical trials.

- A number of recent studies in animals have indicated that the cannabinoid CB1 receptor antagonist rimonabant can reduce ethanol intake in rodent models of voluntary ethanol drinking. A recent study[1] has provided evidence that endogenous cannabinoids acting at CB1 receptors are involved in controlling ethanol preference, which may explain the observed effectiveness of rimonabant in reducing drinking. An intramural NIH study[2] has demonstrated that the CRH1 receptor antagonist antalarmin reduces neuroendocrine and behavioral responses to stress in primates, and a more recent study has shown that antalarmin reduces voluntary ethanol intake in a rat model of drinking. In an ongoing nonhuman primate (NHP) study, antalarmin was found in NHPs to reduce 5-HT1A receptor density in areas of the brain considered to be important in alcohol and other drug reward mechanisms.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Prepare clinical protocol for testing rimonabant in humans.	(FY02) Two drugs have been approved for use in the US to treat alcohol addiction, with limited effectiveness	◆[e]		
Complete a toxicologic evaluation of antalarmin.	(FY03) Antalarmin and rimonabant show promise in nonhuman animal models as excellent candidates for Phase I clinical trials		◇	
Test antalarmin for relapse prevention in alcoholics.	(FY03) Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

[1] Wang L, Liu J, Harvey-White J, Zimmer A, Kunos G. Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice. Proc Natl Acad Sci USA. 2003 Feb 4;100(3):1393-8.
[2] Habib KE et al. Oral administration of a corticotrophin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. Proc Natl Acad Sci USA. 2000 May 23;97(11):6079-84.

SUMMARY OF PERFORMANCE RESULTS

Target

Prepare clinical protocol for testing rimonabant in humans. The FY 2003 target was met. A clinical protocol has been prepared for testing rimonabant for its ability to reduce ethanol drinking in humans ("Clinical Trial of the Cannabinoid CB1 Receptor Antagonist SR141716 [Rimonabant] to Reduce Voluntary Ethanol Drinking in Healthy, Non-Treatment Seeking Individuals Who Consume Between 20 and 40 Drinks Per Week"). The protocol was reviewed by an internal review board in July 2003 and is pending final approval expected January 2004. The study is expected to commence in spring 2004, according to the predicted schedule for the project. Meeting this target facilitates identification of compounds with therapeutic potential for different subsets of alcoholism. A number of recent studies in animals have indicated that rimonabant can reduce ethanol intake in rodent models of voluntary ethanol drinking. A recent NIH study has provided evidence that endogenous cannabinoids acting at CB1 receptors are involved in controlling ethanol preference, which may explain the observed effectiveness of rimonabant in reducing drinking.

Complete a toxicologic evaluation of antalarmin. An NIH intramural study has demonstrated that the CRH type 1 receptor antagonist antalarmin reduces neuroendocrine and behavioral responses to stress in primates (Proceedings of the National Academy of Sciences U.S.A. 97:6079, 2000), and a more recent study by others has shown that antalarmin reduces voluntary ethanol intake in a rat model of drinking. In an ongoing nonhuman primate study, antalarmin was found to reduce 5-HT1A receptor density in areas of the brain considered to be important in other drug and alcohol reward mechanisms.

Test antalarmin for relapse prevention in alcoholics. In human studies, a consortium of NIH intramural programs has contracted toxicology studies of antalarmin for the purpose of obtaining investigational approved new drug from the FDA. The toxicologic evaluation is in progress, and planning is currently under way to design a protocol for testing antalarmin in alcoholics for relapse prevention and reduced ethanol drinking once the IND is obtained.

Implementation Strategy Advances or Other Highlights

The clinical protocol for testing rimonabant in humans has been completed by NIH and submitted for IRB approval, where it was approved pending minor corrections, that were made in August 2003. Final approval of the protocol is expected in late 2003.

Additionally, necessary toxicology studies are under way on antalarmin so that relapse prevention testing in alcoholics can begin.

Efficiency

Target 1 was met ahead of schedule by the NIH staff. In addition, NIH work with cannabinoid receptors has garnered much attention in the scientific press. Endogenous cannabinoids—endocannabinoids—have been shown to affect a wide range of physiologic systems, among them those involved in appetite and feeding, blood pressure, memory, mood, and stress. Recently, NIH researchers showed that endocannabinoids may play a role in aging-related declines in appetite for both food and alcohol. An antagonist for the endocannabinoid receptor CB1 reduced high ethanol preference in young mice (in a strain known for high ethanol preference) to a level seen in older mice and mice in which CB1 receptors were inactivated (CB1 knockouts). The CB1 antagonist also reduced food intake in young, but not old, food-restricted wild-type mice. Data from the study also suggest that these changes are due to changes in the coupling of CB1 receptors to intracellular signaling molecules (G proteins) but not to changes in the level of either the receptor or G proteins. The advance was featured in an editorial in *TRENDS in Pharmacological Sciences* (24:266-268, 2003) and in *Proceedings of the National Academy of Sciences U.S.A.* (100:1393-1398, 2003).

GOAL 1b) BY 2006, DEVELOP ONE OR MORE PROTOTYPES FOR A LOW-POWER, HIGHLY DIRECTIONAL HEARING AID MICROPHONE TO HELP HEARING-IMPAIRED PERSONS BETTER UNDERSTAND SPEECH IN A NOISY BACKGROUND.

BACKGROUND

Prevalence/Incidence

Approximately 20 million Americans are estimated to have sensorineural hearing loss, making this one of the most prevalent disabling conditions in the United States. Hearing loss can be hereditary, or it can result from disease, trauma, or long-term exposure to damaging noise or medications. The condition can vary from a mild but important loss of sensitivity to a total loss of hearing.

Disease Burden

Sensorineural hearing loss affects people of all ages, in all segments of the population, and across all socioeconomic levels. It can harm an individual's physical, cognitive, behavioral, and social functions and is caused by a problem in the cochlea or the auditory nerve, the parts of the ear that help sound impulses reach the brain. Hearing aids are the main form of treatment for this condition; however, only 20 percent of those who could benefit from hearing aids use them.[1]

Rationale

A hearing aid is a battery-operated device that amplifies and changes sound to allow for improved communication. Hearing aids receive sound through a microphone, which then converts the sound waves to electrical signals. The amplifier increases the loudness of the signals and then sends the sound to the ear through a speaker. A vast array of hearing aid technology is available, ranging from simple and relatively inexpensive analog circuits to complex and expensive digital devices that require sophisticated fitting procedures.

Although hearing aid technology has advanced rapidly over the past few decades with the development of microelectronic components, the various hearing aids currently available still do not function well when sound from more than one source is present. Most hearing aids are designed for compensating for high-frequency hearing loss and for suppressing static noise in a room. However, hearing aids are not particularly effective in restoring the listener's ability to sort out a single speech sound from among competing sources (e.g., at meetings, banquets, at sporting events).

NIH-supported scientists have been studying the tiny fly *Ormia ochracea*, which has such acute directional hearing that it has inspired ideas for a new generation of hearing aids. The biological lessons provided by this fly's abilities in hyperacute time coding and localization of sound provide strategies for improved nanoscale and microscale directional microphones in hearing aids that can focus sound amplification on speech. Applications of these new principles may improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

PLANNED IMPLEMENTATION STRATEGIES

NIH has identified three strategies toward developing a prototype using hearing loss technology. First, NIH researchers plan to design and test a device (diaphragm) that responds to sound based on the ears of the fly

[1] Larson V et al. Efficacy of 3 commonly used hearing aid circuits: A crossover trial. NIDCD/VA Hearing Aid Clinical Trial Group. JAMA. 2000 Oct 11;248(14):1806-13.

Ormia ochracea. Second, plans to design and test the electronic circuitry to create a sound output from the diaphragm. Third, NIH seeks to combine the diaphragm and the electronic output circuitry into a directional microphone small enough to fit into a hearing aid worn inside the ear canal. By developing a prototype that mimics the exceptional hearing ability of the fly, NIH anticipates transferring the same advanced hearing to impaired persons.

BASELINE(S)

- Most hearing aids compensate for high-frequency hearing loss and suppress static noise.
- Currently available hearing aids do not enable the user to pay attention to a single voice from among many ongoing sounds; this makes it difficult to hear speech in public venues such as banquets, sporting events, or meetings.
- NIH-supported scientists have been studying the tiny fly *Ormia ochracea*, whose acute directional hearing has inspired the design of a new generation of hearing aids. Using the fly's auditory system as a model, scientists may be able to design a tiny directional microphone for hearing aids that will help individuals with hearing loss better understand spoken language in a noisy environment.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Design and test a device (diaphragm) that responds to sound based on the ears of the parasitic fly *Ormia ochracea.*	(FY02) Small insect model system exists and has hyperacute sound localization	◆		
Design and test the electronic circuitry to create a sound output from the diaphragm.	(FY03) Sound-responsive diaphragm based on an insect model system is available		◇	
Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid.	(FY03) Diaphragm and electronic circuitry combination responds to and processes sound			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

NIH-supported scientists successfully completed design and testing of a novel microphone diaphragm that responds to sound and is based on the ears of the parasitic fly *Ormia ochracea*. The fly's system was selected as a model for this research because its mechanically coupled ears enable its hearing to be directional and because it provides a microscale approach to restoring lost hearing in humans. The diaphragm has several characteristics that make it well suited to its intended use: small size, directionality, and durability. The scientists used silicon microfabrication technology to make a device small enough to be potentially incorporated into a hearing aid. The acoustic response of the diaphragm is directional, and it will reject unwanted sounds that make speech unintelligible for individuals who are hearing impaired.

Implementation Strategy Advances or Other Highlights

Detailed analyses of the diaphragm's durability suggest that it will be strong enough to withstand normal wear if used in a hearing aid worn by either small children or active adults.

GOAL 2a) BY 2007, DEMONSTRATE THE FEASIBILITY OF ISLET TRANSPLANTATION IN COMBINATION WITH IMMUNE TOLERANCE INDUCTION FOR THE TREATMENT OF TYPE 1 DIABETES IN HUMAN CLINICAL STUDIES.

BACKGROUND

Prevalence/Incidence

Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys the insulin-producing islet cells of the pancreas. Approximately 120,000 people with type 1 diabetes are younger than 20 years of age, making this one of the most common chronic diseases of childhood.[1] Approximately 30,000 new cases occur each year, the majority with onset in early childhood and the teenage years; approximately 1 in 300 cases of diabetes with onset in adulthood is autoimmune in origin.[2]

Disease Burden

Type 1 diabetes is a chronic, lifelong disease characterized by elevations in blood sugar that, over time, lead to severe and life-threatening complications, including heart disease, blindness, peripheral neuropathy, foot ulcers, and kidney failure. Treatment requires insulin administration through multiple daily insulin injections or use of an insulin pump and careful attention to diet and activity; blood sugar levels must be measured several times a day by finger pricks. However, even with careful attention to insulin dosing, even the most medically compliant patients are rarely able to maintain "tight" or physiologic control of their blood sugar. As a result, existing treatments can delay and diminish, but not prevent, many of the complications of diabetes. Even with careful attention to control of blood sugar, type 1 diabetes results in a reduction in quality of life and leads to premature death.

Rationale

Whole-pancreas and pancreatic islet transplants offer type 1 diabetics the potential for physiologic control of blood sugar as an alternative to insulin therapy. Whole-pancreas transplantation is a technically difficult procedure, whereas pancreatic islet cell transplantation is a minimally invasive procedure. In islet transplantation, cells from the pancreas called islets are isolated from a donor pancreas and injected into a large blood vessel that supplies the liver. The transplanted islets lodge in the liver where they produce insulin. Until recently, the intermediate and long-term success of this procedure has been disappointing: Of the more than 300 islet transplants performed over a decade, fewer than 10 percent of patients remained insulin independent 1 year after the procedure. However, recent advances in pancreatic islet cell preparation and improvements in immunosuppressive regimens that are required to prevent transplant rejection have dramatically improved the prospects for islet transplantation. If confirmed in larger, multi-site studies, these results suggest that approximately 70 to 80 percent of type 1 diabetics can be expected to remain insulin independent 2 years following islet transplantation. Despite these advances, patients must remain on potent immunosuppressive drugs to prevent immune-mediated rejection of the transplanted islet cells. Immunosuppressive agents may increase the risk of serious infection and other complications, such as hypertension and cardiovascular disease.

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases, including autoimmune disorders such as type 1 diabetes. Research is under way to develop selective, short-term, durable therapies that will eliminate pathogenic immune responses, such as graft rejection and autoimmune injury, while preserving protective immunity. Tolerance induction holds great potential for improving the quality of life of individuals afflicted by type 1 diabetes and other immune-

[1] National Diabetes Data Group. Diabetes in America, Second edition, July 1995; NIH Publication No. 95-1468, p. 1.
[2] National Diabetes Data Group. Diabetes in America, Second edition, July 1995; NIH Publication No. 95-1468, p. 40.

mediated diseases. If successful, tolerance induction would (1) enable lifelong, rejection-free maintenance of islet cells and (2) eliminate ongoing autoimmune injury to transplanted islets without the many adverse effects of broadly immunosuppressive drugs.

PLANNED IMPLEMENTATION STRATEGIES

To accomplish the goal of demonstrating the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies, NIH will initiate, through the ITN, Phase I trials to evaluate the efficacy of CAMPATH1H (anti-CD52 antibody) and of the anti-CD3 antibody to promote the induction of tolerance to transplanted islets. Because the anti-CD3 antibody was not developed as quickly as the anti-CD52 antibody, the Phase I trial start dates have been staggered over the next 3 years.

Through these trials, NIH will evaluate the sufficiency of single islet transplants to achieve insulin independence compared with multiple transplants required in the ITN Edmonton Protocol. NIH will continue the ITN Edmonton Protocol and extend the duration of periodic follow-up to better assess the intermediate safety and efficacy of this particular regimen for islet transplantation and establish its baseline success rate. NIH will expand the medical/surgical capabilities needed for successful islet transplantation in the United States through continued support and monitoring of the ITN- and other NIH-sponsored clinical trials in islet transplantation.

BASELINE(S)

- In FY 2003, the Immune Tolerance Network (ITN) completed enrollment in an experimental islet transplantation protocol for the treatment of brittle type 1 diabetes based on the approach pioneered at the University of Alberta (the "Edmonton Protocol").

- The design and on-target implementation of the Edmonton Protocol study demonstrates the feasibility of evaluating novel therapeutic approaches to tolerance induction and islet transplantation in multi-center settings.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Recruit 12 participants for a Phase I trial to evaluate the safety of anti-CD52 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY02) First trial of anti-CD52 to promote tolerance	→		
Recruit 8-12 participants for a Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY03) First trial of anti-CD3 to promote tolerance		◇	
Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation.	(FY03) An international multi-center trial of islet transplantation using the Edmonton protocol in patients with type 1 diabetes met the target enrollment of 36 subjects			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The protocol for a Phase I trial to evaluate the safety of anti-CD52 antibody to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs has been approved by Health Canada (FDA counterpart), but it is pending approval at the participating clinical sites before enrollment can be initiated. Therefore, the performance target has been extended to February 2004 since site approval is expected by January 2004. The target date for completing enrollment for the trial is February 2005. The accrual target for the trial is 12 participants. It is not anticipated that protocol enrollment or achieving the stated target will be adversely affected.

Implementation Strategy Advances or Other Highlights

In FY 2003, the ITN implementation of the "Edmonton Protocol" for islet transplantation completed patient enrollment. Also, enrollment was initiated in the Phase I trial to evaluate the safety and pharmacokinetics of anti-CD3.

GOAL 2b) BY 2009, EVALUATE THE EFFICACY OF TWO NOVEL APPROACHES TO PREVENT WEIGHT GAIN AND/OR TREAT OBESITY IN CLINICAL TRIALS IN HUMANS.

BACKGROUND

Prevalence

The number of overweight and obese Americans has risen dramatically in the past two decades and is now at epidemic levels.

- Approximately 64 percent of U.S. adults are overweight or obese; nearly 31 percent of U.S. adults are obese.[1]
- About 15 percent of children and teenagers ages 6 through 19 are overweight,[2] with ominous implications for our Nation's future health.
- Racial and ethnic minority populations are disproportionately affected by obesity, particularly African American, Hispanic American, and Native American women and children.

Disease Burden

Obesity is associated with numerous serious diseases, including type 2 diabetes, heart disease, stroke, osteoarthritis, gallstones, breathing problems, and cancer. Type 2 diabetes, formerly viewed as a disease of adults, has been increasingly reported among children. This alarming trend is thought to be a consequence of increased obesity along with decreased physical activity. In addition to the negative impact on quality of life and the increased risk of premature death, overweight and obesity exact enormous economic costs. In 2000 costs associated with obesity were estimated to be $117 billion.[3]

Rationale

Overweight and obesity develop when energy intake (food calories) exceeds energy expenditure. Although genetic factors may contribute substantially to the predisposition for obesity, the recent dramatic increase in obesity prevalence is clearly fueled by environmental and behavioral changes interacting with genetic susceptibility. Results from the NIH-funded Diabetes Prevention Program Clinical Trial (DPPCT) demonstrated a substantially reduced incidence of type 2 diabetes in a high-risk population using an intervention that combined moderate weight loss and exercise; however, these modest lifestyle changes required intensive individual behavioral intervention. In addition, the efficacies of different types of diets for weight loss and maintenance have not been compared in adequately powered trials of sufficient duration. Thus, the goal of obesity prevention may benefit greatly from new approaches to modify factors pervasive in the environment that promote overconsumption of food and sedentary lifestyles, complemented by additional research on strategies to help individuals achieve and maintain behavior changes. For people who are extremely obese, expected weight loss from behavior change alone may not be sufficient to have a major impact on health. Bariatric surgical procedures, which restrict stomach size and/or lead to decreased absorption of nutrients, are being increasingly performed to treat severe obesity. These procedures can have dramatic benefits but also carry substantial risks. Coordinated clinical research on this surgery will enhance patient evaluation, selection, and follow-up care and may also lead to improved understanding of factors underlying the development of obesity, leading to new strategies for prevention and treatment. Finally, the continued elucidation of the molecular factors and pathways responsible for appetite regulation, metabolism, and energy storage offers rich prospects for the development of new drugs that will promote safe and effective

[1] Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1990-2000. JAMA. 2002 Oct 9;288(14):1723-7.
[2] Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in obesity among US adults, 1990-2000. JAMA. 2002 Oct 9;288(14):1723-7.
[3] U.S. Department of Health and Human Services. Public Health Service. *The Surgeon General's Call To Action To Prevent and Decrease Overweight and Obesity*, 2001. p.10.

long-term weight loss. A major goal of NIH-funded research is to develop and evaluate strategies to prevent obesity and promote sustained weight loss among individuals who are overweight or obese. In addition to mechanisms falling within the three broad approaches to weight regulation just described, evaluation of other as yet unknown strategies may also be necessary to achieve success in meeting the goal. If successful, the approaches would decrease the risk of life-threatening diseases that accompany excess weight and also would reduce the social and economic costs of obesity.

PLANNED IMPLEMENTATION STRATEGIES

Because of the complexity of factors associated with weight gain and obesity and the high risk of a goal of evaluating novel approaches to prevent weight gain and/or treat obesity, NIH is pursuing multiple strategies toward achieving this goal. Several of these are relevant to lifestyle modification; others are related to pharmacologic and other medical interventions.

NIH will explore five or more lifestyle-based approaches to obesity prevention, including behavioral or environmental interventions, in settings such as schools, communities, and homes; in addition, at least two studies will evaluate the effects on weight control of worksite interventions that include environmental components. Because maintenance of weight loss is a critical yet particularly difficult element of obesity treatment and prevention, NIH will investigate novel ways to help individuals who have intentionally lost weight to keep the weight off for at least 2 years. Specifically, the Weight Loss Maintenance Trial will compare three different strategies for maintaining weight loss among persons who are successful in losing a targeted amount of weight over the short term. Complementing these areas of investigation relevant to lifestyle interventions will be research to evaluate the efficacy of different types of diets and physical activities. Specifically, a study is being conducted to compare the Atkins diet with a conventional weight loss diet as to long-term effects on weight and other health parameters.

Research on the effects of bariatric surgical procedures designed to restrict food intake in people who are seriously obese may increase the understanding of appetite and metabolism and thus inform the development of new prevention or treatment strategies for obesity. With respect to currently available medications, NIH will investigate the effects of at least one pharmacologic agent, either alone or in combination with behavior modification, on the treatment of obesity among children or adolescents. Finally, genetic and other studies in humans and animal models should reveal at least two new potential targets for drug discovery efforts; such targets could include signaling molecules or pathways that influence appetite or energy expenditure.

BASELINE(S)

- *Lifestyle Interventions:* Results from the NIH-funded Diabetes Prevention Program (DPP) clinical trial nationwide demonstrated a 58 percent reduced incidence of type 2 diabetes—a disease for which obesity is a strong risk factor—in a high-risk population using an intervention that combined moderate weight loss and exercise. The weight loss, which averaged 7 percent of body weight in the first year of the study, was achieved through diet modification and increased physical activity. However, as noted above, these modest lifestyle changes required intensive individual behavioral intervention. Furthermore, participants began to regain some of the lost weight over the next 2 years of the study. End results demonstrated that an intensive lifestyle intervention can result in weight loss; however, how long benefits persist is unknown. A follow-up study to the DPPCT will examine the durability of the lifestyle intervention on weight loss as well as the effect of a group lifestyle intervention that was offered to trial participants who received either placebo or an insulin-sensitizing drug. Other studies testing various approaches to fostering lifestyle changes to promote healthy weight are under way. Thus, increased research on approaches to behavior modification and motivational strategies to promote both initial weight loss and maintenance of that loss, along with innovative studies to investigate potential environmental approaches to obesity prevention, will be critically important.

- *Physical Activity and Diet:* Because few large-scale studies have evaluated the efficacies of different types of diets aimed at weight loss or weight maintenance, additional research in this area will

complement the behavioral and environmental research, as will continued research on the effects of different types of physical activity interventions.

- *Medical Strategies—Pharmacotherapy and Surgery:* Very few drugs approved in the United States for weight loss are currently on the market; only two of these have been approved for long-term use, and none has been approved by FDA for use among children younger than age 16. Thus, the identification of potential new targets for drug development will be valuable. Scientists have discovered the roles of a number of biological signaling molecules, such as brain-, gut-, and fat cell-derived hormones, in processes such as appetite control, the storage of excess calories as fat, and energy expenditure (calorie burning). Recent research is also revealing the elaborate network of biological pathways through which these molecules act. These molecules and pathways have been noted as potential targets for drug development efforts, and the identification of new targets for drug discovery will flow from continued elucidation of signaling molecules and additional delineation of the pathways through which they act. Also, novel studies of currently available medications may broaden their use for weight loss, if that was not their original use, or expand the use of medications to assist with weight loss among children. Clinical research into how bariatric surgical procedures lead to weight loss and other effects on health in severely obese individuals may increase understanding of appetite and energy balance and thus inform the development of novel approaches to obesity prevention and treatment.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Identify two new drug targets that can be used in screens for potentially therapeutic compounds in drug discovery projects or that could be evaluated for use as therapeutic agents for weight control.	(FY02) No highly effective drug therapies exist for overweight or obesity. Potential drug targets need to be identified	◆[e]		
Develop and launch at least two studies to test the effects of worksite interventions on weight control.	(FY03) No programs for weight control at the worksite have been examined in studies with valid designs to clearly evaluate if they are effective		◇	
Enroll and randomize 60 children with hyperinsulinimia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.	(FY03) No clinical trials have demonstrated efficacy of any medication for overweight during childhood. Pilot data suggest metformin may be of benefit for those children with hyperinsulinemia			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The target for FY 2003 was exceeded. Three identified molecules (rather than the targeted two) can be characterized and screened as targets for therapeutic compounds or can be evaluated as potential therapeutic agents for weight control. Achieving this target broadens scientific understanding of the molecular pathways involved in obesity. The three identified molecules are described below:

Melanin-concentrating hormone (MCH)–Removal of the MCH gene, which is expressed in the brain, results in leanness and increased resting energy expenditure in mice. Mice lacking the leptin gene are overweight and overexpress the MCH gene twofold to threefold, suggesting that MCH might mediate some of the physiologic effects of leptin. However, generation of mice that lack both the leptin and MCH genes results in mice that, while overweight, are leaner than those that lack leptin alone, even though both strains of mice overeat to the same extent. The attenuation of obesity in the "double knockout" mice may be due to the fact that these animals have a higher metabolism and are more active than mice lacking the leptin gene only. These findings suggest a critical integrative role for MCH in the regulation of energy balance and make it an attractive target for potential therapies.

Stearoyl CoA desaturase-1 (SCD-1)–Leptin elicits metabolic responses apart from decreasing food intake, such as diminished levels of monounsaturated fatty acids. One possible mechanism for this decrease in fatty acid levels is downregulation of the enzyme that catalyzes the desaturation of long-chain fatty acids, SCD-1. A recent study found that rats engineered to overexpress leptin in their livers had diminished expression of SCD-1. Rats made obese through a high-fat diet also displayed elevated leptin levels and diminished SCD-1 expression. In contrast, obese rats with a mutation in their leptin receptor that are resistant to leptin's effects displayed elevated levels of SCD-1. These findings suggest that strategies to inhibit SCD-1 activity may be a valid way to treat obesity.

Ghrelin–This hormone is secreted primarily by the stomach and stimulates food intake. Weight loss through caloric restriction results in a decrease in circulating leptin levels and an increase in ghrelin levels, which may help explain why it is so difficult for individuals to maintain long-term weight loss. Scientists have recently found that people who consume a normal number of calories on a low-fat, high-carbohydrate diet are able to lose weight and do not exhibit increased ghrelin levels. The researchers hypothesize that these individuals became more sensitive to leptin's actions. This finding suggests that ghrelin and leptin levels may be more responsive to diet composition than previously believed and that strategies to manipulate the activity of these hormones–either through diet or pharmacological interventions–may provide a novel approach to promoting and maintaining weight loss.

Implementation Strategy Advances or Other Highlights

A clinical trial aimed at reducing risk factors for type 2 diabetes in children and adolescents (STOPPT2D) using a school-based program designed to improve physical activity and diet has completed its pilot phase for assessing multiple parameters (including height, weight, lipids, and oral glucose tolerance testing). The pilot phase showed that large numbers of middle-school children were willing to participate in the trial. The physical activity pilot phase is currently ongoing.

In response to the lack of studies examining therapeutic drugs to aid behavioral therapy for weight control in young children, NIH scientists studying growth and obesity initiated a randomized, double-blind, placebo-controlled clinical trial to assess the efficacy of the promising medication metformin for weight control in severely overweight children with hyperinsulinemia. By the end of FY 2003, more than 50 children ages 6 to 13 were enrolled in this trial. The enrollment goals for this trial are to have 60 enrollees by FY 2005 and 100 enrollees by FY 2008. When combined with behavioral therapy, use of metformin is anticipated to decrease future weight gain and delay or prevent the onset of type 2 diabetes in children with hyperinsulinemia, who are considered to be at risk for diabetes.

Efficiency

NIH was able to exceed its target of identifying two drug targets during FY 2003. NIH-supported researchers discovered three molecules that could either be screened as a target for a therapeutic compound or be evaluated as a potential therapeutic agent for weight control.

GOAL 2c) BY 2006, DEVELOP METHODS THAT CAN CLASSIFY AT LEAST 75% OF PROTEINS FROM SEQUENCED GENOMES ACCORDING TO EVOLUTIONARY ORIGIN AND BIOLOGICAL STRUCTURE.

BACKGROUND

Classification of domains by computational sequence analysis is a powerful means to deduce the function of newly discovered proteins. In the context of proteins associated with human disease, this analysis can generate hypotheses concerning the metabolic pathways in which proteins act and greatly accelerate research into the molecular basis of disease and therapy. Domain analysis identifies regions of high sequence similarity with respect to other proteins from a variety of organisms. Conserved domains, as these regions are called, have been shown to be fundamental units of biological function; they adopt similar three-dimensional (3-D) structures and interact with other molecular components of living cells in similar ways. Thus, a comprehensive domain database, searchable over the Internet, will be a powerful research tool for academic and industrial scientists with diverse interests.

Rationale

A comprehensive database is achievable because proteins contain only a few thousand domain families. Maintaining an up-to-date collection with respect to current knowledge nonetheless represents a challenge that can be met only by the development of new methods for large-scale comparative analyses of molecular data that allow curators to focus on functional annotation. The continuing investment by Federal agencies and other organizations in genome sequencing and structural genomics will yield the greatest return when combined with efforts to organize these data in useful ways. Results of related research in comparative genomics and methodology for protein classification will assist in achieving this goal. The anticipated conserved domain database represents an advance over previous efforts because it will apply structure-based alignment and molecular evolutionary classification in a systematic and ongoing manner.

This resource will be particularly valuable to researchers such as medicinal chemists who require a synthesis of information on protein biological function, 3-D structure, and sequence conservation. Effective antiviral drugs have been designed by targeting the conserved regions of viral proteins; for example, the virus is unable to develop resistance to these drugs because sequence changes that block drug binding also block the normal function of the protein. By describing conserved regions in detail, this proposed resource provides information that is directly useful to the medicinal chemist undertaking this research.

PLANNED IMPLEMENTATION STRATEGIES

Production and maintenance of a classification database demand intensive intellectual effort and sophisticated computational and visualization tools. One such tool under development will interactively link displays of evolutionary sequence trees, the taxonomic “tree of life,” and ancient recombination history as inferred from protein domain architecture to facilitate assignment of protein domains into useful subgroups. Other computerized procedures will be used to update structure-based alignments and hierarchies of conserved domains by automatically scanning the PubMed database of biomedical journal literature and identifying new structures, sequences, and citations. For FY 2004 through FY 2005, it is expected that 1,000 domain families will be curated and that coverage will be extended toward the 75 percent goal at the end of FY 2005.

Additional development of these software tools not only will improve the efficiency and quality of the data curation by NLM’s National Center for Biotechnology Information (NCBI) staff but also will provide researchers with powerful discovery tools. Distribution of these tools will also facilitate the submission of outside research results to NCBI, thus further enriching the classification resource. Using NCBI-developed software for structure-based alignments and molecular evolutionary classification, outside experts will be able

to make contributions, based on their own research, in identifying homologous sites and in adding site-specific functional annotation.

Additional refinements in classification will increase the utility of the database in carrying out research in such areas as targeted drug design. Better identification of the conserved regions of viruses, for example, can lead to more effective antiviral drugs. Standard operating procedures will be developed to identify conserved domain subgroups of biomedical importance, including proteins from pathogens and human proteins that are potential drug targets. The database will be expanded to include structure-based sequence alignments for these domains.

BASELINE(S)

- Internet servers for identification of protein domains by comparative sequence analysis are operational and integrated into the PubMed (NLM's search engine) retrieval systems. These services employ a diverse collection of first-generation domain alignments produced by earlier sequence-clustering projects. They provide general functional annotation of variable quality.

- The 3-D molecular graphics software Cn3D supports curator-directed, structure-based alignment. Curators use this software to identify homologous sites based on structure and sequence conservation and to record general and site-specific functional annotation abstracted from scientific literature and 3-D structures of macromolecular complexes.

- Standard operating procedures for domain annotation was developed within an initial team of conserved domain curators. Some 256 domain families are curated by structure-based alignment techniques. Sequence profiles from these alignments annotate 14 percent of protein sequences in PubMed. Coverage has been extended to 67 percent by first-generation domain alignments.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Develop software for making comparative alignments of protein domains according to structure and molecular evolutionary classification, and which provides functions for domain family updates.	(FY02) 256 domain families curated; software to align domains by structure and class unavailable	◆		
Obtain annotation for a total of 1,500 protein domain families in the conserved domain database using two advanced classification methods: (1) structure-based alignment and (2) molecular evolutionary classification. Cover 35% of sequences in PubMed (the National Library of Medicine's database of biomedical research literature), extended to 70% by adding first-generation alignments.	(FY03) 800 domain families curated; 25% coverage of PubMed sequences		◇	
Obtain annotation for total of 2,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 45% of PubMed sequences, extended to 75% by adding first-generation alignments.	(FY03) 1,500 protein domain families curated; 35% coverage of PubMed sequences			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was met in three ways: (1) launching improved software for structure-based alignment (Cn3D Version 4.2 software was deployed in July 2003); (2) launching software for molecular evolutionary classification (Version 1 was deployed in December 2002, and Version 2 was deployed in September 2003); and (3) deploying procedures to efficiently update structure-based alignments and subfamily hierarchies of conserved domains.

Implementation Strategy Advances or Other Highlights

The Cn3D Version 4.2 software supports interactive definition of conserved core substructures and automated structure-based alignment. It provides an expanded library of structure-based alignment algorithms and seamless communication of revised alignments to the CDTree alignment hierarchy editor. The CDTree software implements computational strategies for identification of conserved domain subfamilies with distinct biological function. This software interactively links displays of evolutionary sequence trees and the taxonomic "tree of life," allowing curators to identify and annotate ancient gene duplications. Version 2 adds an improved graphical user interface, simplified data management, and tools to interactively assess performance of protein classification models derived from each alignment.

Standard operating procedures for molecular evolutionary classification have been developed within the curator team. Curators apply an "age limit" principle to identify widely recurrent subfamilies that correspond to ancient gene duplications, as inferred from taxonomic distribution and recombination history. Update procedures automatically scan PubMed databases for new structures, sequences, and citations, while preserving existing general and site-specific functional annotation. Curators routinely use the new information to maintain accurate and up-to-date domain annotation.

GOAL 3a) BY 2013, IDENTIFY AT LEAST ONE CLINICAL INTERVENTION THAT WILL DELAY THE PROGRESSION, DELAY THE ONSET, OR PREVENT ALZHEIMER'S DISEASE (AD).

BACKGROUND

Prevalence/Incidence

Alzheimer's disease (AD) is a progressive, at present irreversible, brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks of daily living.

- A consensus statement developed by the American Association for Geriatric Psychiatry, Alzheimer's Association, and American Geriatrics Society estimates the number of AD cases at 4 million nationally and concludes that AD and related dementias are underdiagnosed.[1]
- The prevalence of the disease doubles with each 5-year increment in age in persons older than 65.
- It is estimated that the prevalence of AD will nearly quadruple in the next 50 years.[2]

Disease Burden

The cost of AD care varies by stage of the disease. In 1996 annual costs of caring for patients with mild, moderate, and severe AD were estimated as $18,408, $30,096, and $36,132, respectively.[3] The national cost of caring for people with AD is now thought to be about $100 billion every year.[4]

Rationale

In 1999, at the direction of Congress, NIH embarked on the Alzheimer's Disease Prevention Initiative. A major focus of this initiative is accelerating the movement of promising new treatments and prevention strategies into clinical trials.

PLANNED IMPLEMENTATION STRATEGIES

NIH plans to accelerate discovery of new risk and protective factors and identify promising targets for treating and preventing disease through basic research. Initiatives will speed progress in identifying non-genetic risk and protective factors and genes associated with AD, including new risk factor genes and their interactions with the apolipoprotein E-4 risk factor gene in different populations. Advances in brain imaging will be another key factor in identifying the first brain regions affected prior to clinical diagnosis, when interventions could be most effective.

NIH also plans to speed drug discovery and movement of promising new treatments and prevention strategies into clinical trials. Neurobiologic and epidemiologic research will continue to pinpoint new targets for drug therapy, such as inflammatory processes and toxic oxidative agents known as free radicals. Additionally, NIH plans to launch clinical trials to prevent AD. Advances in basic research and drug development are likely to include more effective anti-inflammatory compounds and antioxidants—agents that can more effectively prevent brain cell death—and substances designed to stop the deposition of amyloid plaques and neurofibrillary tangles in the brain.

[1] Small GW et al. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. JAMA. 1997 Oct 22-29;278(16):1363-71.
[2] Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health. 1998 Sep;88(9):1337-42.
[3] Leon J, Cheng CK, Neumann PJ. Alzheimer's disease care: costs and potential savings. Health Affairs (Millwood). 1998 Nov-Dec;17(6):206-16.
[4] Ernst RL, Hay JW, Fenn C, Tinklenberg J, Yesavage JA. Cognitive function and the costs of Alzheimer disease. An exploratory study. Arch Neurol. 1997 Jun;54(6): 687-93.

Finally, NIH plans to expand strategies for improving patient care and alleviating caregiver burdens. Effective pharmacologic and non-pharmacologic methods to treat and manage behavioral symptoms in AD patients could help prevent hospitalizations, decrease unscheduled visits to care providers, delay nursing home admission, delay progression to more intense levels of institutional care, avoid preventable illnesses unrelated to AD, and prevent caregiver burnout.

BASELINE(S)

- Advances in genetic, molecular, and epidemiological research have increased understanding of the biologic processes involved in the onset and progression of AD and have provided important opportunities to test promising new interventions.

- Clinical research is rapidly developing ways of identifying persons early in the course of AD and better ways of predicting and following the progression of the disease.

- Ongoing clinical trials and those in the planning stages are focusing on specific biological processes—including inflammation, free radical damage, amyloid (starch) deposition, and cell death—that scientists believe are among the first changes to appear in the brains of patients with AD. Completing these long-term human trials will identify ways that specific drugs can be used to most safely and effectively intervene to delay the progression, delay the onset, or prevent AD.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Initiate a double-blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether it can slow the rate of progression of AD.	(FY02) Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of AD	◆		
Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	(FY03) Estimated 30 compounds are presently or will soon be tested in human AD clinical trials but additional targets are needed		◇	
Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment (MCI) and AD, and use as potential surrogate markers for drug development and clinical trials.	(FY03) Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was met through the initiation of the CLASP (Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease) study, a double-blind, parallel group, placebo-controlled trial of simvastatin, a compound that lowers plasma cholesterol and lipoprotein levels in patients with AD. NIH initiated this study as a result of growing evidence from clinical, epidemiological, and laboratory studies that cholesterol may play a role in the pathogenesis of AD. Patients (400 total) are assigned on a 1:1 ratio to receive either simvastatin or an identical placebo with stratification for apolipoprotein E-ε4 genotype (which increases the risk of AD). Study duration, originally set for 12 months, was extended to 18 months so that it would be comparable to an ongoing study of another statin drug. This will allow some comparability between the two studies and may help address the issue of the effects of statin drugs that do and do not cross the blood-

brain barrier. The primary outcome measure will be the longitudinal decline in the ADAS-Cog, an AD assessment scale in which a higher score denotes poorer performance, in the 1-year treatment period. Secondary outcomes will include measures using a number of other cognitive and neuropsychometric instruments. Biomarkers will be collected to assess the relationship between treatment response and oxidative stress. Enrollment began in January 2003, and 137 subjects have been enrolled to date.

Implementation Strategy Advances or Other Highlights

Consensus was achieved in meetings with the Institute for the Study of Aging and others regarding the development of a joint program announcement for preclinical drug discovery and development. The program announcement is an additional strategy identified as part of the FY 2004 target.

The RFA for the Alzheimer's Disease Neuroimaging Initiative, a U01 cooperative agreement, was released on October 2, 2003, and funding is anticipated to begin in September 2004. The initiative is planned as a partnership among NIH and other relevant organizations.

GOAL 3b) BY 2010, DEVELOP ONE UNIVERSAL ANTIBIOTIC EFFECTIVE AGAINST MULTIPLE CLASSES OF BIOLOGICAL PATHOGENS.

BACKGROUND

In the 1940s the widespread availability of newly discovered antibiotics led to a dramatic reduction in illness and death from infectious diseases. However, bacteria and other disease-causing organisms are remarkably resilient and have developed mechanisms of resistance that thwart or block the action of antimicrobial drugs. Microbes that were once easily controlled by antimicrobial drugs are causing infections that no longer respond to treatment with these drugs. In addition, new, serious, and unforeseen infectious disease threats have emerged, including those posed by agents of bioterrorism. The global burden of established and emerging infectious diseases, the threat of bioterrorism, and the increasing problem of antimicrobial resistance underscore the importance of research to develop new and improved antimicrobial treatments. A "universal antibiotic," a drug effective against a wide spectrum of infectious diseases, would help address these challenges.

Rationale

Drug-resistant infectious agents—those that are not killed or inhibited by antimicrobial drugs—are an increasingly important public health concern. Tuberculosis, gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat due to the emergence of drug-resistant pathogens. Antimicrobial resistance has become a factor in virtually all hospital-acquired (nosocomial) infections. Many physicians are concerned that several bacterial infections soon may be untreatable due to the rise in resistant organisms. A key factor in the development of antimicrobial resistance is the ability of infectious organisms to adapt quickly to new environmental conditions. Even a single random gene mutation can have a large impact on their disease-causing properties, and since most microbes replicate very rapidly, they also can evolve rapidly, acquiring new immune-evasion abilities and drug resistance.

In addition to concern about the emergence of microbes with naturally evolving resistance to commonly used antimicrobial drugs, the potential for the use of microbes with engineered resistance to antimicrobials as agents of bioterrorism raises another area of concern. The release of microbes specifically engineered to be unresponsive to currently available antimicrobial drugs could be a serious threat to public health. The Federal Government's ability to counter a biological attack requires basic research aimed at understanding both the organisms that might be used as agents of bioterrorism and how the human immune system responds to those organisms. Characterization of the genetic and biochemical requirements of intracellular infections, as well as the aspects of immune response common to several types of microbial infections, could lead to new therapeutic targets such as one universal antibiotic effective against multiple classes of bacterial/biological pathogens. In addition, genomics, the science of deciphering and drawing information from the genetic code of an organism, is a powerful tool that NIH is using to understand the microbes that cause disease and design strategies to overcome them.

PLANNED IMPLEMENTATION STRATEGIES

To accomplish the goal of developing one universal antibiotic effective against multiple classes of biological pathogens, NIH will expand by 20 percent its capacity for medicinal and combinatorial chemistry, library and database resources, and screening assays for use in identifying novel antimicrobial drugs. The availability of new methodologies, chemical libraries, and software tools will expand the pool of compounds that can be screened for antimicrobial properties. NIH will also expand by 20 percent the NIH-supported Pathogen Functional Genomics Resource Center (PFGRC), based at The Institute for Genomic Research (TIGR). The Center will provide the research community with the needed resources and reagents, including microarray technology and new genomic software tools, to conduct both basic and applied research on microorganisms

responsible for emerging and reemerging infectious diseases, including those considered potential agents of bioterrorism. Genomic information will aid in the identification of gene products critical to bacterial growth and pathogenicity that may serve as targets for broad-based antimicrobials.

NIH will support ongoing and new clinical studies of three interventions for addressing serious fungal and health care-associated resistant bacterial infections through the Bacteriology and Mycology Study Group (BAMSG) contract. Also, NIH will support studies on protective mechanisms against infection with the CDC Category A-C priority pathogens through the Biodefense and Emerging Infectious Diseases Research Opportunities initiatives. A better understanding of the innate immune system will aid in the identification of genetic changes and proteins that are triggered by encounters between innate immune cells and infectious pathogens.

NIH will launch the initiative Identifying Targets for Therapeutic Interventions Using Proteomic Technologies, which will support the development and application of innovative proteomic technologies for the discovery and identification of novel targets for therapeutics, vaccines, and diagnostics; awards are planned for FY 2004. Other efforts in the area of microbial proteomics include support for large, multidisciplinary efforts focused on the proteomics of multiple microorganisms. NIH also will launch interagency and public-private collaborative research projects to develop new antimicrobial strategies. NIH's VATID Program will support interdisciplinary and public-private collaborative research to develop vaccines, therapeutics, adjuvants, and diagnostics for biodefense. This Program will help translate research from the target identification stage through target validation to early product development.

BASELINE(S)

- NIH supports a broad portfolio of research on antimicrobial resistance, including investigator-initiated research on the molecular mechanisms responsible for drug resistance and epidemiologic studies that seek to define how bacterial pathogens acquire, maintain, and transfer antibiotic-resistant genes. In 2002 NIH supported the initiative Innovative Approaches for Combating Antimicrobial Resistance to encourage novel and innovative research projects on the basic molecular biology and genetics of resistance among bacteria, viruses, fungi, and parasites; the development of new tests for detecting resistance; identification of new classes of antimicrobial agents; and the evaluation of alternative treatments of drug-resistant infections. In addition, NIH-supported microbial genome sequencing activities are providing insight into the genetic basis of resistance and may identify new proteins and genes that are potential targets for broad-spectrum antimicrobial drugs.

- NIH supports applied research to develop and evaluate new or improved therapeutics for infectious disease intervention and prevention. Several innovative NIH funding mechanisms have facilitated partnerships between the public sector and private industry to develop new biomedical products, including new antimicrobial treatments. For example, through the NIH Challenge Grants: Joint Ventures in Biomedicine and Biotechnology initiative, which uses matching funds from industry to promote joint ventures between NIH and industry for research and development on products to treat infectious diseases, NIH is funding a study of thiolactomycin, a central component of the bacterial fatty acid biosynthesis machinery, which may have potential as a novel target for broad-spectrum antibacterial drug development. The success of the Challenge Grants initiative has led to additional NIH initiatives to encourage research collaborations between government and industry. For example, the Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense and SARS (VATID) Program and the Biodefense Partnership Program support interdisciplinary and public-private collaborative research to develop proven concepts involving a pathogen or host target toward development of vaccines, adjuvants, therapeutics, and diagnostics for biodefense.

- NIH supports interagency efforts to investigate enhanced broad-spectrum applications of currently licensed antibiotics. In collaboration with the U.S. Army Research Institute of Infectious Diseases

(USAMRIID) and FDA, NIH is supporting the testing of licensed antibiotics for efficacy against pneumonic plague and anthrax. Five currently licensed drugs—gentamycin, doxycycline, ciprofloxacin, levofloxacin, and ceftriaxone—are being tested for efficacy in African green monkeys exposed to aerosolized *Yersinia pestis*, the causative agent of plague. Studies are currently under way to determine the pharmacokinetics and toxicity of the drugs in this animal model.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Identify one molecule with a common role in bacterial and viral infections that may serve as a target for broad-spectrum antimicrobial drug development.	(FY02) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule with a common role in both bacteria and viruses	◆		
Identify one molecule or mechanism that is shared by a class or across different classes of microbes that may serve as a target for broad-spectrum antimicrobial drug development.	(FY03) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes		◇	
Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad-spectrum antimicrobial drug development.	(FY05) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was met and exceeded. Two different molecules (rather than the target one molecule) with a common role in different classes of microbes were identified through two NIH-funded research projects. First, in FY 2003, a single protein called Trif, which acts as a key switch point in frontline immune system reactions to both bacterial and viral infections, was discovered in mice. This finding explains why certain symptoms, such as fever, occur even with very different types of infections. Trif is a critical first-line signal for the mouse innate immune system and alerts immune-signaling proteins to the presence of infectious agents. Once activated by invading pathogens, these signaling proteins relay the alarm to other actors in the immune system. The innate immune system then responds with a surge of chemicals that together cause inflammation, fever, and other responses to infection or injury. This finding provides a new potential target for the development of broad-spectrum antibiotics.

The second finding includes certain defensive molecules secreted by the innate immune system that were shown in FY 2003 by NIH-supported researchers to possess both antibacterial and antiviral activity. Peptides (small protein fragments) of the alpha-defensin and theta-defensin groups, which act against a broad range of bacteria, also inhibit replication of HIV-1 virus in cultured cells. Defensins block early stages of the HIV infection process. Recent findings demonstrate that the antiviral activity of a novel anti-HIV theta-defensin is likely based on its ability to attach strongly to sugar molecules found on the virus surface, thereby preventing cell entry by viral particles. Alpha-defensins also may interrupt early intracellular stages of HIV infection. Because these dual-activity defensins are natural mammalian cell products, they potentially may lead to less toxic antimicrobial drugs than those derived from other sources. Studies are needed to test whether these results obtained in isolated cells can be developed for use as systemic therapeutics or topical microbicides.

Implementation Strategy Advances or Other Highlights

In FY 2003, NIH supported the initiative “Innovative Approaches for Combating Antimicrobial Resistance” to encourage novel and innovative research projects on the basic molecular biology and genetics of resistance among bacteria, viruses, fungi, and parasites; development of new tests for detecting resistance; identification of new classes of antimicrobial agents; and evaluation of alternative treatments of drug-resistant infections. In addition, NIH-supported microbial genome sequencing activities have provided clues to the genetic basis of resistance and

may lead to the identification of proteins and genes that are potential targets for broad-spectrum antimicrobial drugs. In FY 2003, NIH funded the complete genome sequencing of a vancomycin-resistant strain of the human pathogen *Enterococcus faecalis***.**

Also in FY 2003, NIH made multiple awards through a variety of initiatives to expand antimicrobial research, including the "Collaborative Research for Vaccines, Therapeutics, Adjuvants and Diagnostics" and "Partnerships for Novel Therapeutic, Diagnostic and Vector Control Strategies in Infectious Diseases" initiatives. Together, these initiatives will support a spectrum of drug research from target identification through product development and early clinical testing of candidate drugs. In addition, in FY 2003, five awards for the development of antimicrobial drugs were made under the small business grant program.

GOAL 3c) BY 2013, DETERMINE THE EFFICACY OF USING SALIVARY DIAGNOSTICS TO MONITOR HEALTH AND DIAGNOSE AT LEAST ONE SYSTEMIC DISEASE.

BACKGROUND

For many serious health conditions, early detection offers the best hope for cure. However, many individuals obtain a correct diagnosis only after they experience symptoms—and then it may be too late. The composition of saliva and other oral fluids reflects serum levels of substances that may be useful for diagnostic applications—such as therapeutic and recreational drugs, hormones, immunoglobulins, and toxic molecules. Oral fluids also can be used as a source of host or pathogen DNA. Thus, oral fluids could potentially be used to assess and monitor systemic health and disease as well as determine exposure to environmental and occupational hazards. Real-time monitoring of oral fluids may also have a role in biodefense by facilitating early detection of agents used in bioterrorism.

Rationale

Saliva is easy to collect and poses none of the risks, fears, or "invasiveness" concerns occasioned by blood tests. Miniaturization of the "lab on a chip" may allow placement of the detection device directly in the mouth, making sample collection unnecessary. However, because oral levels of most analytes are lower than blood levels, sensitive analytical techniques are required. (An analyte is any substance or chemical constituent of a body fluid that is analyzed.) To overcome this challenge and demonstrate the feasibility of salivary diagnostic tools, NIH is taking steps to accelerate the technology needed to analyze oral fluids. These efforts will require highly sensitive and accurate methods for the rapid detection of informative analytes in saliva, thus indicating the early stages of emerging disease. In addition, NIH will create a catalog of all proteins in human saliva as a starting point in distinguishing between health and disease states. The goal is to determine the efficacy of salivary diagnostics to monitor health and diagnose at least one systemic disease by 2013. If successful, this line of research could yield improved detection for a number of diseases as well as dramatically reduce the cost and risk associated with blood test-based diagnostics. This could catalyze a shift in the current system of disease detection to one of health surveillance within the community and the home.

PLANNED IMPLEMENTATION STRATEGIES

First, NIH plans to implement research projects directed at developing integrated technologies to create tools that can efficiently and simultaneously analyze several key molecules in human saliva. Second, NIH plans to develop integrated microsystems to detect disease-associated biomarkers in human saliva. Finally, NIH plans to develop an improved understanding of how salivary components change in the presence of disease or disorders by implementing research projects to catalog the salivary secretory (i.e., parotid, submandibular, and sublingual) proteins.

BASELINE(S)

- In monitoring a number of systemic diseases and conditions as well as substance abuse, progress in developing salivary diagnostics has not been as swift as had been hoped. A key challenge has been the need for fast, reliable, sensitive techniques to detect components in oral fluids, since levels of these substances are lower in oral fluids than in blood or plasma.

- However, techniques are emerging from a combination of miniaturization technologies and discoveries in biology, chemistry, physics, and engineering that are expected to lead to low-cost, more efficient, and more rapid biochemical analyses.

- Furthermore, the field of proteomics has created new opportunities to advance the field of salivary diagnostics. For example, advances in mass spectrometry will allow researchers to analyze ever-diminishing quantities of proteins. Identification of the salivary proteomes is an important step in helping scientists detect changes in saliva that are associated with specific diseases or conditions. This project serves an initiative toward identifying the salivary proteomes.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Implement at least five research projects directed at developing integrated technologies for the efficient and simultaneous detection of key molecules in human saliva.	(FY02) No integrated technologies to quickly and efficiently measure multiple substances in saliva	◆		
Implement research projects directed at identifying and cataloging saliva proteomes. Identification of salivary proteomes will help scientists detect changes in saliva that are associated with specific diseases or conditions.	(FY03) Technology available to help identify salivary proteomes		◇	
Develop electronic microfluidic assay systems (e.g., microchip-based systems that are replacing large and costly instruments) that can quantify C-reactive protein (a biomarker for cardiovascular disease) in saliva.	(FY03) Systems to quantify C-reactive protein in saliva have not yet been developed			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

In FY 2003, NIH implemented a series of seven research projects in the form of cooperative agreements, all focused on developing strategies to measure and analyze multiple substances in saliva quickly and simultaneously. These strategies will lead to new technology aimed at helping clinicians detect the complex metabolic processes associated with disease before symptoms appear. Working in partnership with colleagues in industry and academia, NIH scientists are already using microchip technology to develop salivary diagnostic tests that can be applied to a wide variety of conditions, including AIDS, oral infections, and potential agents of bioterror. Proof-of-principle exists for some of these technologies, and the salivary diagnostics program has been established to take the technology from the laboratory to the clinic. The cooperative agreements implemented by NIH have brought scientists, engineers and other researchers together to make this vision a reality.

Implementation Strategy Advances or Other Highlights

Progress in this new program has been made in several areas. For example, scientists are progressing on the validation of the first generation of an oral chip for the identification and quantification of oral microbes. This chip platform will also have the potential to be used for rapid, early diagnosis and epidemiological analysis of severe acute respiratory syndrome (SARS), a condition that emerged in November 2002 as a major global health risk. In addition, progress in the development of comprehensive and reliable multi-input/multioutput software packages has been made to assist in the interpretation of these very complex data. A Web site has been developed to share data on the project; this is available at http://nidcr.bioeng.washington.edu/index.html. Progress has also been made in the fabrication of enzyme-based sensor arrays for the efficient and simultaneous analysis of glucose, lactate, glycerol, and cholesterol as well as for the detection of C-reactive protein, a biomarker for cardiovascular disease. Furthermore, scientists are moving toward using this sensor system to detect oral cancer using antibodies to specific biomarkers. Finally, a microfluidic system is under development to detect pathogens in saliva. This system will be designed to be able to detect microbial antigens in even very small amounts of saliva. Although the salivary diagnostics program is relatively new and the ultimate goal is a long-term one, the initial progress is highly encouraging.

GOAL 3d) BY 2010, DEVELOP AN HIV/AIDS VACCINE.

BACKGROUND

Prevalence/Incidence

Since the epidemic began, nearly 60 million people worldwide have been infected with HIV. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that AIDS has killed more than 22 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. In 2002 alone, over 3 million people died from AIDS, and 5 million people were newly infected with HIV. Of the 5 million new infections, 800,000 were children. More than 95 percent of new HIV infections occur in the developing world, with 70 percent occurring in sub-Saharan Africa and 20 percent in Asia and the Pacific rim.[1] A recent Central Intelligence Agency (CIA) report stated, "By 2010, we estimate that five countries of strategic importance to the United States—Nigeria, Ethiopia, Russia, India, and China—collectively will have the largest number of HIV/AIDS cases on earth."[2] In the United States, close to 950,000 people are living with HIV/AIDS. The number of new infections has remained relatively stable at approximately 40,000 new infections each year; however, CDC recently announced an increase in new HIV diagnoses. HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people older than 50 years of age.[3]

Disease Burden

According to UNAIDS, "AIDS has become the most devastating disease humankind has ever faced." The impact of AIDS on developing nations and many countries of the former Soviet Union is profound. UNAIDS states, "the epidemic is driving a ruthless cycle of impoverishment." AIDS is reversing decades of progress from important public health efforts; lowering life expectancy; and significantly affecting education, agricultural output, and commerce of all kinds. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. AIDS is affecting the military capabilities of some countries, as well as international peacekeeping forces. In Africa, the epicenter of the pandemic, AIDS is sabotaging economic development, leading to famine and massive social breakdown and creating a generation of orphans.

Rationale

Safe and efficacious vaccines to prevent HIV infection and disease and/or transmission are essential for global control of the AIDS pandemic. NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical research on AIDS vaccines. As promising candidates move further in the vaccine pipeline, expanded clinical trials with populations at increased risk for HIV infection will become increasingly important. In addition, many new approaches to HIV vaccines are being pursued.

NIH is designing and testing new vaccine candidates, building on the foundation of recent basic research findings on the structural components of HIV and studies on immune responses in small animals and nonhuman primates (NHPs). Vaccine candidates also are being constructed based on isolates from many regions of the world, and several NIH-sponsored research groups are exploring mixtures of viral components from different isolates and clades. NIH is testing several newer vaccine strategies using different adjuvants, immune modulators, and other delivery components to optimize the immune responses that result from vaccine candidates. NIH will fund additional basic research to better understand what makes some

[1] World Health Organization. 2002. Joint UN Programme on HIV/AIDS. *AIDS Epidemic Update: December 2002.*
[2] Central Intelligence Agency. *The Next Wave of HIV/AIDS: Nigeria, Ethiopia, Russia, India, and China*. September 2002.
[3] Centers for Disease Control and Prevention. U.S. HIV and AIDS reported through December 2001. Year-end edition. HIV/AIDS Surveill Rep. 13(2):2002.

individuals either resistant to infection when they are exposed to HIV or able to control the infection so that disease progression is slowed.

Suitable animal models, especially NHPs, are crucial to the development and preclinical testing of vaccine candidates. A key priority for testing vaccine candidates continues to be the resolution of the crises in the supply of these monkeys for AIDS vaccine studies, as well as available space for conducting experiments that require adequately controlled biosafety housing. NIH is working with various research institutions and other organizations to find solutions to these obstacles.

Although production of some candidate vaccines for clinical study has proceeded slowly, at least 10 new candidate vaccines will enter NIH-funded Phase I trials in the next 2 years. Several new combinations of products, which are expected to provide even better immune responses in combination, will also be tested in Phase I or II trials. The NIH Dale and Betty Bumpers Vaccine Research Center recently launched the first Phase I clinical trial of a multi-clade, multi-gene vaccine candidate. Since January 2003 three vaccine candidates supported through NIH grants or contracts have entered trials in the United States and/or in international sites.

The 2007 AIDS vaccine goal was based in large part on the anticipated success of AIDSVAX, a candidate vaccine tested by VaxGen, Inc. However, recent Phase III trial results found that, overall, AIDSVAX did not prevent infection. In the past year, trials of a recombinant canarypox vector vaccine candidate (from Aventis) demonstrated that this product was not sufficiently immunogenic to warrant testing beyond the Phase II level. Products that are currently in the pipeline might prove to be effective either in preventing HIV infection or in slowing disease progression in those already infected. However, because these products are unlikely to complete testing by 2007, this goal has been changed to the more realistic date of 2010. In striving to meet the goal, a significant investment of NIH resources has been made in product development. This will ensure that there is a vibrant pipeline to support HIV vaccine research efforts. Significant additional resources will be required to support large-scale manufacture of vaccine and conduct large efficacy trials.

PLANNED IMPLEMENTATION STRATEGIES

Testing a vaccine in monkeys, especially macaques, is a critical and necessary step before a vaccine can be tested in humans. NIH will expand breeding and increase output of specific pathogen-free macaques at three or more primate centers for the preclinical testing of vaccine candidates. In addition, NIH will produce and test at least one new virus stock for challenge of vaccinated animals. Two vaccine candidates will be tested in animals for immunogenicity, safety, and toxicity.

To prepare for future large-scale clinical trials and build necessary infrastructure, NIH will compile seroincidence data from at least three sites that focus on populations of minorities in the United States, or on heterosexual transmission in either domestic or international settings, and develop at least two key regional or national laboratories capable of evaluating the safety of candidate vaccines in resource-poor settings. These capacity-building efforts will include providing the necessary training of personnel and developing quality assurance/quality control programs for these activities.

NIH will advance at least one lot (qualified according to Good Manufacturing Practices) of a novel vaccine candidate into Phase I human trials. NIH also will prepare for and initiate at least four Phase I and/or II trials of new HIV vaccine candidates. On the basis of success in a Phase II trial, NIH will scale up production of the candidate vaccine (with or without company involvement) for launch of a Phase III clinical trial.

BASELINE(S)

- To date, NIH has conducted, in collaboration with academic researchers and industry co-sponsorship, 64 vaccine trials, including 60 Phase I and 4 Phase II trials. These studies have involved over 4,186 volunteers, 36 vaccines, and 13 adjuvants. NIH has 14 vaccine candidates in the preclinical pipeline that are expected to enter Phase I studies in the next 2 years. These candidate vaccines will be evaluated in animals and then in early safety studies in humans. Seven HIV vaccine candidates are currently in active clinical trials.

- NIH has a range of programs to support preclinical vaccine development, including resources for the manufacture of vaccines for NHP studies and for human trials, safety and immunogenicity testing in animals, and animal model studies.

- NIH established the HIV Vaccine Trials Network (HVTN), a global network that supports all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. In addition to 13 domestic sites, the HVTN includes 12 sites in the Caribbean basin, South America, Africa, and Asia. NIH supports training and infrastructure development in resource-poor countries to enhance their ability to conduct future HIV vaccine trials. An interagency agreement with the U.S. Department of Defense, Walter Reed Army Institute of Research (WRAIR) and a memorandum of understanding with the Centers for Disease Control and Prevention, which will expand and strengthen HIV vaccine research capabilities and help coordinate Federal Government vaccine development efforts, particularly in international settings is in place.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Design and develop new or improved vaccine strategies and delivery/production technologies.	(FY02) Existing DNA and viral-vector vaccines strategies require further evaluation	◆		
Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	(FY03) HIV Vaccine Trials Network currently supports clinical trials at 12 international sites		◇	
Initiate four new Phase I or II trials of new or improved concepts and designs and expand capacity to conduct clinical trials in three international sites.	(FY03) NIH has conducted 68 phase I and phase II HIV vaccine trials to date			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was met as indicated by the following scientific advances: (1) HIV-1 vaccination administered intramuscularly can induce both systemic and mucosal T-cell immunity in HIV-1 uninfected individuals; (2) prime-boost regimens with live viral vectors expressing HIV-1 gag and env proteins induce robust recall and long-term memory T-cell responses; (3) a novel, nonhuman (replication-defective) adenoviral recombinant vaccine to HIV-1 gag circumvents the interference observed with human serotype-based adenoviral recombinants; and (4) a novel vaccine strategy that uses synthetic genes for HIV envelope glycoprotein can enhance humoral immune responses.

The FY 2003 target was also met by progress made by the HIV Vaccine Design and Development Teams (HVDDTs), which are public-private partnerships that are given financial incentives to move strong HIV/AIDS vaccine candidates out of the laboratory and into human testing. Prior to FY 2003, NIH awarded

five contracts under this mechanism; all of these contractors are now moving vaccine products rapidly through production and preclinical testing.

One of the original four contactors, a consortium headed by the University of New South Wales in Australia, had its two vaccines (DNA and fowlpox-vectored vaccines) enter into human clinical trials in early 2003. The other three original awardees are on schedule to have their vaccine products ready for human clinical trials in early FY 2004. They include Chiron (DNA and protein-based vaccine constructs for a DNA plasmid prime/protein boost vaccine that will be based on a clade B HIV-1 vaccine for testing in the United States and an analogous clade C HIV-1 vaccine for testing in South Africa and/or India), Wyeth Lederle Vaccine (DNA and peptide-based vaccines), and Advanced BioSciences Laboratories (DNA and protein-based vaccines for a DNA prime/multiepitope peptide boost vaccine).

In order to extend efforts to design and develop new or improved vaccine strategies and delivery/production technologies, NIH committed $81 million in FY 2003 for the next 5 years to fund four additional HVDDT contracts that will further develop and explore four unique vaccine strategies. First, nonreplicating alphavirus particles as a vector to deliver the genes to make four HIV proteins (gag, pol, env and nef). The genes in this vaccine have been taken from HIV strains in circulation in South Africa to maximize the probability that the vaccine would be successful in populations with the highest prevalence of HIV/AIDS (Alphavax). Second, epitope-based HIV vaccine to be given in a prime/boost regimen. Epitope-based vaccination is a promising but as yet unproven technology that could be applied to many infectious diseases (Epimmune). Third, a novel virus-like particle (VLP) vaccine formed from self-assembled structural proteins of HIV. These protein-based vaccines will be devoid of viral genes (Novavax). Fourth, modified HIV envelope subunit vaccine. The structure of the HIV envelope protein will be modified to enhance its ability to generate broadly reactive, neutralizing antibodies (Progenics Pharmaceuticals).

Implementation Strategy Advances or Other Highlights

HIV/AIDS vaccine-related solicitations made during FY 2003 include the Innovation Grant Program and the HIV Vaccine Research and Design Program. New grants also have been awarded in the Integrated Preclinical/Clinical AIDS Vaccine Development Program, HIV Vaccine Research and Design Program, and New Technologies for HIV and HIV Vaccine-Related Research Program. Studies on the scope and relationship of viral and human genetic variation in the context of vaccine development are being supported by an expanded contract for HLA Typing and Epitope Mapping Relative to HIV Vaccine Design.

Since January 2003, six new preventive HIV vaccine clinical trials have been initiated to evaluate different types of DNA vaccines, Adeno 5 vector (Clade B) vaccine, and Venezuelan Equine Encephalitis (VEE) replicon vector (clade C) vaccine. Fourteen Phase I trials and one Phase III trial are planned for FY 2004. Clinical trial research capacity was also expanded by adding sites to the HIV Vaccine Trials Network (HVTN) in Dominican Republic and Puerto Rico and by providing research training support for all international HVTN sites through the AIDS International Training and Research Program.

Through the Adolescent Trials Network, NIH is developing trust-building partnerships in 15 cities in the United States and Puerto Rico to enable racial and ethnic minority communities to identify and address the prevention needs of their youth. This program, Connect to Protect, will establish and use a research infrastructure that will be able to support future vaccine research in adolescents.

NIH also has engaged in public-private collaborations, exemplified by the independent evaluation of VaxGen's Phase III trial of AIDVAX in the United States conducted by NIH. Partnerships have also been established with VaxGen, the Centers for Disease Control and Prevention (CDC), the Gates Foundation, and the Foundation for the National Institutes of Health (FNIH).

NIH also has strengthened collaborations with the U.S. Department of Defense (DoD) and is working closely with the HIV Research and Development Program of the U.S. Army Medical Research and Materiel

Command (USAMRMC) to support a Phase III vaccine efficacy trial of ALVAC (vCP1521) plus AIDSVAX (B/D) in Thailand (commenced in October 2003). NIH has also established the Partnership for AIDS Vaccine Evaluation (PAVE) program, a partnership among NIH, CDC, and DoD to ensure coordination and efficiency among U.S. Government agencies and their partners working on HIV vaccine development.

GOAL 4a) BY 2004, DEVELOP TWO NEW ANIMAL MODELS TO USE IN RESEARCH ON AT LEAST ONE AGENT OF BIOTERROR.

BACKGROUND

Deliberate exposure of the civilian population of the United States to *Bacillus anthracis* (anthrax) spores revealed a gap in the Nation's overall preparedness against bioterrorism. These attacks uncovered a need for tests to rapidly diagnose, vaccines and immunotherapies to prevent, and drugs and biologics to cure disease caused by agents of bioterrorism. The lack of routine clinical importance, and thus the absence of scientific and clinical expertise associated with a microbe, is a hallmark of a successful bioterrorist agent. The development of centralized sources of generalized as well as specific expertise in bioterrorism areas will be required to speed the development of new-generation products. The *NIAID Strategic Plan for Biodefense Research* (February 2002) offers more detailed information on the types of biodefense research supported by NIH, including specific goals for each research category.

Rationale

New products and ideas must be thoroughly tested in the laboratory to ensure that they are safe and that they work. *In vitro* and animal models provide a way to test the safety and effectiveness of new treatments and products in the laboratory prior to testing them in human clinical trials. Appropriately, validated animal models are critically needed for biodefense research for the development and testing of vaccines, therapeutics, and prevention strategies and for the preclinical safety testing that will be required to speed the development of new-generation products. FDA's newly implemented Animal Efficacy Rule will allow testing of biodefense therapies and vaccines in animal models (either in a single well-characterized animal model or in two different animal models) to suffice for FDA approval of new products, since in most cases, human clinical trials to test efficacy are not possible due to ethical considerations.

Animal models will play an essential role in addressing the following issues in NIH's biodefense and emerging infectious disease program: understanding disease-causing mechanisms and pathogen-host interactions; defining the body's natural and learned protective immune mechanisms; studying vaccines, diagnosis, and treatment regimens for pathogens; defining how these infections affect the immune system; determining how microbial pathogens have adapted to avoid detection by immune cells; studying the mechanisms of vaccination adverse events, including those in at-risk populations; identifying methods for avoiding the introduction of adventitious agents during vaccine manufacture; and developing novel methods of vaccine production to enhance vaccine safety.

A number of promising candidate therapies and vaccines have been identified for bioterrorism organisms/diseases; however, development has been delayed because of the lack of standardized animal models in which to evaluate these candidates. New models need to be developed; in particular, there is a need for additional NHP models. The similarity of NHPs to humans in the progression of infectious diseases and their responses to therapies make them an especially useful and important class of models for biodefense research. However, the use of NHPs is limited by their cost and difficulty in acquiring and maintaining them. For example, the shortage in supply of rhesus macaques, one of the most widely used NHP models for biomedical research, is severely limiting the development of new vaccines and therapies. Therefore, research to develop alternative NHP models is a high priority. In addition, expansion of current NIH resources to include new small-animal models will provide additional avenues for the development of therapeutics and vaccines. Small-animal models for biodefense-related and emerging infectious diseases will accelerate product development by allowing earlier stage testing to be done in small animals, which can be obtained and maintained more easily and at lower cost, prior to testing in NHP models.

PLANNED IMPLEMENTATION STRATEGIES

To accomplish the goal of developing two new animal models to use in research on at least one agent of bioterror, NIH will launch the new initiative *In Vitro* and Animal Models for Emerging Diseases and Biodefense to expand on previous efforts to develop animal models of viral diseases. This initiative will support the development, validation, and use of small-animal and NHP models to screen and test the efficacy of therapeutics, diagnostics, and vaccines for both viral and bacterial pathogens, including emerging infectious agents and Bioterrorism Category A-C agents. New small-animal and NHP models will ameliorate the bottleneck caused by the shortage of validated models and accelerate the rate of product development. Awards for the expanded animal model contract initiative will be made in late FY 2003.

To increase the capacity to evaluate products for biodefense in NHPs, NIH will expand appropriate containment facilities as part of a cooperative research program with USAMRIID. Construction is under way, with commissioning scheduled for FY 2004. NIH also will expand an intramural research support contract to provide additional NHPs and animal biosafety level-3 (BSL-3) facilities for biodefense research and studies of emerging and reemerging diseases. Intramural BSL-3 capacity will expand in January 2004 on opening the new Lab at Twinbrook (Rockville, Maryland), which contains facilities for the study of vector-borne diseases (West Nile virus) and for pandemic influenza.

In collaboration with FDA and USAMRIID, NIH will support the development, standardization, and transfer of pneumonic- and bubonic-plague animal models to a central repository. NHP models will be used to screen five licensed antibiotics for efficacy in treating pneumonic plague, and the data obtained will be submitted to an FDA file for pharmaceutical companies to sponsor new label indications.

Under a coordinated network of contracts, NIH will support the development of mouse models and screen compounds for activity against orthopox viruses (e.g. vaccinia, cowpox, mousepox) and respiratory viruses (e.g., influenza A and B). NIH's intramural programs will develop a mouse aerosol challenge model of Q fever, as well as guinea pig and NHP models of Ebola virus infection.

BASELINE(S)

- NIH support for basic research performed in animal model systems provides information to characterize mechanisms of pathogenesis and pathogen-host interactions; define innate and adaptive protective immune mechanisms; allow for validation of vaccine, diagnosis, and treatment regimens for pathogens; and define mechanisms of immunopathology and immune evasion.

- A golden hamster model was developed by NIH-supported researchers for use in drug screening and research on factors that contribute to immunity.

- NIH's animal model resources currently include mouse models for *Burkholderia pseudomallei, Burkholderia mallei*, *Brucella abortus*, and *Brucella melitensis*. There are three well-characterized mouse models of disseminated endothelial infection by *Rickettsia*, as well as guinea pig and rhesus monkey models for *Rickettsia prowazekii* and *Rickettsia rickettsii*. There are mouse, guinea pig, rabbit, and NHP models of tuberculosis, including inhalational models. There are hamster models for some of the viral encephalitides and for West Nile virus infection. Some animal models of ricin poisoning (*Clostridium perfringens* infection) exist. There is a piglet model of *Cryptosporidium parvum*. There are mouse, NHP, rabbit, and guinea pig models of anthrax. There are mouse and rabbit models of vaccinia and poxviruses. Mice are currently the most commonly used model for tularemia, botulism, and for *Yersinia pestis* infection.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Conduct validation studies of new monkey models of smallpox by employing them in testing new smallpox vaccines and therapies.	(FY02) Previous non-human primate models of smallpox/orthopox diseases inadequately modeled the progression of human smallpox disease	◆		
Expand by 25% the animal model resources available for use by the research community and for licensing products under the FDA Animal Efficacy Rule.	(FY03) 8 animal models available		◇	

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was met. Both human variola and monkeypox models have been tested for protection against disease when administered the Modified Vaccinia Ankara (MVA) or Dryvax smallpox vaccines and for positive response to the antiviral drug cidofovir. To meet the need for nonhuman primate models for smallpox, researchers with the U.S.A.M.R.I.I.D. and CDC are continuing to work on the development of two models for studying smallpox in cynomolgus monkeys–one with human variola virus and one with monkeypox virus. In FY 2003, both models were developed to the point of being able to be employed in testing of new smallpox vaccines and therapeutics. Both models are an improvement over previous animal models because they are less susceptible to the pulmonary infections that prevented previous models from progressing to systemic disease like that seen in humans. Researchers have found the monkeypox model to be particularly promising. After intravenous challenge with monkeypox virus, the monkeypox model animals die of a disease that is very similar to human smallpox but that progresses over a shorter period of time.

Implementation Strategy Advances or Other Highlights

In FY 2003, NIH established new, or modified existing, research programs to incorporate the development and availability of animal models for agents of bioterror.

In Vitro and Animal Models for Emerging Infectious Diseases and Biodefense RFP. The goal of the program is to provide a range of animal models, including nonhuman primate models, for preclinical testing of new therapies and vaccines. In FY 2003, NIH awarded four contracts that will support the development and validation of small-animal models for anthrax, as well as expand the capability to conduct anthrax aerosol challenge studies in animal models. In FY 2004, the program will be expanded to include models for poxviruses and SARS and testing of neutralizing agents for inhalational anthrax. The contracts will cover safety, toxicology, and pharmaceutical testing in small and large animals, including the capability for conducting challenge studies.

Expansion of Collaborative Antiviral Testing Group Contract. Under a coordinated network of contracts, NIH supports the development of animal models and screening of compounds for activity against orthopoxviruses (murine models of vaccinia, cowpox, and ectromelia) and respiratory viruses (murine models of influenza A and B). The contract with Utah State University was expanded to include viral hemorrhagic fevers and encephalitis. The new models developed as a result of this expansion are Bunyavirus: Punta Toro virus in mice; Arenavirus: Pichinde virus in hamsters; Flavivirus: Banzi virus in mice; and Togavirus: Semliki Forest virus in mice.

Expansion of NIH Research Support Contract. The NIH Intramural Program expanded a research support contract to provide additional nonhuman primates and animal biosafety level 3 (BSL-3) facilities for biodefense research and studies of emerging and reemerging diseases. Intramural BSL-3 capacity will expand in January 2004 on the opening of the new laboratory at Twinbrook in Rockville, Maryland.

Establishment of several large multidisciplinary research programs that include the development of animal models of agents of bioterror. Eight Regional Centers of Excellence in Biodefense and Emerging Infectious Diseases, two National Biocontainment Laboratories, and nine Regional Biocontainment Laboratories were established. NIH also supports the National Primate Research Centers (NPRC), which serve as a major source of animals, and provides expertise in animal testing and husbandry for investigators at the Regional Centers of Excellence.

GOAL 4b) BY 2005, DEVELOP IMPROVED ANIMAL MODELS THAT BEST RECAPITULATE PARKINSON'S DISEASE (PD) BASED ON EMERGING SCIENTIFIC FINDINGS OF GENETIC OR ENVIRONMENTAL INFLUENCES OR INTERACTIONS OF GENES AND THE ENVIRONMENT ON THE DEVELOPMENT OF PD.

BACKGROUND

Prevalence/Incidence

PD is a neurodegenerative disease for which there is no known cure.

- Incidence: 50,000 cases per year[1]; increases dramatically after age 50.
- Prevalence: Estimates range from 500,000 to 1 million individuals in the United States.[2]

Disease Burden

PD is a devastating, progressive motor disorder, characterized by rigidity, poor balance, and uncontrollable shaking or tremors; those affected by PD eventually lose their independence. PD is marked by a loss of neurons that produce the neurotransmitter dopamine; these neurons are an essential part of the brain pathways controlling purposeful movement. The total economic cost per year was estimated to be $6 billion in 1992.[3] Most individuals with PD are treated with pharmacologic agents that mimic the actions of the lost dopamine. Although these drugs provide symptomatic relief, they do not cure or slow disease progression, are of limited benefit in later stages of the disease, and can produce undesirable side effects.

Rationale

To facilitate the understanding and treatment of any human disease, it is desirable to create animal models that recapitulate (i.e., reproduce all key features of the disease process, including pathways of disease causation and the impact of the disease on cellular processes, organ function, and, ultimately, behavior). With such models in hand, researchers can track the earliest molecular events in the disease and develop intervention strategies to delay, or even prevent, its progression. In the case of PD, researchers would like to have access to an inexpensive, reproducible animal model that captures both the genetic and environmental roles in causation, reproduces the cellular changes that occur in PD over an appropriate period of time, and leads to behaviors in the animal that approximate the effects of the disease on humans.

Over the years, the research community has developed several animal models of PD that have been instrumental in accelerating the understanding of the disease process.[4] One such model is produced through the exposure of primates to MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), a chemical substance with structural similarities to some pesticides. Although this model is likely to remain useful for predicting therapeutic efficacy, it is costly and does not reproduce some key features of PD (e.g., the progressive nature of the disease, some cellular features of affected neurons, and the combined effects of the environment and genes on disease causation). By contrast, NHP models have offered important practical benefits for dissecting gene-environment interactions in PD. For example, the creation of mice and fruit flies expressing mutant forms of a gene (alpha-synuclein) implicated in PD have provided an opportunity for studying the effects of environmental agents on key genes and proteins involved in the disease process. Furthermore, the recent discovery that pesticide exposures (e.g., rotenone) can produce Parkinson-like effects on neurons and behavior in rodents offers another possible strategy for understanding the effects of the environment on this disease.

[1] National Institutes of Health. *Cost of Illness Report*. 2000, p. 98.
[2] Herndon CM, Young K, Herndon AD, Dole EJ. Parkinson's disease revisited. J. Neurosci. Nurs. 2000 Aug;32(4): 216-21.
[3] National Institutes of Health. *Cost of Illness Report*. 2000, p. 98.
[4] Betarbet R, Sherer TB, Greenamyre JT. Animal models of Parkinson's disease. Bioessays. 2002. Apr;24(4):308-18.

Together, these models have enabled researchers to learn a great deal about the neural systems that are affected by PD, the molecules within cells that may play a role in the disease process, and the potential for various therapies to treat the disorder. However, each has its merits and limitations, and an optimal model is still not available to the PD research community.[1] For this reason, a collaborative effort will be needed in the future to capitalize on findings related to environmental and genetic influences on PD, develop this knowledge into inexpensive, reproducible animal models of PD that simulate the disease process even more accurately than do the models that are currently available, and improve the ability to test therapies.

PLANNED IMPLEMENTATION STRATEGIES

During FY 2003, NIH plans to establish a mouse model repository that will house PD genetic models and make them available to the PD research community. This is intended to facilitate the use of genetic models in various capacities, including the development of gene-environment combined models. In addition, NIH will ensure that the mouse repository contains a variety of genetic models (through the animal models supplements initiative for those investigators currently developing models), including transgenics (biotechnology) and KO models for each of the known proteins mutated in PD.

NIH also plans to develop a rotenone mouse model that mimics aspects of human PD. The model (1) will assess the utility of co-administration of selective P-450 inhibitors (if use of an inhibitor enhances model development, dose and timing will be adjusted with respect to rotenone administration); (2) will characterize the resulting neuropathological, behavioral, and chemical effects; and (3) will file the protocol in the transgenics repository so that it is available to other investigators, providing the model fulfills its promise. If the rotenone mouse model reliably produces selective death of dopamine neurons and appearance of Lewy bodies (abnormal structures), then NIH will combine it with one or more genes implicated in PD (e.g., alpha-synuclein, parkin) to study gene-environment interactions.

Additionally, NIH plans to develop a "slow" unilateral 6-hydroxy-dopamine (6OHDA) model, which involves injection of 6OHDA into the striatum in rats, eliciting a slow (approximately 2 weeks) degeneration of the ipsilateral nigral dopaminerginic (DA) neurons. This will allow experimental interventions when symptoms start but before degeneration is complete. NIH will also investigate the utility of a Nurr-1 rodent model. Nurr-1 is an orphan nuclear receptor that is needed for phenotypic development of midbrain DA neurons. Animals homozygous for a null mutation in the Nurr-1 gene die at birth. Heterozygous animals, however, survive but show increased vulnerability to MPTP, a compound that elicits Parkinson-like symptoms in people and in laboratory animals.

The planned end result of these strategies is to replicate PD in animal models to better understand the effects of PD in humans. The greater the enhancement PD effects in animal models, the greater opportunity to find a cure for PD.

BASELINE(S)

- The Collaborative Centers for Parkinson's Disease Environmental Research has begun developing several laboratory models for investigating gene-environment interactions. A particular focus is to build on the rat rotenone model, which produces selective death of dopamine neurons and the appearance of dense intracellular inclusions within remaining dopamine neurons. These intracellular deposits are known as Lewy bodies, a hallmark feature of the human disease. This model will be converted from rat to mouse to allow it to be combined, through genetic manipulations, with known and unknown PD-susceptibility genes. It has now been found that mouse metabolizes rotenone 300 percent faster than rat, creating a hurdle in creating the mouse model. The cytochrome P-450 enzyme responsible for this metabolism has been identified, and the use of an enzyme inhibitor to enhance model development is being investigated.

[1] Beal MF. Experimental modes of Parkinson's disease. Nat Rev Neurosci. 2001 May;2(5);325-334.

- Currently, a number of NIH-supported investigators, including those at the Morris K. Udall Parkinson's Disease Centers of Excellence, are developing both overexpression and knockout (KO) models for the proteins known so far to be mutated in PD. In addition to these, investigators are working on making toxicant exposure models, which are chronic instead of acute and more readily recapitulate PD pathogenesis.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Establish a mouse model repository at a Morris K. Udall Center of Excellence for Parkinson's Disease Research to house PD genetic models and make them available to the PD research community.	(FY02) No repository with this specific housing and distribution capacity exists for PD research	◆		
Determine if slowing the metabolism of rotenone through cytochrome P-450 inhibition facilitates creation of a mouse model for PD.	(FY03) Cytochrome P-450 accelerates rotenone metabolism in mice so that the PD phenotype cannot be shown		◇	
Combine the mouse model with at least one genetic model of PD and assess its interaction with rotenone.	(FY03) A rotenone mouse model is not yet available			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

As part of the effort to accelerate Parkinson's disease (PD) research, NIH and the University of California at Los Angeles (UCLA) created a repository in FY 2003 that will distribute transgenic mouse models of human PD that are not yet available through other national resources. Investigators who are willing to share mice with the PD research community may arrange with NIH to have the mice deposited at UCLA. Investigators who need mouse models may arrange to obtain two breeding pairs from the repository.

The repository infrastructure was established in 2003 and is now ready to accept mice. NIH sent a letter in October 2003 to approximately 2500 researchers to strongly encourage contributions to this resource. Through a previous NIH PD supplements initiative, an extramural investigator developed a novel mouse model based on nicotinic receptors, and he has already agreed to place it in the repository. In addition, an NIH intramural laboratory has pledged to deposit a transgenic model of a recently discovered genetic form of PD.

Implementation Strategy Advances or Other Highlights

There are several efforts under way to develop new PD laboratory models. One promising avenue has focused on duplicating the success of the rat rotenone model in mice, a species that is more suitable for genetic manipulation. While working on the mouse system, researchers discovered that the mouse metabolizes rotenone 300 percent faster than the rat, making it more difficult to demonstrate the drug's effects on selective neurons. The cytochrome P-450 enzyme responsible for this metabolism has now been identified as CYP3A4. An inhibitor for this enzyme, piperonyl butoxide, is available. Investigators are currently developing and testing a protocol that allows for administration of both the inhibitor and rotenone, thereby enhancing the ability to create a mouse rotenone model for PD. If the rotenone mouse model reliably produces selective death of dopamine neurons and appearance of Lewy bodies, then it could be combined with transgenic mice available through the UCLA Udall Center repository to study gene-environment interactions in PD development and progression.

Concurrently, a number of NIH-supported investigators are developing and further characterizing both overexpression and knockout models for the proteins known to be mutated in PD. In addition, investigators

are working on developing toxicant exposure models that are chronic instead of acute and that more readily recapitulate PD pathogenesis.

GOAL 5a) BY 2007, EVALUATE THE EFFICACY OF THREE NEW TREATMENT STRATEGIES FOR HIV INFECTION IN CLINICAL TRIALS IN AN EFFORT TO IDENTIFY AGENTS OR COMBINATIONS OF AGENTS THAT ARE MORE EFFECTIVE, LESS TOXIC, AND/OR SIMPLER TO USE THAN THE CURRENT RECOMMENDED HIV TREATMENT REGIMENS.

BACKGROUND

Prevalence/Incidence

Since the epidemic began, nearly 60 million people worldwide have been infected with HIV. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that AIDS has killed more than 22 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. In 2002 alone, over 3 million people died from AIDS, and 5 million people were newly infected with HIV. Of the 5 million new infections, 800,000 were children. More than 95 percent of new HIV infections occur in the developing world, with 70 percent occurring in sub-Saharan Africa and 20 percent in Asia and the Pacific rim.[1] A recent Central Intelligence Agency (CIA) report stated, "By 2010, we estimate that five countries of strategic importance to the United States—Nigeria, Ethiopia, Russia, India, and China—collectively will have the largest number of HIV/AIDS cases on earth."[2] In the United States, close to 950,000 people are living with HIV/AIDS. The number of new infections has remained relatively stable at approximately 40,000 new infections each year; however, CDC recently announced an increase in new HIV diagnoses. HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people older than 50 years of age.[3]

Disease Burden

According to UNAIDS, "AIDS has become the most devastating disease humankind has ever faced." The impact of AIDS on developing nations and many countries of the former Soviet Union is profound. UNAIDS states, "the epidemic is driving a ruthless cycle of impoverishment." AIDS is reversing decades of progress from important public health efforts, lowering life expectancy, and significantly affecting education, agricultural output, and commerce of all kinds. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. AIDS is affecting the military capabilities of some countries, as well as international peacekeeping forces. In Africa, the epicenter of the pandemic, AIDS is sabotaging economic development, leading to famine and massive social breakdown and creating a generation of orphans.

Rationale

NIH supports a comprehensive therapeutics research program with the goal of developing new and better approaches to prevent, treat, and control HIV infection and its associated illnesses. Basic research on HIV continues to provide a strong foundation for the identification of new viral and cellular targets, as well as the design and development of better antiretroviral drugs and treatment regimens. Groundbreaking NIH-sponsored structural biology research has provided important insight into key viral proteins and enzymes and has been translated into the design of lead compounds with specific anti-HIV activity.

NIH-supported clinical trial networks, with over 100 U.S. and international sites at major medical centers, academic institutions, and community-based clinics, conduct Phase I, II, and III clinical studies designed to evaluate the safety and efficacy of drug regimens to treat and control HIV disease among adults, adolescents, and children as well as to prevent mother-to-child transmission (MTCT). NIH has worked closely with

[1] World Health Organization. 2002. Joint and United Nations Programme on HIV/AIDS. *AIDS Epidemic Update*: *December 2002*.
[2] Central Intelligence Agency. *The Next Wave of HIV/AIDS: Nigeria, Ethiopia, Russia, India, and China*. September 2002.
[3] Centers for Disease Control and Prevention. U.S. HIV and AIDS reported through December 2001. Year-end edition. HIV/AIDS Surveill Rep 13(2):2002.

industry in the design and conduct of clinical protocols at these network sites. The standards of care for the treatment of HIV infection and its associated illnesses in the United States and Western Europe are based on important clinical findings from NIH-sponsored clinical trials.

Building on the successful demonstration in NIH-sponsored studies in 1996 that antiretroviral therapy (ART), including a protease inhibitor (PI) and two other antiretroviral drugs, results in significantly decreased viral loads and increased CD4 levels, NIH-supported studies have continued to define treatment regimens that slow disease progression from HIV infection to AIDS. The widespread implementation of ART has resulted in extended survival and improved quality of life for many HIV-infected individuals in the United States and Western Europe. These powerful drug combinations have resulted in a decline in the incidence of new AIDS cases and HIV-related death rates. Since 1996 several new classes of antiretroviral drugs, including fusion inhibitors, PIs, and nucleotide analogs, have been developed and have been shown to be safe and efficacious. Although these multiple drug combinations successfully reduce viral load and restore immune responses in many HIV-infected individuals, these regimens also can result in serious toxicities and side effects, single-drug and multidrug resistance, and other complications that make them unacceptable for some individuals. The metabolic and morphologic complications associated with these treatment regimens present significant morbidity and mortality, thus warranting additional investigation.

NIH will continue to support research efforts to develop better antiretroviral drugs and treatment regimens that demonstrate less toxicity, improved activity in viral and cellular reservoirs, reduced development of drug resistant virus, improved pharmacodynamics and pharmacokinetics, easier compliance, and more affordability in U.S. and international settings.

PLANNED IMPLEMENTATION STRATEGIES

HIV therapeutics research entails the development of drugs and drug regimens to target HIV infection; prevent MTCT; and prevent and treat the various opportunistic infections, co-infections, cancers, and other clinical manifestations associated with HIV disease. In the area of anti-HIV drugs, NIH will develop a minimum of three new anti-HIV compounds from existing and new classes of antiretrovirals, including agents that interfere with the viral life cycle. NIH will initiate four new clinical trials of anti-HIV drugs and/or anti-HIV multidrug regimens to identify treatment regimens with fewer toxicities and side effects, improved bioavailability, minimal development of drug resistance, and easier compliance. NIH plans to recompete the grants supporting the therapeutic clinical trials networks to achieve a more effective and efficient system for the conduct of Phase I, II, and III clinical trials in domestic and international settings.

NIH also will develop and/or test one new, less complicated, and less toxic approach that may inhibit MTCT of HIV. The clinical evaluation of this regimen will be conducted in both domestic and international clinical trial sites.

NIH plans to develop and/or test two agents that may prevent or treat complications associated with anti-HIV drugs. NIH also will develop and/or test two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections with hepatitis virus type C or hepatitis virus type B, opportunistic infections (including tuberculosis), cancers, neurological disorders, or organ-specific complications.

BASELINE(S)

- NIH-sponsored studies have contributed to the licensing of one fusion inhibitor, six PIs, one nucleotide analog, six nucleoside reverse transcriptase inhibitors (NRTIs), and four non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been licensed. A two-PI drug combination, a two-NRTI drug combination, and a three-NRTI drug combination also have been recently approved. The next generation of fusion inhibitors is currently undergoing extensive clinical testing. Lead compounds representing integrase inhibitors also are being evaluated in clinical trials. Structural biology and targeted drug design programs are continuing to provide lead agents that are targeted to interfere with specific stages of HIV replication.

- NIH is continuing the development and testing of interventions to halt MTCT of HIV, especially treatment regimens that can be implemented in developing nations. Although there has been success in the United States and many developed nations, MTCT continues to be a significant problem in developing countries and resource-poor settings, particularly in settings where breast-feeding is prevalent and replacement feeding is not feasible.

- NIH supports the development of critical research infrastructure, capacity building, and training in many developing nations so that these sites can participate in the design, conduct, and analysis of clinical trials of drugs and drug regimens to prevent, treat, and control HIV disease.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Increase the ability of resource-poor countries to conduct clinical trials for the treatment and prevention of HIV disease by providing training and capacity building at 4 sites.	(FY02) 12 AACTG sites and 10 PACTG sites	◆		
Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	(FY03) 23 approved antiretroviral drugs exist for HIV infection treatment		◇	
Initiate clinical trials of new anti-HIV drugs and/or anti-HIV multidrug regimens in U.S. and international clinical trial sites.	(FY03) Clinical trials for the next generation of fusion inhibitors and lead compounds representing integrase inhibitors are being completed			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The target has been met. NIH-supported clinical trial networks, with over 100 U.S. and international sites at major medical centers, academic institutions, and community-based clinics, conduct Phase I, II, and III clinical studies designed to evaluate the safety and efficacy of drug regimens to treat and control HIV disease among adults, adolescents, and children and prevent mother-to-child transmission (MTCT). NIH has worked closely with industry in the design and conduct of clinical protocols at these network sites. The standards of care for the treatment of HIV infection and its associated illnesses in the United States and Western Europe are based on important clinical findings from NIH-sponsored clinical trials. The Adult AIDS Clinical Trials Group (AACTG) and the Pediatric AIDS Clinical Trials Group (PACTG) have established and continue to work with sites in resource-poor developing countries (RPDCs).

Capacity building and training also have occurred at 12 international AACTG sites in 8 nations (Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, and Zimbabwe) with support through the AIDS International Training and Research Program. In addition to training offered during onsite visits, the AACTG held three regional trainings in Latin America, Africa, and Asia on good clinical practices and the clinical management of HIV disease. Training on data management and standardized laboratory procedures has been provided to site personnel by the AACTG data management center and the Virology Quality Assurance Laboratory, respectively. In addition, each international AACTG site has been paired with a U.S. network site to provide training and assistance with capacity building.

NIH is continuing to develop and test interventions to halt MTCT, especially treatment regimens that can be implemented in RPDCs. Although there has been success in the United States and in many other developed nations, MTCT continues to be a significant problem in settings where breast-feeding is prevalent and replacement feeding is not feasible. There are currently two PACTG sites in Thailand and three PACTG sites

in South Africa. The NICHD International and Domestic Pediatric and Perinatal HIV Clinical Trials Network conducts trials in collaboration with the PACTG. The Network's international component includes five sites in Brazil and one site in the Bahamas. Additional PACTG sites are planned.

The NIH-sponsored Comprehensive International Program of Research on AIDS (CIPRA) provides long-term support to RPDCs to enhance the infrastructure necessary to plan and implement comprehensive HIV/AIDS prevention and treatment research and clinical trials. Ongoing CIPRA planning and organizational awards are underway in Brazil, Cambodia, Congo, Dominican Republic, India, Mexico, Russia, Peru, Tanzania, Thailand, Trinidad, Vietnam, Zambia, and Zimbabwe. Multiproject research grants have been awarded to researchers in China and South Africa.

In FY 2003, seven planning and organizational CIPRA awards were granted to institutions in RPDCs, including Argentina, Brazil, Egypt, Republic of Georgia, Kenya, Malaysia, and Mozambique. Many of these sites are planning to conduct clinical trials to identify appropriate strategies to prevent, treat, and control HIV disease and its coinfections and complications.

The NIH International Site Development Initiative (NISDI) is providing training and infrastructure development at clinical trials sites in Latin America and the Caribbean. NISDI is being conducted in new sites in Mexico, Argentina, and Brazil, as well as in other existing international sites. As these sites demonstrate capacity, they will be eligible to enroll in PACTG treatment studies.

Implementation Strategy Advances or Other Highlights

NIH supports a comprehensive therapeutics research program with the goal of developing new and better approaches to prevent, treat, and control HIV infection and its associated illnesses. NIH-sponsored research also is developing and testing treatment regimens for HIV-associated opportunistic infections, co-infections, and malignancies and the neurologic, metabolic, ocular, and other manifestations of HIV disease. Basic research on HIV continues to provide a strong foundation for the identification of new viral and cellular targets, and the design and development of better antiretroviral drugs and treatment regimens. Groundbreaking NIH-sponsored structural biology research continues to provide important insight into key viral proteins and enzymes that will be translated into the design of lead compounds with specific anti-HIV activity.

Building on the successful demonstration in NIH-sponsored studies in 1996 that antiretroviral therapy (ART), including a protease inhibitor and two other antiretroviral drugs, results in significantly decreased viral loads and increased CD4 levels, NIH-supported studies have continued to define treatment regimens that slow disease progression from HIV infection to AIDS. The widespread implementation of ART has resulted in extended survival and improved quality of life for many HIV-infected individuals in the United States and Western Europe. These powerful drug combinations have resulted in a decline in the incidence of new AIDS cases and HIV-related death rates. Since 1996, several new classes of antiretroviral drugs have been developed and shown to be safe and efficacious. Although these multiple drug combinations successfully reduce viral load and restore immune responses in many HIV-infected individuals, these regimens also can result in serious toxicities and side effects, single- and multiple-drug resistance, and other complications that make them unacceptable for some individuals. The metabolic and morphologic complications associated with these treatment regimens present significant morbidity and mortality, thus warranting further investigation.

Scientific advances resulting from NIH-sponsored studies in FY 2003 may lead to the discovery and development of novel therapeutics and strategies, including a potential new class of anti-HIV drugs that block HIV capsid formation and reduce viral infectivity, as well as new agents that can turn on HIV genes that may lead to the development of targeted therapies. NIH-funded studies also demonstrated the benefit of short postexposure prophylaxis in newborn babies to reduce MTCT.

GOAL 5b) BY 2009, DETERMINE THE EFFICACY OF STATINS IN PREVENTING PROGRESSION OF ATHEROSCLEROSIS IN CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE, OR LUPUS).

BACKGROUND

Disease Burden

Lupus is a disorder of the immune system known as an autoimmune disease. In autoimmune diseases, the body harms its own healthy cells and tissues, leading to inflammation and damage to various body tissues. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Although people with the disease may have many different symptoms, some of the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.

Lupus is a complex disease whose cause is unknown. It is likely that there is no single cause but rather a combination of genetic, environmental, and possibly hormonal factors that work together to cause the disease. Scientists are making progress in understanding the processes leading to lupus. Lupus is three times more common among African American women than among Caucasian American women and is also more common in women of Hispanic, Asian, and Native American descent. Age at disease onset is a predictor of outcome, and children often have severe end organ disease. At present, there is no cure for lupus. Lupus is the focus of intense research as scientists try to determine what causes the disease and how it can best be treated.

Rationale

Atherosclerosis is a thickening of the inside walls of arteries that is caused by the gradual buildup of fatty substances in arteries. This thickening narrows the space through which blood can flow and can result in heart attacks or strokes. Atherosclerosis usually occurs when a person has high levels of cholesterol (a fat-like substance), which can build up on the walls of arteries. Women and children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis. The data on cardiovascular and lipid abnormalities in children with lupus implicate atherosclerosis as an important potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease (CVD). Statins not only decrease mortality and morbidity from coronary artery disease in adults but also have intrinsic anti-inflammatory properties, which may be especially beneficial in lupus.

PLANNED IMPLEMENTATION STRATEGIES

When a new clinical trial is initiated, a number of steps must be completed in launching the study. A key dimension is training staff members who will be involved in the conduct of the study in the sophisticated techniques that will be used. In this study, this includes both complete training and full certification of sonographers who will be involved in establishing the degree of atherosclerosis in the children participating in the study as well as training for the Interactive Voice Response System that will be used for trial randomization and drug kit assignment that will take advantage of novel and efficient technologies that improve trial conduct and cost-effectiveness.

Patient enrollment is one of the most critical aspects of a trial. This trial involves recruitment at 20 sites, and it is important that the participating sites achieve successful patient enrollment of the targeted numbers of patients.

Conducting additional related studies increases the value of a clinical trial, and the design of this trial includes the development of ancillary, mechanistic substudies to explore the processes that contribute to disease

progression. These additional studies will leverage the value of the investment made by NIH in terms of scientific knowledge as well as improve the integration of translational research from this clinical trial.

BASELINE(S)

There are no longitudinal atherosclerosis studies in a population of children with lupus. NIH recently launched a prevention trial in cardiovascular lupus in children. As stated above, women and children with lupus have a significantly increased risk of cardiovascular complications. NIH-funded researchers are working to uncover the bases for these life-threatening complications. In addition, NIH has launched a study that will evaluate whether the long-term complications of CVD in childhood lupus can be prevented. The data on cardiovascular and lipid abnormalities in children with lupus implicate atherosclerosis as an important potential source of long-term morbidity and mortality. The study is designed to test the efficacy of statins (cholesterol-lowering agents) in delaying the progression of atherosclerotic arterial thickening in children with lupus. Not only do statins decrease mortality and morbidity from coronary artery disease in adults, but also they have intrinsic anti-inflammatory properties, which may be especially beneficial in lupus. This is a multi-center, prospective, randomized, double-blind intervention study for children with lupus and involves 20 centers from the Childhood Arthritis and Rheumatology Research Alliance (formerly the Pediatric Rheumatology Research Network) and will enroll 280 children with recent-onset lupus who will be treated with the medication atorvastatin for 36 months, establishing the largest cohort of pediatric lupus patients ever prospectively studied in the United States.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Complete the training of personnel involved in conducting the trial, including sonographers and those operating the Interactive Voice Response System.	(FY02) Standard operating procedures are being completed but training not yet done	→		
Launch patient enrollment in at least 10 of the 20 planned sites.	(FY03) Protocol for patient enrollment established		◇	
Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	(FY03) One ancillary study approved to assess the effect of statins on blood cells			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The training of personnel involved in conducting the trial, including investigators, coordinators, nurses, and individuals to operate the Interactive Voice Response System, was completed in April 2003. However, training of sonographers was completed in only 17 of 20 sites because of the lack of sufficient numbers of sonography machines for use by the training staff. The investigators are negotiating with the manufacturer to obtain additional machines at no cost to the Government to expedite the training and certification of sonographers. The target is expected to be achieved by December 2004. The certification of the remaining sonographers will not delay the initiation of recruitment at any of the sites anticipated for FY 2004.

Implementation Strategy Advances or Other Highlights

Two sites began enrolling patients in 2003. To date, two patients have been enrolled, and four additional patients were screened. The FY 2003 target extension will not affect the estimated time of trial completion.

GOAL 5c) BY 2009, EXPAND THE RANGE OF AVAILABLE METHODS USED TO CREATE, ANALYZE, AND UTILIZE CHEMICAL LIBRARIES, WHICH CAN BE USED TO DISCOVER NEW MEDICATIONS. SPECIFICALLY, USE THESE CHEMICAL LIBRARIES TO DISCOVER 10 NEW AND UNIQUE CHEMICAL STRUCTURES THAT COULD SERVE AS THE STARTING POINT FOR NEW DRUGS.

BACKGROUND

The Nation is facing a pressing need for new drugs. Many existing medicines are becoming ineffective due to antibiotic resistance. In other cases, the side effects of existing drugs are as severe as the diseases they are designed to treat. Most drugs are discovered by randomly screening thousands of chemical compounds for desired biological effects. To speed the discovery of new medicines, scientists need to have access to larger collections of chemicals to test. An especially promising approach to invigorating and strengthening the new drug pipeline is by using a new and powerful chemical strategy called diversity-oriented synthesis. This method can quickly generate a large number of potential drug compounds (a "chemical library"). Such a library could contain anywhere from a few chemical compounds to millions and can be designed to include either related versions of a single molecule or a wide variety of completely new chemical structures. This new technique offers unprecedented opportunities for the discovery of molecules that may be developed into lifesaving drugs more efficiently.

Rationale

Since diversity-oriented synthesis is such a new and intellectually challenging endeavor, the number of methods for designing, making, and analyzing chemical libraries is still limited. This restricts the variety of structures that chemists can make. Although the pharmaceutical industry has embraced chemical library screening as a useful drug discovery strategy, it has not invested in the long-term research needed to improve the technique. Similarly, few academic scientists have made a special effort to develop chemical library-related methods. The investment will likely enrich the field of diversity-oriented synthesis and give pharmaceutical scientists important tools for discovery of molecules that show promise as future medicines.

Using a promising new strategy called diversity-oriented synthesis, chemists can efficiently generate relatively large numbers of unique chemical compounds (a "chemical library"). NIH funding is leading to the discovery of new chemical library methods, which in turn will enhance the range and quality of chemical compounds available for drug discovery. Rapid and efficient biological screening of improved chemical libraries may speed the discovery of new medicines.

PLANNED IMPLEMENTATION STRATEGIES

Two additional Centers of Excellence in Chemical Methodologies and Library Development, bringing the number of Centers established to work in this area to four. Intermediate strategies include (1) increasing the sharing of knowledge among researchers, (2) increasing access to research results by exploring and developing systematic means to inventory newly created chemical libraries and methods of synthesis, (3) biologically screening the libraries and inventorying the outcomes of these screening procedures as new libraries are created, and (4) coordinating and setting priorities for the Centers' operations through the use of scientific advisory groups.

BASELINE(S)

- The number of methods for designing, making, and analyzing chemical libraries is limited. The pharmaceutical industry has embraced chemical library screening as a useful drug discovery strategy, but it has not invested in the long-term research needed to improve the technique.

- Few academic scientists have made a special effort to develop chemical library-related methods.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	(FY02) Prior to FY 2003, only two centers existed	◆		
Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through the funded Centers. Ensure that inventories of libraries and successful methods are established so that the results of this work can be readily accessible to the scientific community for drug development.	(FY03) High throughput methods for making chemical libraries for drug development are limited		◇	
Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	(FY03) CMLD centers are currently being established; screening of their libraries has not yet begun			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

In FY 2003, two additional Centers of Excellence for Chemical Methods and Library Development (CMLDs) were established at Harvard Medical School and the University of Kansas. With funding from five-year grants, these Centers will investigate innovative methods to synthesize chemical libraries and will create new libraries using both of these new methods as well as existing methods. Researchers at these Centers will collaborate with biologists to screen libraries to identify biological probes and compounds that may be promising therapies.

Implementation Strategy Advances or Other Highlights

In addition to establishing the CMLDs, NIH has established a Cooperative Research and Development Agreement with a small pharmaceutical company through which it has been able to screen four novel chemical libraries to identify compounds that affect the D1 dopamine receptor. These chemicals may have therapeutic application as medications for cocaine and other stimulant addictions.

The International Cooperative Biodiversity Groups Program, managed by NIH and funded cooperatively with the NSF and the USDA, has awarded 12 new grants to develop natural product drug discovery programs. The programs are led by U.S. investigators who are collaborating with scientists in low and middle-income countries with significant biodiversity, where will be collected terrestrial plants, marine plants and invertebrate animals, and terrestrial and marine microorganisms. The projects will isolate and screen candidate compounds in multiple therapeutic areas, including high-throughput screens in collaboration with pharmaceutical or university laboratories. Some of these projects will develop new high-throughput assays and new methods for rapid chemical characterization from natural product sources. It is expected that libraries of natural product compounds will be assembled and characterized over the course of these awards. The projects will also develop contracts for the treatment of intellectual property and access and benefit sharing regarding genetic resources that will contribute models in this area for international chemical library projects.

GOAL 5d) BY 2007, IDENTIFY 20 SMALL MOLECULES THAT ARE ACTIVE IN MODELS OF NERVOUS SYSTEM FUNCTION OR DISEASE AND SHOW PROMISE AS DRUGS, DIAGNOSTIC AGENTS, OR RESEARCH TOOLS.

BACKGROUND

Disease Burden

Diseases of the nervous system—stroke, trauma, drug addiction, alcoholism, autism, unipolar major depression, epilepsy, Parkinson's disease (PD), schizophrenia, multiple sclerosis, chronic pain, and hundreds more—collectively constitute one of the largest disease burdens in terms of disability, economic costs, personal tragedy, and death.

Rationale

This goal addresses the shortage of new drugs emanating from the private sector that target the nervous system, including those for low-prevalence "orphan" diseases, many of which are neurological. Translation of basic research discoveries into new therapeutics is not occurring at the rate expected by the public or the private sector. This goal aims to speed this translation by expanding the role of the public sector in therapeutics development and engaging the public sector in the early stages of drug discovery.

Recent advances in understanding the nervous system and the completion of the Human Genome Project have provided an enormous cache of new biology to be studied and potential new drug targets to be investigated, most of which are not being studied in the private sector. Carefully designed small molecules can be powerful modulators of gene function; this principle underlies their use as basic research tools and as pharmaceuticals. The objectives of this goal are to (1) identify research tools and candidate therapeutics among currently available small molecules and (2) make new small molecules available to the public sector to further stimulate basic research and drug discovery.

PLANNED IMPLEMENTATION STRATEGIES

Through collaboration among institutes, industry, and academia, NIH will create a publicly available physical repository of 750 selected bioactive compounds to facilitate access and evaluation for therapeutic potential, diagnostic use, or use as research tools in neurobiological and other research. On the basis of the precedent of FDA-approved drug collections, a collection of 750 compounds would be sufficient to yield multiple hits in most assays (tests), yet is small enough to be tested in any relatively simple benchtop assay without the need for robotic equipment, so would be broadly and immediately useful to investigators in both academia and industry. Steps to creating this database will involve identifying candidate compounds from ongoing programs, with additional compounds added from academic and commercial sources; evaluating the quality of the existing bioactivity, bioavailability, and toxicity data for candidate compounds; creating a database of the chemical, pharmacological, and toxicological properties of selected existing compounds; and creating physical repositories of selected compounds and drugs for use in neurobiological and other research.

Utilizing HTS approaches, NIH will identify potential research tools and drug leads for neurological disorders. Activities will include soliciting neurodegenerative disease assays (e.g., proteins, cells, or simple organisms) from investigators in the neurodegeneration research community to be adapted by the HTS Facility into automated formats (at least three assays per year will be screened with the set of 100,000 compounds); assembling the data derived from individual screens at the HTS Facility into a central database to be analyzed for commonalities among assays to facilitate additional testing and, potentially, the understanding of disease mechanisms; developing a cost-effective, high-throughput behavioral screen to identify molecules with promise for treating alcohol abuse and dependence; and completing the screening of

four novel chemical libraries—with a total of more than 80,000 compounds—for activity at D1 dopamine receptors to develop a selective D1-dopamine receptor agonist as a potential treatment for cocaine addiction.

Through the ASP, small molecules will be identified that can be used for potential anticonvulsant treatments, including drug-resistant epilepsy and epileptogenesis. This program will need to enroll new industrial and/or academic suppliers of small molecules with potential anticonvulsant activity and test additional compounds to identify potential drug development leads. A nonproprietary Web site of ASP data will be created to facilitate data sharing and foster goal completion.

A pilot translational project for therapeutics development in SMA, the most common lethal neurogenetic disease in infancy, will be initiated. A contract-based approach will be developed to explore a new paradigm for accelerated funding and milestone-driven management for therapy development in rare diseases. Calls for research proposals will be issued in accordance with a 4-year research plan that will address all aspects of therapeutics development.

The NCDDG Program model, long used by NCI to establish long-term drug development partnerships among NIH, academia, and industry, will be expanded to advance the development and testing of fundamentally new, rationally designed medications and treatments for mental disorders and nicotine addiction (MD/NA). The NCDDG-MD/NA will (1) accelerate the discovery of new therapeutics for mood disorders and nicotine addiction, (2) increase the availability of pharmacologic research tools for basic and clinical research, and (3) facilitate the development and validation of models to evaluate novel therapeutics in mood disorders.

Tremendous opportunities exist for the application of positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in studies of the pathophysiology and treatment of brain disorders, but relatively few radioligands are currently available for functional imaging of target molecules implicated in normal brain function and aging and in brain and behavioral disorders. Radioligand development would be immensely valuable for determining the interaction of a drug or drug candidate with a specified target, guiding initial dosing of new therapeutic agents and determining central biomarkers of the illness, with the potential to assess the efficacy of therapeutic compounds. Several NIH ICs will stimulate collaborations with industry and academia to create novel radioligands for PET and SPECT imaging in the human brain. This initiative is intended to facilitate the development of (1) PET and SPECT probes for molecular targets (e.g., receptors, intracellular messengers, disease-related proteins) that are of broad interest to the neuroscience research community and (2) new technologies for radiotracer development. Additional development of this technology will lead to a better understanding of and enhanced therapies for nervous system anomalies. This activity is necessary to assess the ASP.

BASELINE(S)

- The Neurodegeneration Drug Screening Consortium has compared results from testing 1,040 drugs (most approved by FDA for other uses) against 29 screens for specific neurodegenerative diseases and for common disease processes. The preliminary data have identified more than 200 drugs active in neurodegeneration models, warranting additional testing for potential therapeutic applications. In addition, the contract-based High-Throughput Screening (HTS) Facility for Neurodegenerative Disease provides services to test a collection of approximately 100,000 chemically diverse, nonproprietary small molecules for activity in neurodegenerative diseases, such as PD, amyotrophic lateral sclerosis (Lou Gehrig's disease, or ALS) and spinal muscular atrophy (SMA). Researchers participating in the program are provided with the identity of compounds active in their neurodegeneration assays; these compounds will be useful as research tools and drug leads.

- Several ongoing drug discovery programs provide screening, synthesis, and/or safety assessment services to academic investigators to identify novel compounds (e.g., drugs, ligands, neuropeptides) as therapeutic candidates for drug development, or as research tools such as imaging agents, for use in research on

psychiatric diseases; alcohol tolerance, craving, and dependence; and narcotic and psychostimulant addiction.

- The Anticonvulsant Screening Project (ASP), a public-private partnership, was established to identify and develop therapeutic agents for epilepsy. Since 1975 the ASP has tested over 23,000 compounds, obtained from 146 companies and 229 academic investigators. This project has been successful in identifying many treatment options for epilepsy. However, approximately 35 percent of epilepsy patients remain resistant to all medications, and there is no treatment to prevent or intervene in the progression of epilepsy following initiation of the disease.

- NIH supports specific initiatives and established programs, such as the National Cooperative Drug Discovery Groups (NCDDGs), to facilitate the translation of basic science discoveries to the development of therapeutics. Investigator-initiated research also contributes to the scientific knowledge base—or directly develops, uses, or disseminates research technologies—with broad applicability to the discovery, development, and testing of drugs.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	(FY02) None of the NCDDG Programs focus on mood disorders and nicotine addiction	◆		
Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	(FY03) 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened		◇	
Create a publicly available collection of 750 bioactive compounds, with defined activity in the nervous system, from industry, academia, and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	(FY03) Known bioactive compounds require further evaluation of activity and improved availability			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The NIH awarded three 5-year grants in FY 2003 to establish the National Cooperative Drug Discovery Group Program for the Treatment of Mood Disorders and Nicotine Addiction (NCDDG-MD/NA). NIH also funded a grant to Novartis and the Scripps Research Institute for a multidisciplinary project aimed at developing molecules that target the GABA B neurotransmitter receptor; these molecules may serve as novel research tools and lead drug candidates for a large number of disorders, including depression, nicotine addiction, and anxiety disorders. NIH is sponsoring a collaborative project involving Emory University, the NIH intramural research program, and GlaxoSmithKline to evaluate the potential of five novel compounds, each representing a different pharmacological class, for the treatment of depression, anxiety, and posttraumatic stress disorder. In a third study sponsored by NIH, researchers will use an integrative approach (i.e., medicinal chemistry, pharmacokinetics, pharmacology, psychology, and neuroscience) to develop a new class of selective nicotinic receptor antagonists as therapeutic agents to treat nicotine dependence. These novel drug candidates may also prove to be useful in developing new treatments for depression.

Implementation Strategy Advances or Other Highlights

Several NIH programs to develop potential research tools and drug leads have advanced during FY 2003. For example, NIH held a meeting to select an assay (test) for ataxia telangiectasia to be utilized by its contract-based High-Throughput Screening (HTS) Facility for Neurodegenerative Diseases and funded seven new grants to develop new neurodegenerative disease HTS assays. The screening facility is evaluating the feasibility of using the ataxia telangiectasia assay and three other assays applicable to ALS. NIH also successfully established 13 new partnerships under its Anticonvulsant Screening Project (ASP) in 2003, which is three to four times the typical accession rate. As of September 2003, approximately 600 new drug candidates have been submitted for clinical testing under this program.

NIH has also facilitated the development of new radioligands for central nervous system imaging. In April 2003, NIH issued a Program Announcement to foster partnerships with scientists from the pharmaceutical industry and academic nuclear medicine research centers to develop ligands for positron emission tomography (PET) and single photon emission computed tomography brain imaging. A new molecule that binds with high specificity at a nicotinic acetylcholine receptor was synthesized and tested under an NIH contract; the FDA recently approved an Investigational New Drug application for human PET imaging studies of a radiolabeled version of this molecule. NIH funded two new projects to create novel radioligands for imaging metabotropic glutamate receptors in the brain. Disruption of signaling through these receptors has been implicated in several psychiatric and neurological disorders.

NIH launched its pilot translational project for therapeutics development in spinal muscular atrophy (SMA), the most common lethal neurogenetic disease in infancy. NIH released a Request for Proposals for a contract-based SMA therapeutics development program, established a steering committee to oversee the program, and awarded the contract in September, 2003. With the ongoing consultation of the steering committee, the contractor will be responsible for soliciting and coordinating individual milestone-driven research projects in areas of immediate promise, such as drug development, gene therapy, and stem cell therapy.

NIH continues to make progress in preclinical testing of drug candidates. In FY 2003, NIH funded four new projects to develop pharmacological treatments for alcoholism and test these treatments in animal models. NIH awarded 13 grant supplements to support the testing of candidate neurodegeneration drugs in rodent models. Two new compounds were advanced from discovery to early preclinical development under NIH contracts: a selective kappa-opioid receptor antagonist with potential use in opiate addiction relapse prevention, developed through the Opioid Treatment Discovery Program, and an inhibitor of the dopamine transporter with the potential to treat cocaine addiction. NIH-supported researchers also designed and tested in preclinical models a compound that may be useful in the treatment of neuropathic pain and is unlikely to have addictive liabilities.

In an August 2003 NIH-sponsored workshop, scientists established criteria for selecting the 750 bioactive compounds that will populate a publicly available collection for future screening.

GOAL 5e) BY 2008, DEVELOP AND TEST TWO NEW EVIDENCE-BASED TREATMENT APPROACHES FOR DRUG ABUSE IN COMMUNITY SETTINGS.

BACKGROUND

Prevalence

Drug abuse and addiction are complex public health problems that impact society at multiple levels. An estimated 68.7 million Americans age 12 or older used an illicit drug or a tobacco product in 2002. Recent epidemiologic studies have shown that between 30 and 60 percent of drug abusers have concurrent mental health disorders, in addition to comorbid alcohol abuse. Despite the extensive prevalence of drug abuse and addiction, the lack of effective treatment for certain types of addictions or population groups, and the lack of utilization of those treatments known to be effective, continue to be substantial barriers to reducing the prevalence and impact of this major health problem.

Disease Burden

The total costs of illicit drug abuse and nicotine addiction to our Nation are almost $300 billion a year, including health care expenditures, lost earnings, and costs associated with crime and accidents. Drug addiction is a biologically-based illness that is influenced by genetic and environmental factors, and it is a chronic disease similar to Type II diabetes, cancer, and, cardiovascular disease. Furthermore, drug abuse is a major vector in the spread of infectious diseases such as HIV/AIDS, tuberculosis, and hepatitis C. Given all of these factors, one can begin to see the devastation that drugs can inflict on individuals, families and communities.

Rationale

Although research has demonstrated that drug abuse treatment can be effective in reducing drug use and addiction, few science-based interventions have been developed and tested widely within the health care field. The reasons for this are, in part, related to cultural, financial, and institutional barriers. In an effort to narrow the drug abuse treatment gap, recent drug abuse treatment studies have focused on deploying interventions in the community. To move research forward in this arena, two new drug abuse treatment approaches will be tested within community-based settings.

One important tool to treat substance abuse is behavioral treatment, which has been documented to be effective in improving drug abuse and drug addiction outcomes. Recent promising findings have been achieved by two interventions that target two specialized populations: minority adolescents and women diagnosed with Post-Traumatic Stress Disorder (PTSD). The first, Brief Strategic Family Therapy (BSFT), is a family-based intervention aimed at preventing and treating child and adolescent behavior problems, including substance abuse, in inner city, minority families. The second, Seeking Safety, is a cognitive-behavioral substance abuse intervention for women with a DSM-IV diagnosis of PTSD. This treatment intervention is tailored to concurrently address the co-morbidity issues associated with substance abuse and trauma.

PLANNED IMPLEMENTATION STRATEGIES

In FY 2004, NIH will use the Clinical Trials Network to adapt and test two drug abuse treatment approaches in an effort to more rapidly bring research-based treatments to communities. These drug abuse treatment interventions, BSFT and Seeking Safety will be designed to reach specialized populations that are frequently under-represented in drug and alcohol abuse research and are often underserved in drug and alcohol abuse treatment centers.

To measure the adaptation of the two treatment approaches in community-based settings, treatment providers will be videotaped, supervised and monitored to ensure treatment protocol adherence. Outcome data will be collected at regular intervals on patient substance abuse use, risk behaviors and symptoms to determine the overall treatment effects of the evidence-based interventions.

Drug and alcohol treatment providers will be trained to deliver standardized behavioral treatment interventions of BSFT and Seeking Safety to patients within the framework of the clinical trials research design. Treatment providers will also be trained to maintain data on patient behavior, status and progress to measure clinical and research outcomes. Participation of the treatment providers in the clinical trials process will promote treatment fidelity. Training manuals and clinician guidebooks will be developed and tested.

During FY 2005, approximately 700 patients will be recruited to participate in BSFT treatment protocol and approximately 350 patients will be recruited for the Seeking Safety treatment protocol.

BASELINE(S)

- NIDA's Clinical Trials Network (CTN) was established in 1999 to conduct studies of treatment interventions in rigorous, multi-site clinical trials to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations. The CTN will serve as the vehicle for deploying two evidenced-based treatments into the community.

- BSFT has been shown in research settings to increase participation rates of adolescents and family members in drug abuse treatment, to decrease adolescent externalizing behavior problems, and to sustain abstinence.

- Seeking Safety has been shown to be effective in research settings. This program is designed to help women develop strategies to address substance abuse.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Develop and test evidence-based drug and alcohol abuse behavioral treatment in community settings with inner city, minority adolescents and family members, and women with concurrent substance abuse and post traumatic stress disorder.				
Adapt two treatment approaches from small-scale research settings to community-based settings for the purpose of bringing research-based treatments to communities.	(FY03) No randomized clinical trials have delivered BSFT and Seeking Safety to these specialized populations		◇	
Build capacity for targeted treatments by training 90 treatment providers to: (a) participate in clinical trials to promote treatment fidelity; and (b) deliver evidenced-based behavioral treatment to target populations in community settings.	(FY03) Less than 25 treatment providers have been trained to deliver BSFT and Seeking Safety to these specialized populations in randomized clinical trials in community settings			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Performance results will be reported in February 2005.

GOAL 6a) BY 2012, IDENTIFY THE GENES THAT CONTROL THE RISK OF DEVELOPMENT OF AGE-RELATED MACULAR DEGENERATION (AMD) AND GLAUCOMA IN HUMANS.

BACKGROUND

Prevalence/Incidence

Age-related macular degeneration (AMD) is a sight-threatening degenerative eye disease that affects the part of the retina known as the macula and leads to varying degrees of vision loss depending on the form and severity of the disease. Of the nearly 60 million people in the United States age 55 or older in the year 2000,[1] approximately 8 million are at risk of developing advanced, sight-threatening AMD in one or both eyes within 5 years.[2] Glaucoma is a group of eye disorders that shares a distinct type of optic nerve damage that can lead to blindness. Approximately 2.2 million Americans have glaucoma,[3] and an estimated 2 million more are unaware that they have the disease. As many as 120,000 people are blinded from this disease.[4]

Disease Burden

AMD is the leading cause of irreversible vision loss in the United States among persons older than 65 years of age, the fastest growing segment of the U.S. population. AMD threatens the eyesight and independence of the growing U.S. population of older Americans. People older than 60 are at greatest risk for AMD. Glaucoma is a major public health problem and is the number one cause of blindness among African Americans. It is often described as a "silent thief" of sight, because there may be no symptoms in the early stages of the disease process until the loss of side or peripheral vision becomes noticeable. As the disease progresses, the field of vision narrows until blindness results. African Americans older than age 40, everyone older than age 60, and people with a family history of glaucoma are at increased risk for glaucoma.

Rationale

The development of effective treatments for AMD has been limited by the complicated nature of the disease and the fact that the pathophysiology of the disease is poorly understood. The genes for other forms of macular degeneration, including Stargardt disease and Best macular dystrophy, have been identified and are being studied to learn whether similar disease mechanisms are involved in AMD. These genes have also been considered as candidate genes for AMD, but the results suggest a complex underlying genetic predisposition or susceptibility to biological and environmental factors in the pathogenesis of this complex disorder. Additional investigation of the genes that control this predisposition or susceptibility may improve understanding of the disease process and ultimately lead to improved treatments or the means to prevent this disease. Glaucoma is not a single disease but rather a group of diseases characterized by a particular type of retinal ganglion cell death that is usually, but not always, associated with an increase in intraocular pressure. Current treatments, whether surgical or pharmacologic, are aimed at reducing intraocular pressure and are often inadequate in preventing vision loss. A variety of mutations have been identified that may play a role in the development of primary open-angle glaucoma. The multiple genetic loci and gene associations linked to various forms of glaucoma are other indications of the complex nature of this disease and underscore the need for additional research to clarify the roles of environmental and genetic risk factors in the pathology of this heterogeneous disease.

[1] U.S. Census. *Profile of General Demographic Characteristics for the United States: 2000.*
[2] Age-Related Eye Disease Study Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related mascular degeneration and vision loss. AREDS Report No.8. Arch Ophthalmol 2001 Oct;119(10):1417-36.
[3] Prevent Blindness America. *Vision Problems in the U.S.: Prevalence of Adult Vision Impairment and Age-Related Eye Diseases In America*. 2002. 36 pp.
[4] Kahn HA, Moorhead HB. *Statistics on Blindness in the Model Reporting Area, 1960-70.* U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Eye Institute, 1973; NIH Publication No.73-427.

PLANNED IMPLEMENTATION STRATEGIES

NIH will begin to implement strategies for achieving this long-term goal by increasing the scope and availability of the genomic resources to researchers via NEIBank, an Internet-accessible database of genes and proteins expressed in the eye and visual system, and via several related trans-NIH activities. Expanding the available genomic resources (e.g., information on DNA sequences from human and other species, new and variant forms of genes, unique human eye- expressed genes) will enable researchers to accelerate the identification of genes that control risk for AMD and glaucoma.

Another important implementation strategy will require developing standards for AMD phenotyping and agreement on precise definitions of the diverse retinal phenotypes found in macular disease. Future work on AMD human genetics requires common disease descriptors and a systematic phenotyping system. This can be accomplished through an existing network of reading/grading centers that review photographs of ocular pathology, both nationally and internationally. Currently, these centers have established in-house methodologies and phenotypic definitions that are specific to an individual reading center. Representatives from each of these centers will be asked to help set uniform standards, examine existing descriptors to find common elements, pool data, and determine mechanisms for sharing data. Using a consensus approach, a descriptive manual with standards will be developed that will allow investigators around the world to have a "common language" to describe different stages and forms of macular disease.

Also important in progress toward this goal is making genetic material and information from well-characterized patients available to investigators. Population-based resources of blood, transformed lymphocytes, and DNA from patients with well-characterized AMD and glaucoma will be made available to investigators nationally. Because of the rigor and uniformity in characterizing the disease status of the participants, ongoing clinical trials will be used to collect specimens and create large databases of genetic information for additional analysis. It will also be necessary to accelerate the application of candidate gene and other genetic approaches to the study of AMD and glaucoma. Candidate genes will be characterized at the molecular level and screened for mutations.

BASELINE(S)

- To determine the genes that control the predisposition or susceptibility to AMD or glaucoma, it is necessary to have a better understanding of the genes that are expressed in the eye. The NEIBank (http://neibank.nei.nih.gov) is an initiative that makes ocular genomic resources and associated data available to the vision research community. In the initial phase of the project, high-quality cDNA libraries have been made from dissected human and animal eye tissues, and large numbers of individual clones have been sequenced and analyzed. This has allowed identification of a large number of genes expressed in the eye, discovery of new genes and variant forms, and creation of DNA resources and sequence information for functional and expression studies. By the end of FY 2002, scientists had access to over 31,000 expressed sequence tags that had been collected from NEIBank human libraries, and over 12,000 unique genes had been defined.

- The *fibrillin-6* gene has recently been reported to be linked to AMD. Several other genes have been identified that cause diseases with clinical features that overlap with AMD. Although none of these genes causes a significant fraction of AMD, the Stargardt gene (*ABCA4*) may contribute to a small percentage of AMD. There is also evidence for a genetic association of apolipoprotein-E with AMD. Mutations in the gene for optineurin have been associated with low-tension glaucoma, and mutations in a gene that produces a protein in the trabecular meshwork have been associated with primary open-angle glaucoma.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Expand the genomic resources available to vision researchers through NEIBank and related trans-NIH activities.	(FY02) 31,000 human gene sequences; 12,000 unique human eye-expressed genes	◆		
Reach consensus on a descriptive manual with standards that can be used to describe the diverse retinal phenotypes found in macular degeneration.	(FY03) No consensus descriptions on AMD phenotypes exist		◇	
Collect and make available to investigators genetic material and information from over 4,000 well-characterized patients with either AMD or glaucoma.	(FY04) DNA specimens from large numbers of well-characterized AMD or glaucoma patients are not available			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The NEIBank expanded the available genomic resources to over 40,000 human gene sequences and over 30,000 sequences from other species by the end of FY 2003. A collection of 13,000 unique human eye-expressed genes has been defined and is now available in a DNA microarray for use in comparisons of normal and diseased eye tissues and model systems. (See Appendix 4, Source Validation Table, 1-5)

High-quality libraries have been made from dissected human and animal eye tissues, and large numbers of individual clones have been sequenced and analyzed. This has allowed identification of a large number of new genes and variant forms and creation of DNA and sequence information for functional and expression studies. Analyzed sequence data are available to all vision scientists through the NEIBank Web site, and clones are distributed through OpenBiosystems.

Implementation Strategy Advances or Other Highlights

NIH-supported researchers recently identified a mutation in a gene called HEMICENTIN-1 that causes an autosomal dominant form of AMD. The HEMICENTIN-1 gene is similar to another gene called EFEMP1 that is implicated in malattia leventinese, a rare form of macular degeneration that shares pathologic similarities to AMD. (See Appendix 4, Source Validation Table, 6)

A cDNA library was constructed through the NEIBank project from dissected human trabecular meshwork (TM) tissue, an eye tissue involved in the inflow and outflow of the fluid controlling the pressure in the eye, and the library characterized. This analysis yielded 3,459 independent TM-expressed clones. Transcripts for the myocilin gene, a locus for inherited glaucoma, formed the third most abundant cluster in the TM collection; while several other genes implicated in glaucoma (PITX2, CYP1B1, and optineurin) were also represented. (See Appendix 4, Source Validation Table, 7)

GOAL 6b) BY 2011, ASSESS THE EFFICACY OF AT LEAST THREE NEW TREATMENT STRATEGIES TO REDUCE CARDIOVASCULAR MORBIDITY/MORTALITY IN PATIENTS WITH TYPE 2 DIABETES AND/OR CHRONIC KIDNEY DISEASE.

BACKGROUND

Prevalence

The prevalence of both diabetes and kidney disease are rising. These diseases markedly increase the risk for life-threatening cardiovascular disease (CVD).

- In 2000 the prevalence of diagnosed diabetes in the United States was 7.3 percent, a 49 percent increase since 1990.[1] Currently, an estimated 17 million Americans suffer from diabetes; of these, approximately 16 million have type 2 diabetes.[2]
- CVD accounts for two-thirds of deaths among people with diabetes.[3]
- Chronic kidney disease affects an estimated 10 to 20 million Americans[4] and can lead to kidney failure.
- The number of patients with kidney failure or end-stage renal disease (ESRD) has doubled over the past decade and now stands at nearly 400,000.[5]
- Heart disease and stroke are the leading causes of death in patients with ESRD.[6]

Disease Burden

The Nation faces national epidemics of both type 2 diabetes and ESRD. In 2002 the economic cost of diabetes in the United States was estimated at $132 billion.[7] Once considered a disease of adults, type 2 diabetes now increasingly strikes during childhood. Rates of type 2 diabetes are approximately twice as high among African Americans and Hispanic Americans as among Caucasian Americans and are even higher among Native Americans.[8] Among adults with diabetes, heart disease death rates are two to four times higher than in the general population.[9] Diabetes also negates the protection gender affords non-diabetic women.[10] Even among individuals with impaired glucose tolerance, in which glucose levels are higher than normal but do not yet indicate diabetes, CVD death rates are elevated 1.4 fold.[11] Chronic kidney disease is also a significant health burden. In its most severe forms, it leads to ESRD, where either dialysis or kidney transplantation is required to

[1] Mokdad AH et al. The continuing epidemics of obesity and diabetes in the United States. JAMA. 2001 Sep 12;286(10):1195-200.
[2] National Diabetes Information Clearinghouse. *National Diabetes Statistics.* NIH Publication No. 02-3892, March 2002.
[3] Geiss LS. Mortality in noninsulin-dependent diabetes. In: *Diabetes in America*. Second Edition. National Institutes of Health. pp. 233-57, 1995.
[4] National Kidney Foundation. *Am J Kidney Dis. 2002* 39:S1-S266 (suppl).
[5] United States Renal Data System 2002 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, pp. 44-50.
[6] Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis. 2000 Apr;35(4 Suppl 1):S117-31. United States Renal Data System 2002 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, p. 167.
[7] Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. Diabetes Care. 2003 Mar;26(3):917-32.
[8] Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardinal infarction. N Engl J Med. 1998 Jul 23;339(4):229-34.
[9] Wingard DL, Barrett-Conner E. Heart disease and diabetes. In: *Diabetes in America*. Second Edition. National Institutes of Health pp. 429-48.
[10] Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Subclinical states of glucose intolerance and risk of death in the U.S. Diabetes Care. 2001 Mar 24(3):447-53.
[11] United States Renal Data System 2002 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, pp. 60-70.

maintain life. About one-half of new cases of ESRD have kidney disease as a consequence of diabetes.[1] The number of patients with ESRD has doubled over the past decade, with the increasing disease burden most marked among minority populations, especially African Americans and Native Americans.[2] The markedly reduced life expectancy of patients with ESRD is due largely to death from heart disease and stroke; rates of CVD are tenfold to a hundredfold greater than in the general population.[3] Notably, even among chronic kidney disease patients with a mild to moderate reduction in kidney function, CVD rates are increased twofold to fourfold.[4] The cost of caring for the ESRD population was $19.4 billion dollars in 2000[5] and consumed about 6 percent of the Medicare budget.[6]

Rationale

For both diabetes and kidney disease, premature CVD is the major cause of death. CVD among patients with type 2 diabetes and with kidney disease is associated with some of the same risk factors as in the general population, including obesity, hypertension, and abnormal blood lipid levels, but these diseases confer substantial additional risk for CVD. Recent clinical trials have established the benefit of the management of both blood pressure and low-density lipoprotein-cholesterol (LDL) in reducing CVD risk, but a number of potential strategies to reduce the risk of CVD in these conditions require more exploration. Although even moderate weight loss can dramatically reduce the development of type 2 diabetes among those at high risk, a benefit of weight loss in preventing cardiovascular complications in people with diabetes has not yet been established. Even though improved blood glucose control dramatically reduces the eye, kidney, and nerve complications of diabetes, its benefits in reducing CVD are not fully established, and it is not known whether insulin-providing or insulin-sensitizing strategies for glucose control are optimal for reducing CVD.

Lowering of LDL cholesterol has been shown to prevent CVD, but type 2 diabetes is associated with a distinct lipid profile, with low high-density lipoprotein (HDL) cholesterol and increased triglycerides, and research is needed to establish optimal management of lipids and blood pressure to reduce CVD in type 2 diabetes. Homocysteine (an amino acid produced in the body that can lead to blockages in the arteries) levels rise as the kidneys fail, and homocysteine has long been known as a risk factor for CVD. Folate and B-vitamin supplementation can normalize homocysteine levels in patients with mild chronic kidney disease. It is not yet clear, however, whether this will reduce the risk of CVD. A major goal of NIH-funded research is to discover and evaluate strategies to reduce risk factors for, and to effectively treat, CVD in patients with diabetes and/or kidney disease. If successful, this research would extend the lifespan and improve the quality of life for persons facing heart disease related to kidney disorders.

PLANNED IMPLEMENTATION STRATEGIES

NIH will conduct a clinical trial to compare major cardiovascular events (defined as heart attack, stroke, or cardiovascular death) in adults with type 2 diabetes. Study participants will receive either standard or intensive glycemic (blood sugar) control and either intensive blood pressure control or intensive lipid (fat) management compared with standard treatment. NIH will also conduct the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetics clinical trial to compare 5-year mortality in adults with type 2 diabetes and coronary artery disease (CAD) who are treated with (1) aggressive medical management of CAD alone or revascularization and aggressive medical management and (2) insulin-sensitizing therapy or insulin provision.

[1] United States Renal Data System 2002 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, pp. 60-70.
[2] United States Renal Data System 2002 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, pp. 44-50.
[3] Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. A J Kidney Dis. 2000 Apr;35(4 Suppl 1):S117-31; United States Renal Data System 2002 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, p. 167.
[4] Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. A J Kidney Dis. 2000 Apr;35(4 Suppl 1):S117-31.
[5] United States Renal Data System 2002 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, p. 18.
[6] Eggers PW. A quarter century of Medicare expenditures for ESRD. Semin Nephrol. 2000 Nov;20(6):516-22.

NIH will also conduct the Folic Acid for Vascular Outcome Reduction In Transplantation clinical trial to determine whether lowering homocysteine levels with a multivitamin containing folic acid, vitamin B6, and vitamin B12 will reduce the occurrence of fatal and nonfatal arteriosclerotic cardiovascular outcomes in individuals with mild to moderate renal insufficiency (kidney dysfunction). The comparison group will receive an identical multivitamin containing no folic acid. Trial participants will be kidney transplant recipients who have moderately elevated total homocysteine levels. Also, the ACCORD study is comparing effects on CVD of intensive versus standard lowering of blood glucose, intensive versus standard lowering of blood pressure, and treating blood lipids with fibrate plus statin (to raise "good" HDL cholesterol and lower triglycerides plus lower "bad" LDL cholesterol) versus treatment with statin alone, in diabetic patients at high risk for CVD. Finally, NIH will conduct the Look AHEAD clinical trial to examine the long-term effects on heart attacks, stroke, and cardiovascular-related death of a lifestyle intervention designed to achieve and maintain voluntary weight loss in individuals with type 2 diabetes who are also overweight or obese.

BASELINE(S)

- The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood sugar dramatically reduced the incidence of eye, nerve, and kidney disease compared with conventional therapy in people with type 1 diabetes. This finding has been confirmed and extended to type 2 diabetes, but the effect of glycemic control on CVD, the major cause of death for those with diabetes, is not established in clinical trials for either type 1 or type 2 diabetes. The Epidemiology of Diabetes Interventions and Complications (EDIC) study is a 10-year follow-up observational study that is monitoring patients formerly enrolled in the DCCT for microvascular and macrovascular complications.

- It also remains to be established whether lowering blood pressure below the current guideline of 130/80 mm Hg, use of medications to raise HDL cholesterol and lower triglyceride levels, lifestyle change aimed at weight loss, and the type of medication used to control blood sugar (insulin providing versus insulin sensitizing) will affect the development of CVD among patients with diabetes.

- It is well known that patients with chronic renal disease are at high risk of CVD. Some of this elevated risk is due to a higher prevalence of established arteriosclerotic risk factors such as advanced age, hypertension, dyslipidemia, diabetes, and physical inactivity, but unique renal insufficiency/uremia-related risk factors also may exist. Prominent among these unique risk factors in the chronic renal disease population are elevated levels of homocysteine. Despite the well-documented correlation between homocysteine levels and cardiovascular mortality, it is not clear that lowering homocysteine levels will lead to a lower rate of cardiovascular events.

- At the end of FY 2002, the Look AHEAD: Action for Health in Diabetes had recruited 2,500 patients.

- The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was in its Vanguard (pilot) phase at the end of FY 2002. Recruitment for the main trial began in February 2003. Current enrollment is about 3,000, including participants in the Vanguard phase.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	(FY02) No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	◆		
Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	(FY03) Look AHEAD had recruited about half (2,500) of its patients		◇	
Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	(FY03) ACCORD had recruited 1,184 participants in a Vanguard phase			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The target for FY 2003 was met, in that the effect of intensive vs. conventional glycemic control on intima media thickening of the carotid artery was assessed as part of the EDIC study. This study is a followup of subjects enrolled in the DCCT, a randomized, controlled clinical trial that compared intensive vs. conventional blood glucose control in patients with type 1 diabetes.

Diabetes is accompanied by a substantial increase in the risk of cardiovascular disease (CVD). The Thickness of the intim amedia wall of the carotid artery is an indicator of heart disease and stroke risk. Earlier in the EDIC study, an initial ultrasound examination revealed that carotid intim amedia thickness of study participants was similar to that of nondiabetic controls matched for age and gender. There was also no difference between standard and conventional blood glucose control on this indicator of CVD risk. Subsequently, a second ultrasound revealed that study participants had thicker arterial walls than those of the nondiabetic group, suggesting the emergence of elevated CVD disease risk. Significantly, however, the thickness of the carotid walls had increased less in individuals who managed their blood glucose intensively than in the conventionally treated group. This is the first report from a randomized clinical trial to show that glucose levels can alter a measure of atherosclerosis. This finding, (as well as findings of sustained benefit from intensive therapy on development of microvascular complications persisting 8 years after the DCCT ended), suggests that aggressive management of blood glucose levels can produce not only short-term improvements but also lasting benefits that persist for years. To build on this finding, investigators will continue to monitor EDIC participants for cardiovascular events such as heart attack, stroke, and death from CVD. The study likely will include a third ultrasound measurement of carotid intima media thickness in the coming years to confirm and extend the results seen in the study described above.

Implementation Strategy Advances or Other Highlights

Look AHEAD has enrolled 90 percent of its target of 5,000 obese participants who have type 2 diabetes and is on schedule to complete recruitment in spring 2004. Each Look AHEAD participant will receive either a more intensive lifestyle intervention program or a standard diabetes support and education program for 4 years and then will be seen less frequently during an additional followup period of 5 to 7.5 years, depending on the time of entry into the trial. The trial will examine the effect of this lifestyle intervention on the incidence of cardiovascular events in the study population.

Recruitment for the Folic Acid for Vascular Outcome Reduction in Transportation (FAVORIT) trial began in July 2002. The study will recruit a total of 4,000 renal transplant recipients. Participants are being randomized to receive either a multivitamin containing high doses of folic acid and vitamins B6 and B12 or one with no folic acid and the estimated average daily requirements of vitamins B6 and B12. This study will test the important question of whether multivitamin supplementation can reduce cardiovascular events in this population. The study is very close to its recruitment goal, and it is anticipated that the study will meet its recruitment goal within the 2-year time frame.

The ACCORD trial has enrolled over 4,000 participants, which is 40 percent of the total eventual target of 10,000 and 99 percent of the planned recruitment goal to date. The study is on target to complete participant enrollment by the end of June 2005. The participants are being randomized to receive either intensive glycemia treatment (HbA1c goal of <6%) or standard glycemia treatment (HbA1c goal of 7.0%-7.9%). About half of the participants are additionally randomized to be treated to a systolic blood pressure goal of <120 mmHg vs. a blood pressure goal of <140 mmHg; the other half are additionally randomized to be treated with a fibrate plus a statin vs. a statin alone. All participants are being followed to determine effects of the treatments on major cardiovascular events, defined as acute heart attack, stroke, or cardiovascular death. The study is performing well in achieving the treatment targets.

GOAL 6c) BY 2012, DEVELOP A KNOWLEDGE BASE ON CHEMICAL EFFECTS IN BIOLOGICAL SYSTEMS USING A SYSTEMS TOXICOLOGY OR TOXICOGENOMICS APPROACH.

BACKGROUND

Disease Burden

Chemicals in the environment (including arsenic, lead, mercury, polychlorinated biphenyls [PCBs]) and other air and water pollutants contribute to the burden of human disease. In addition, lifestyle exposures to alcohol and nicotine compound adverse environmental health outcomes. Public health is also adversely influenced, for example, by exposure to household chemicals such as pesticides and through abuse of common over-the-counter pharmaceuticals such as analgesics. The problems of identifying environmental factors involved in the etiology of human disease and performing safety and risk assessments of drugs and chemicals have long been formidable issues. The prediction of potential human health risks involves consideration of (1) the diverse structure and properties of thousands of chemicals and other stressors in the environment, (2) the time and dose parameters that define the relationship between exposure and disease, and (3) the genetic diversity of organisms used as surrogates to determine adverse chemical effects. Toxicogenomics is a new scientific field that examines how chemical exposures disrupt biological processes at the molecular level. The pattern of regulation of various genes is different for different chemicals, creating characteristic "signatures," which scientists hope will be useful in classifying chemicals and other stressors by their biological activity. These signature patterns provide a means of potentially predicting effects on human health from chemicals about which little is known. To enable this predictive capability, a toxicogenomics knowledge base must be established. The result will be the emergence of "systems toxicology" as an information science that will facilitate thorough analysis, iterative modeling, and discovery across biological species and chemical classes.

Rationale

The global techniques evolving from successful genomics efforts are providing exciting new tools with which to address the formerly intractable problems of environmental health and safety assessment. Identifying molecular events that serve as precursors of adverse health outcomes early in the development process would eliminate much of the expense (estimated in billions of dollars annually) associated with the development of new pharmaceutical products. Similar considerations apply to prevention of disease associated with common environmental exposures. To benefit from these new technological advances, environmental toxicology and safety assessment must develop into an information science in which experimental toxicogenomics data sets are compiled and where computational and bioinformatics tools are applied to systematically develop a new understanding of toxicant-related disease. NIH is creating a knowledge base on Chemical Effects in Biological Systems (CEBS). More than a database, the CEBS knowledge base will contain data on global gene expression, protein expression, metabolite profiles, and associated chemical/stressor-induced effects in multiple species. With such information, it will be possible to derive functional pathways and network information based on cross-species homology. The CEBS knowledge base will develop relational and descriptive compendia on toxicologically important genes, groups of genes, polymorphisms, and mutants and their functional phenotypes that are relevant to human health and environmental disease. Designed initially as an interpretive tool for toxicogenomics, the CEBS knowledge base will ultimately become a knowledge base to support both discovery- and hypothesis-driven research.

PLANNED IMPLEMENTATION STRATEGIES

Part of NIH's strategies to reach this goal will be to capture and present quality control parameters, basic data preprocessing and normalization, basic visualization and statistical summary information, and basic annotation. This will provide the set of tools needed for microarray data analysis.

NIH also seeks to implement international standard file format for data exchange, extend the database object model to include toxicology/pathology fields, and create a data portal that will load National Toxicology Program (NTP) and commercial Xybion toxicology data. This will create the capability to import (and export) and link molecular expression data to animal effects data so as to evaluate global changes in gene and protein expression as a function of dose, time, and severity of toxic effect.

In addition, NIH plans to develop quality control indicators for submitted data sets and implement microarray cross-platform gene mapping, advanced data preprocessing and normalization, statistical comparisons, and automated gene annotation. This will enable automated loading and quality checking of data and automated full-chip gene annotation.

NIH ICs, international counterpart databases (e.g., European Bioinformatics Institute Tox-ArrayExpress), industry, and academia will collaborate to create a repository of high-quality toxicogenomics data sets on selected bioactive compounds to facilitate access and evaluation for discovery- and hypothesis-driven research.

BASELINE(S)

- To phase the development of the CEBS knowledge base and test the design and implementation of the knowledge base components and system information technology architecture, a CEBS prototype database system was constructed and used to explore the management, integration, mining, and analysis of microarray, histopathology, and clinical chemistry data.

- A laboratory management information system was developed for CEBS proteomics lab data management, and a rudimentary CEBS sample submission module was developed to facilitate the tracking of microarray and proteomics data submissions to the database. CEBS development has extended the Gene Expression Data Portal developed for the NCI Center for Bioinformatics (NCICB) to make it fully compliant with the MicroArray Gene Expression-object model (MAGE-OM) and the associated data exchange format (MAGE-ML). The CEBS knowledge base adopted the NCICB bioinformatics infrastructure and annotation engine, caBIO, to provide automated microarray annotation for the initial release of the CEBS in August 2003. caBIO provides access to genomic data sources, including GenBank, Unigene, LocusLink, Homologene, BioCarta, Ensembl, and UC Santa Cruz Genome Browzer, the latter two data sources via an automated annotation system.

- The CEBS knowledge base features enhanced capability to project expressed genes onto BioCarta molecular interaction pathways with full gene annotation. The CEBS knowledge base has extended the MAGE-OM for microarrays to model proteomics data and has integrated elements of the protein expression model PEDRo to capture minimum information for protein expression data sets.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	(FY02) Intramural databases and commercial software to build ProtoCEBS available	◆		
Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields, and by creating a data portal that will load toxicology data.	(FY03) CEBS object model to capture molecular expression data (only) designed but not tested		◇	
Create and provide public access to a global molecular expression and toxicology/pathology database of environmental chemicals and drugs (CEBS), featuring simple query download capability.	(FY03) CEBS version 1.0 launched in August 2003 contains only microarray data			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The target was met because NIH launched, tested, and implemented a prototype version of the Chemical Effects in Biological Systems (CEBS) database, designated as "ProtoCEBS Model A." This was accomplished through the application and integration of software developed by and for NIH, the National Toxicology Program, the European Bioinformatics Institute, and a commercial vendor. The ProtoCEBS Model A database has been developed as a workbench for concept definition and systems integration and evaluation to support the further development of the CEBS database.

Implementation Strategy Advances or Other Highlights

In addition to implementing the ProtoCEBS Model A database as described above, NIH also has implemented CEBS version 1.0 (online as of August 2003), which is a production database for microarray data. In addition, drawing on the consensus recommendations of the Microarray Gene Expression Database Society, NIH—in collaboration with the European Bioinformatics Institute and the International Life Sciences Institute-Health Effects Sciences Institute—has developed Minimal Information About a Microarray Experiment guidelines in the Toxicogenomics domain. This accomplishment will help NIH meet the FY 2004 performance target. Also, NIH is currently pursuing requirements definition and object modeling for both proteomics and toxicology/pathology to facilitate a seamless future integration of gene, protein, and toxicology/pathology data sets. The current version of the object model is referred to as the "CEBS Systems Biology Object Model" (CEBS SysBio-OM). The Rational Rose Universal Modeling Language representation of CEBS SysBio-OM can be found at http://cebs.niehs.nih.gov/protein. The two major developments (implementing CEBS version 1.0 online and extending the object model to capture proteomics data sets) will help NIH meet the FY 2005 performance target.

GOAL 7a) BY 2005, EVALUATE 10 COMMONLY USED BOTANICALS FOR INHIBITION/INDUCTION OF ENZYMES THAT METABOLIZE DRUGS AS A METHOD OF IDENTIFYING POTENTIAL BOTANICAL-DRUG INTERACTIONS.

BACKGROUND

Prevalence/Incidence

CDC reported that 29 percent of American adults used at least one complementary and alternative medicine therapy in the past year, of which nearly 10 percent used a botanical product.[1] A separate study reported that 18 percent of individuals taking prescription drugs were concurrently using botanical products, high-dose vitamins, or both, estimating that 15 million adults are at risk for interactions between drugs and dietary supplements (a large category that includes botanicals, vitamins, amino acids, and similar products other than drugs).[2]

Disease Burden

Heterogeneous in nature, interactions between botanicals and drugs demonstrate potential for a wide range of effects. Peer-reviewed scientific research literature has documented such events. For example, one study of St. John's wort showed it greatly reduced plasma concentrations of the anti-HIV medication indinavir. Similar phenomena have been observed with the cancer drug irinotecan, the immunosuppressant drug cyclosporine, and certain birth control medications. A study of garlic indicated interaction with saquinavir, another anti-HIV medication.

Rationale

Although botanical products are widely used in the United States, little or no authoritative information is available on potential botanical-drug interactions to either consumers or health care providers. Likewise, the systematic evaluation of the potential of botanicals to interact with conventional medications has largely gone unexplored. Botanicals are complex mixtures of naturally occurring chemical compounds, some of which proved sufficiently potent to serve as the basis for many current drugs. It could be expected, then, that botanical products could manifest a broad array of interactions with conventional drugs so as to enhance their activity and evoke greater drug toxicity or to accelerate their metabolism and impair their therapeutic benefits. Compounds contained in some botanical products have already been proven to interact with drugs by inhibiting or inducing specific hepatic cytochrome P-450 enzymes that are critical for drug metabolism and elimination. Of this large enzyme system, two specific enzymes, CYP 3A4 and CYP 2D6, are involved in the metabolism of approximately 80 percent of all marketed drugs, thereby providing a rational starting point from which to examine the potential for botanical-drug interactions.

PLANNED IMPLEMENTATION STRATEGIES

NIH's strategic approach to fulfilling this goal is to provide continual support of solicited and unsolicited studies of botanicals and review investigator progress annually. In addition, under the NTP, NIH will continue studies of goldenseal and ginkgo and initiate studies on milk thistle (*Silybum marianum*) and grapeseed oil (*Vitis* sp.). These strategies should lead to the discovery of additional botanical/drug interactions.

[1] Ni H, Simile C, Hardy AM. Utilization of complementary and alternative medicine by United States adults: results from the 1999 national health interview survey.
[2] Eisenberg DM et al. Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. JAMA. 1998 Nov 11;280(18):1569-75.

BASELINE(S)

- Thus far, the most extensively characterized botanical has been St. John's wort (*Hypericum perforatum*).
- Already under way are several research projects, both solicited and unsolicited, that examine the capability of botanicals to inhibit/induce enzymes that metabolize drugs.
- The NTP is examining several common herbal extracts in 90-day and (selectively) 2-year rodent bioassays. Of those selected for 2-year studies, *in vitro* tests are done to assess their ability to inhibit the activity of seven common human P-450 enzymes. To date, studies on kava kava (*Piper methysticum*) have been completed and published. Studies on goldenseal (*Hydrastis canadensis*) and ginkgo (*Ginkgo biloba*) are ongoing.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Identify results of studies on three botanicals that show inhibition/induction of enzymes that metabolize drugs.	(FY02) Some characterization of St. John's wort; very little known about other botanicals	◆[e]		
Identify results of studies on three additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	(FY03) St. John's wort better characterized. Good characterization of ginkgo, garlic, saw palmetto, 2 species of ginseng, and PC-SPES		◇	
Identify results of studies on four additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	(FY03) Characterization of additional botanicals from FY 2004			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was exceeded: The effects of seven botanicals (rather than the target three) were characterized on the inhibition or induction of drug metabolizing enzymes of the cytochrome P-450 pathway. The botanicals are as follows: St. John's wort, Ginkgo biloba, garlic, Siberian ginseng, saw palmetto, PC-SPES, and North American ginseng. During FY 2003, NIH researchers learned that when extracts of garlic, Ginkgo biloba, saw palmetto, and Siberian ginseng were administered at doses comparable to those in dietary supplements no effects on either CYP2D6 or CYP3A4 enzymes were seen. This suggests that they are unlikely to alter blood levels and activities of most drugs. Conversely, studies on St. John's wort and the proprietary botanical mixture PC-SPES showed an induction of the CYP3A4 enzyme, potentially accelerating the elimination rate of certain drugs, reducing their effectiveness. Likewise, North American ginseng inhibited CYP1A1, CYP1A2, and CYP1B1 enzymes, showing the potential for this botanical to slow the clearance of certain drugs. In some cases, this could lead to the accumulation of otherwise beneficial drugs at toxic levels. These studies illustrate the importance of examining the impact of commonly used botanicals on drug metabolism to prevent the possibility of adverse events such as toxicity or even death when botanicals and drugs are taken together.

Implementation Strategy Advances or Other Highlights

Research on botanical induction/inhibition of enzymes, initiated under two Requests for Application (RFAs), continues. Research results were published in peer-reviewed scientific journals.

Efficiency

This goal may be met sooner than planned since NIH researchers are more than halfway through the goal. The researchers conducted targeted research and examined multiple botanicals according to their specific area of expertise, which facilitated greater results. The speed with which the researchers characterized the botanicals allowed the examination of a greater number of botanicals than anticipated.

GOAL 7b) BY 2006, INTEGRATE NANOTECHNOLOGY-BASED COMPONENTS INTO A SYSTEM CAPABLE OF DETECTING SPECIFIC BIOMARKERS (MOLECULAR SIGNATURES) TO ESTABLISH PROOF OF CONCEPT FOR A NEW APPROACH TO THE EARLY DETECTION OF CANCER AND, ULTIMATELY, CANCER PREEMPTION.

BACKGROUND

Prevalence/Incidence

Cancer is the second leading cause of death in the United States. In 2001 an estimated 1,268,000 persons in the United States were diagnosed with cancer, including 198,100 prostate cancers, 192,200 female breast cancers, 169,500 lung cancers, and 135,400 cancers of the colon/rectum.[1] These estimates do not include most skin cancers; new cases of skin cancer are estimated to exceed 1 million per year. One-half of all cases of cancer occur among people age 65 years and older.[2]

Disease Burden

The Nation's past investments in cancer research are paying major dividends; for example:

- Americans are increasingly adopting good health habits to reduce their cancer risk.[3]
- Overall, cancer rates are dropping, especially for cancers that are diagnosed prior to metastatic spread.[4]
- Overall, the more than 9 million cancer survivors in America are enjoying a higher quality of life than was possible just a few years ago.[5]

However, in the face of these significant advances, cancer remains a major public health problem, and with the aging and changing demographics of America, expected increases in numbers of new cancer cases loom as a potential health care crisis.[6]

- The incidence rates of certain cancers continue to rise. For example, rates of lung cancer in women, non-Hodgkin's lymphoma, and melanoma are increasing.[7]
- The cost of the cancer epidemic is estimated to be in excess of $180 billion per year, and this burden will continue to rise as cancer moves to become the number one killer of Americans in the next few years.[8]
- The rates of both new cases and deaths from cancer vary by cancer site, socioeconomic status, sex, and racial and ethnic group.[9]

Rationale

Recent advances in understanding the molecular basis of cancer and the associated development of novel molecular technologies in areas such as proteomics, portend a future where cancer can be detected early and preempted before it spreads, perhaps on an individual basis. For example, nanoscience offers unparalleled opportunities to measure and monitor changes within cells at the level of multiple atoms. Nanoscience

[1] *Cancer Progress Report 2001*. NIH Publication No. 02-5045, December 2001. p. 18. (http://progressreport.cancer.gov/).
[2] Ries LAG, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK (eds). SEER Cancer Statistics Review, 1973-1996, National Cancer Institute. Bethesda, MD, 1999.
[3] *Cancer Progress Report 2001*. NIH Publication No. 02-5045, December 2001. p. 18. (http://progressreport.cancer.gov/).
[4] Edwards BK et al. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. Cancer. 2002 May 15;94(10):2766-92.
[5] *Cancer Progress Report 2001*. NIH Publication No. 02-5045, December 2001. p. 18. (http://progressreport.cancer.gov/).
[6] Edwards BK et al. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. Cancer. 2002 May 15;94(10):2766-92.
[7] *Cancer Progress Report 2001*. NIH Publication No. 02-5045, December 2001. p. 18. (http://progressreport.cancer.gov/)
[8] Edwards BK et al. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. Cancer. 2002 May 15;94(10):2766-92.
[9] *Cancer Progress Report 2001*. NIH Publication No. 02-5045, December 2001. p. 18. (http://progressreport.cancer.gov/).

researchers are developing "nanospheres" that can be deployed in the body to detect real-time changes in normal cells. These nanoparticles can carry a variety of specially designed, molecular-size attachments, allowing them to act as biosensors that can be programmed to detect malignant changes in normal cells and potentially deliver treatment without harming healthy cells. Applications of nanotechnology have the potential to shift the paradigm of cancer toward earlier detection and prevention and provide a new platform for eventual high-throughput diagnostics and, ultimately, real-time monitoring of patients.[1]

PLANNED IMPLEMENTATION STRATEGIES

At present, specific implementation strategies are still evolving and include (1) continued support of the three programs noted above (i.e., UIP, FTDBS, and EDRN); (2) establishment of joint intramural and extramural collaborations to make use of substrate nanotechnology fabrication techniques, thereby enabling proteomics analyses; (3) establishment of a core laboratory at NIH combining extramural and intramural fabrication technologies capable of deriving targets; and (4) development of a platform technology for applied research settings.

BASELINE(S)

- The Unconventional Innovations Program (UIP) has led the way in bionanotechnology innovations. The UIP began in 1999 and is targeted to invest $50 million over a 10-year period in the development of radically new technologies for detecting, diagnosing, and intervening in cancer at its earliest stages of development. Details on awards and progress by year can be found at http://otir.nci.nih.gov/tech/uip_awards.html.

- Complementary to the UIP, the Fundamental Technologies for the Development of Biomolecular Sensors (FTDBS) program, initiated in partnership with the National Aeronautics and Space Administration (NASA), solicits projects to develop the fundamental elements of technology systems or system components that will measure, analyze, and manipulate molecular processes at the appropriate scale in the living body. The discoveries from this program are intended to enable the development of complete systems for the in vivo sensing of signatures of pathologic cell types or closely associated microenvironmental factors. These systems will provide a seamless interface between sensing/detection and delivery of signature-specific intervention. This program was started in 2001 and is targeted to invest $35 million by 2006. In 2002 six contracts were issued totaling nearly $10.3 million over 3 years. Details on awards and progress can be found at http://otir.nci.nih.gov/tech/ftbs_awards.html.

- The Early Detection Research Network (EDRN) was established to identify and evaluate biomarkers and technologies for earlier detection and risk assessment. The EDRN is a national network of academic and industry investigators with expertise in the laboratory and clinical sciences, biostatistics, informatics, and public health issues. This work is conducted through EDRN's 18 Biomarkers Developmental Laboratories, three Biomarkers Validation Laboratories, eight Clinical/Epidemiology Centers, and a Data Management and Coordinating Center.

[1] *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004.* NIH Publication No. 03-4373, October 2002, p. 69.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Establish intramural and extramural collaborations to select and employ substrate nanotechnology fabrication techniques to enable high-throughput and highly reliable/reproducible proteomic analyses.	(FY02) Lack of relevant collaborations	◆[e]		
Establish a core laboratory at NIH to bring together extramural and intramural fabrication technologies with the capability to derive targets, identify the most promising applications for combined functionalized nanoparticles, and steward therapeutic nanotechnologies through validation.	(FY03) No current core laboratory with needed capacity		◇	
Integrate nanosensors and nanoparticles into a platform technology for development in applied research settings.	(FY03) Existing nanosensors and nanoparticles not integrated into a common platform			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

NIH is engaged in over 60 projects related to cancer nanotechnology. These projects lay the groundwork for future collaborations necessary to bridge the gap between cancer research and nanotechnology advances. Examples of the ongoing research include:

- Nanoparticles for detection, drug delivery, toxicity monitoring, gene therapy, and tumor vascularity determination
- Multimeric ligands, molecular machines that will recognize the surface of cancer cells, but not of normal cells, for use in medical diagnosis of cancer, molecular imaging, and cancer therapeutics
- Protein expression and signature detection
- Novel imaging techniques, including real-time imaging
- Contrast agents

To address the goal, NIH has developed collaborations between scientists in the Unconventional Innovations Program (http://otir.nci.nih.gov/tech/uip.html), the Intramural Research Program, and the private sector. The range of science covered in these collaborations addresses cancer sites such as prostate, breast, and brain and include:

- nanoparticles for imaging, protein identification and analysis
- high-throughput strategies for protein analysis (See Appendix 4, Source Validation Table, 1)
- silicon-based nanoparticles for improved protein fractionation capabilities to lead to the discovery of sensitive and specific biomarkers for cancer (See Appendix 4, Source Validation Table, 2 and 3)

A collaboration between extramural investigators and a small business is already underway to develop adaptable assays to detect cell signaling molecules that play a central role in carcinogenesis and are the targets for a new generation of drugs that inhibit protein kinases (See Appendix 4, Source Validation Table, 4). The movement of protein kinase inhibitors and related compounds into clinical trials will increase the demand for such assays.

Other extramural investigators are using nanotechnology to develop high-throughput, highly-sensitive proteomic and genomic analyses that are critical in the early diagnosis, monitoring, and prognostic evaluation of cancer. **Bioc**hemo-**o**pto-**m**echanical (BioCOM) chips produce a color-based optical signal. This technology offers a new paradigm in the evaluation of multiple proteins from serum or from a single tissue,

allowing a cost-effective way to assess multiple cancer antigens in screening and monitoring programs (See Appendix 4, Source Validation Table, 5).

Implementation strategies progress or other highlights

Key strategies employing nanotechnology beyond protein detection are being applied to detect biological fluid changes inside cancer cells. Researchers have developed and characterized a highly-selective magnesium fluorescent optical nanosensor using PEBBLE (**p**robe **e**ncapsulated **b**y **b**iologically **l**ocalized **e**mbedding) technology. Further advances may provide insight into cancer initiation and progression (See Appendix 4, Source Validation Table, 6).

NIH is spearheading and coordinating the development of the Cancer Nanotechnology Plan (CNPlan), which will integrate nanotechnology into the discovery, development, and delivery aspects of cancer research. In addition, two working groups (one for intramural and one for extramural) have been meeting to integrate nanotechnology into NIH's strategic priority areas. These working groups have membership from Institute divisions as well as from the FDA and extramural researchers.

A contract with an extramural nanofabrication laboratory was awarded recently to provide rapid access to engineering nanoparticles for detection, molecular targeting, and drug delivery.

Plans are underway for a national nanotechnology characterization laboratory that will enable the establishment of highly needed data about the profiles of nanoparticles in biological systems.

Efficiency

The joint efforts of academia, industry, and small businesses enhance the likelihood of commercialization potential for new diagnostic, prevention, and treatment modalities. Cancer nanotechnology research programs also are linked to basic nanotechnology research and engineering associated with the national nanotechnology initiative (http://www.nano.gov/). The FDA will assist in the development of regulatory sciences for clinical nanotechnology applications. In summary, these focused strategies are shortening the time from discovery to the clinic and hold promise for improved options for patients, thereby contributing to the goal of eliminating suffering and death from cancer by 2015.

GOAL 7c) BY 2005, CREATE THE NEXT-GENERATION MAP OF THE HUMAN GENOME, A SO-CALLED HAPLOTYPE MAP ("HAPMAP"), BY IDENTIFYING THE PATTERNS OF GENETIC VARIATION ACROSS ALL HUMAN CHROMOSOMES.

BACKGROUND

Prevalence/Incidence

Virtually all diseases have a genetic component. The DNA sequences of any two people are 99.9 percent identical. However, there are at least 10 million DNA sites where people commonly differ, and these variations may greatly affect an individual's risk for disease or response to drugs.

Disease Burden

The goal of much genetic research is to identify genes that contribute to disease. Finding these genes allows an understanding of the disease process, thus enabling development of methods for disease prevention and treatment. For single-gene disorders, diseases with a relatively straightforward genetic basis, current methods are often sufficient to find the genes involved. Most people, however, do not have single-gene disorders but develop common diseases such as diabetes, cancer, and psychiatric disorders, which occur because of interactions of genetic and environmental factors. Strategies that work well for single-gene disorders lack the power to map such multigene disorders; thus, relatively little is known about the genetic basis of these common diseases or the factors that determine individual risk of disease, clinical course, or response to treatment.

Rationale

By understanding the way in which genetic variations are correlated in DNA "neighborhoods" or "haplotypes," considerable savings in time, effort, and cost can be achieved in uncovering the hereditary factors in disease. Sites in the genome where individuals differ in their DNA spelling by a single letter are called single nucleotide polymorphisms (SNPs). Recent work has shown that about 10 million SNPs are common in human populations. SNPs are not inherited independently; rather, sets of adjacent SNPs are inherited in blocks. The specific pattern of particular SNP spellings in a block is called a haplotype. Although a region of DNA may contain many SNPs, it takes only a few SNPs to uniquely identify or "tag" each of the haplotypes in the region. This presents the possibility of a major shortcut in identifying hereditary factors in disease. Instead of testing 10 million SNPs, a rigorously chosen subset of about 400,000 SNPs could provide most of the essential information.

Most common haplotypes occur in all human populations, although their frequencies may vary considerably. Initial studies also indicate that the boundaries between the blocks are remarkably similar among populations in Europe, Asia, and Africa. These data indicate that a human haplotype map (HapMap) built with samples from these three geographic areas would apply to most populations in the world, although additional testing of this conclusion is needed.

NIH has taken a leadership role in the development of the HapMap, a catalog of the haplotype blocks and the SNPs that tag them. The HapMap is a tool that can be used by researchers studying many diseases to find the genes and variants that contribute to those diseases. In addition, the HapMap will be a powerful resource for studying the genetic factors contributing to variation in individual response to disease once it does occur as well as to drugs and vaccines.

The haplotype map, or "HapMap," will be a description of the patterns of human genetic variation. It will be a tool that researchers will use to find genes and genetic variations that affect health and disease. The HapMap will reduce the number of SNPs required to examine the entire genome for association with a

phenotype from the 10 million SNPs that exist to roughly 500,000 tag SNPs. This will make genome scan approaches to finding regions with genes that affect diseases much more efficient and comprehensive, since efforts will not be wasted typing more SNPs than necessary and all regions of the genome can be included. In addition to its use in studying genetic associations with disease, the HapMap should be a powerful resource for studying the genetic factors contributing to variation in response to environmental factors, in susceptibility to infection, and in the effectiveness of and adverse responses to drugs and vaccines. This new tool will enable biomedical science to identify the genes and genetic variants that contribute to common diseases, allowing researchers to then study how the disease processes work, which will lead to interventions to prevent, delay, or cure the diseases. Despite the progress this map will enable, it will be difficult to fully quantify the impact of the HapMap for some 5-10 years beyond its completion. During that time, it will be possible to quantify the amount that the HapMap data are used, and to monitor the diseases and other phenotypes that will be studied using the HapMap.

PLANNED IMPLEMENTATION STRATEGIES

To conduct the HapMap project, NIH organized an international consortium of researchers in Canada, China, Japan, Nigeria, the United Kingdom, and the United States, including eight genotyping research groups, five data analysis groups, a data coordination center, and four sample collection groups. The consortium will identify an additional 3 million SNPs needed to fill in areas where the current density of SNPs in public databases is not sufficient. The consortium will collect samples from four populations (CEPH [U.S. residents with ancestry from Western and Northern Europe], Yoruba in Nigeria, Chinese, and Japanese). The consortium is also developing scientific strategies to choose which SNPs to study, assess the quality of the data, and derive haplotypes from the SNP data. The genotyping research groups will test the samples for about 1.6 million SNPs to discover the pattern of variation among the samples. These genotype data will be analyzed to derive haplotypes, develop the HapMap, and then choose the SNPs that contain the most information on the patterns of genetic variation to make the HapMap most useful for later studies relating genetic variation to health and disease.

BASELINE(S)

Haplotype methods have already been used successfully for finding genes contributing to disease for both rare, single-gene disorders and more common, complex diseases. An initial meeting was held in July 2001 to discuss how the HapMap could be used for finding genes contributing to disease, the methods for constructing such maps, the data about haplotype structure in populations, the types of populations and samples, the ethical issues of studying identified populations, and how such a project could be organized.

- NIH ICs and the Office of the Director have solicited research proposals and cooperative agreement applications for the large-scale genotyping across the genome of samples from four populations to be used to develop a map of the haplotype patterns and of the genetic variants that are most informative for detecting these patterns.

- A group of advisors was established consisting of geneticists, social scientists, and experts on the ethical and societal implications of genetic research to develop a sampling strategy that meets both the need for high-quality, scientific research and the need for the project to adhere to the highest ethical standards to protect participants.

- Although members of the CEPH population (U.S. residents of Western and northern European ancestry) have donated samples for other studies in the past, it is necessary for these participants to give their consent for the HapMap study. The reconsent process consists of asking the participants to complete a new consent form that explains the project, and then the researchers discuss the project with each individual subject.

- Currently, no SNPs have been collected. SNPs will be validated by genotyping the samples. If the genotyping works for a sample, then it will be a successful SNP; if genotyping does not work, the SNP will not be valid.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
For existing blood samples from U.S. residents of Western and northern European ancestry, obtain additional consent from the donors for this new use and begin genotyping 300,000 single nucleotide polymorphisms (SNPs, sites in the human genome where individuals differ by a single letter) in those samples.	(FY02) 90 existing samples, none of which included the necessary consent for genotyping	◆[e]		
Collect samples from populations in Japan, China, and Nigeria; complete collection of additional 3 million SNPs and release in public databases.	(FY03) 2.4 million SNPs in database		◇	
Develop a first-pass draft HapMap containing 600,000 SNPs.	(FY03) 2.4 million SNPs in database but none of the samples genotyped to produce any part of the HapMap			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

NIH has met the targets of obtaining additional consent from U.S. sample donors (U.S. residents of western and northern European ancestry) for this new use of their existing samples and beginning genotyping 300,000 SNPs in those samples.

By the end of FY 2003, all of the living donors who provided the (previously existing) 90 U.S. samples used for the project specifically consented to their samples being used for developing the HapMap. Some of the samples are from deceased individuals and therefore do not need to be reconsented. A total of six research groups have performed genotyping for 132,000 SNPs in these samples to date.

Implementation Strategy Advances or Other Highlights

In order to plan the project NIH held an initial meeting in July 2001 to discuss the need for the HapMap, the methods for constructing such maps, the types of populations and samples needed, the ethical issues of studying identified populations, and how such a project should be organized. Funding for the project began in FY 2002. To conduct the project, NIH helped initiate and continues to coordinate an international consortium of researchers in Canada, China, Japan, Nigeria, the United Kingdom, and the United States, including 10 genotyping research groups, 4 sample collection groups, 5 data analysis groups, and a data coordination center.

By FY 2004, the consortium will have identified an additional 3 million SNPs needed to fill in areas where the current density of SNPs in public databases is not sufficient. The consortium will collect consents and samples from a total of 270 individuals who come from one of four populations (U.S. residents with ancestry from western and northern Europe and individuals from Japanese, Han Chinese, or Yoruba [Nigeria] populations). The consortium is also developing scientific strategies to choose which SNPs to study, assess the quality of the data, and derive haplotypes from the SNP data. The genotyping research groups will test the samples for at least 1 million SNPs to discover the pattern of variation among the samples. These genotype data will be analyzed to derive haplotypes, develop the draft HapMap by FY 2005, and then choose the SNPs that contain the most information on the patterns of genetic variation to make the HapMap most useful for later studies relating genetic variation to health and disease.

An international consortium partnership is vital for undertaking the project, but could affect the time needed for completion. NIH is supporting genotyping of 30 percent of the genome; changes in support of science in the other countries could accelerate or decelerate their efforts and thus the time it takes to finish the entire project. There are many challenges in collecting blood samples in Japan, China, and Nigeria, so these sample collections could be delayed or even cancelled. The HapMap is based on pilot data showing how genetic variation is organized in parts of the genome; it is possible that the entire genome will turn out to have different patterns than seen initially, so more or fewer SNPs may be needed to develop the HapMap than currently thought. Finally, the study of additional populations from other geographic areas, currently being collected as part of a pilot project, may indicate that additional DNA samples from other parts of the world need to be included in the HapMap to make this powerful research tool more applicable to all human population groups.

Efficiency

The HapMap project has already discovered many more SNPs and is currently ahead of schedule in this regard. These additional SNPs not only will speed the pace of the HapMap project's completion but also will greatly enhance other basic biomedical research efforts that are dependent on SNP analysis.

GOAL 8a) BY 2007, DETERMINE THE GENOME SEQUENCES OF AN ADDITIONAL 45 HUMAN PATHOGENS AND 3 INVERTEBRATE VECTORS OF INFECTIOUS DISEASES.

BACKGROUND

Genomics, the science of deciphering and drawing information from the genetic code of an organism, is a powerful tool that NIH is using to understand the microbes that cause disease and design strategies to overcome them. The potential payoffs of sequencing pathogens are enormous. Genome sequence information can be used in many ways to identify molecules for vaccine and drug development, identify mutations that contribute to drug resistance, compare the genomes of different strains of pathogens and note differences that may affect the virulence of a microbe or its ability to evoke disease, and trace microbial evolution. When scientists identify genes that are unique to a particular microbe, drugs can be targeted to these genes, and the products of these genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Moreover, genetic variations detected in different strains of the same pathogen can be used to study the population dynamics of these strains, such as the spread of a virulent form of an organism in a susceptible population. Understanding the genetic basis for both virulence and drug resistance may help predict disease prognosis and influence the type and extent of patient care and treatment. Recognizing the incredible potential of microbial genomics research, NIH has made a significant investment in the large-scale DNA sequencing of the genomes of human pathogens and invertebrate vectors of disease, including microorganisms considered to be potential agents of bioterrorism.

NIH has funded projects to sequence the full genomes of a number of medically important microbes, including the bacteria that cause tuberculosis, gonorrhea, chlamydia, cholera, strep throat, scarlet fever, and food-borne diseases. The genome sequences of 39 bacterial pathogens, 3 parasitic protozoa, and 1 invertebrate vector (an organism that spreads disease, e.g., a mosquito) have been completed with NIH support, and these sequences have been released rapidly to the scientific community through a publicly accessible Web site. The complete genome sequences of *Plasmodium falciparum* and *Anopheles gambiae*, the most lethal malaria-causing parasite and its mosquito vector, respectively, were published in 2002, providing a valuable resource to the scientific community. This work, which was supported in part by NIH, will provide the basis for additional experimental studies to understand the pathogenesis of the parasite and its vector and lead to potential targets for the next generation of drugs, vaccines, and diagnostics.

Rationale

Genomic information will aid in the identification of gene products critical to growth and pathogenicity of microbes and their vectors; these may serve as targets for new therapeutics, vaccines, and diagnostics. Significant progress in DNA sequencing technology has allowed genomic DNA to be sequenced more efficiently and cost-effectively. It is now possible to sequence a bacterial genome in a month or less. DNA sequencing technology is being improved further, and innovative new sequencing technologies that will revolutionize the speed, efficiency, and cost by several orders of magnitude are in the immediate future. A critical companion to state-of-the-art DNA sequencing techniques are the bioinformatics, computational tools, and databases that provide the scientific community with the needed resources to query, analyze, and annotate the sequencing data and assemble genomes.

PLANNED IMPLEMENTATION STRATEGIES

To accomplish the goal of determining the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases, NIH will support the sequencing of the genomes of 24 disease-causing organisms, including 9 bacteria, 5 fungi, 9 parasites, and 1 disease vector.

NIH will launch the NIH Proteomic Centers. Proteomics is the study of all or large groups of proteins in cells, tissues, and organs and how they respond, interact, and change. This initiative will develop and enhance innovative proteomic technologies and methodologies and apply them to the understanding of the pathogen and/or host cell proteome (all proteins in cells, tissues, and organs) for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics, and immunotherapeutics against microorganisms considered agents of bioterrorism.

NIH will expand microbial genomics activities by 50 percent as measured by technology. NIH has developed several FY 2003 initiatives to provide comprehensive genomic, bioinformatic, and proteomic resources to the research community for basic and applied research to rapidly address the Nation's biodefense needs. Activities to be expanded include (1) the NIH Microbial Genome Sequencing Centers, which allow for rapid and cost-efficient production of high-quality, microbial genome sequences to meet national needs and government agencies' priorities for genome sequencing, forensic strain identification, and target identification for development of drugs, vaccines, and diagnostics; (2) the Bioinformatics Resource Centers, a companion initiative to the Microbial Genome Sequencing Centers, which will develop, populate, and maintain comprehensive, relational databases. These databases will enable NIH to collect, store, display, annotate, query, and analyze genomic, functional genomic, structural, and related data for microorganisms responsible for emerging and reemerging infectious diseases, including those considered agents of bioterrorism; and (3) the NIH-supported Pathogen Functional Genomics Resource Center to provide the research community with the needed resources and reagents to conduct both basic and applied research on disease-causing microbes, including those considered to be potential agents of bioterrorism.

BASELINE(S)

- NIH supports development of critical genomic resources, including DNA sequences of disease-causing microorganisms, and organisms considered to be potential agents of bioterrorism and invertebrate animal vectors that carry disease. Information from these individual sequences and genomic comparisons across multiple species will provide greater understanding of the disease processes as well as a basis for novel, molecularly targeted therapeutics and vaccines.

- In FY 2001 and FY 2002, the genome sequences for 21 bacterial pathogens were completed, including those of species that cause salmonella, streptococcal pneumonia, tuberculosis, gonorrhea, anthrax, and plague. In addition, sequences have been completed for the protozoan parasites that cause malaria, cryptosporidiosis, Chagas, and Leishmania disease and the mosquito that carries malaria. To date, 44 organisms related to infectious diseases have been sequenced, including 39 bacteria, 4 parasitic protozoa, and 1 disease vector organism.

- NIH participates in the Microbe Project Interagency Working Group, which developed a coordinated, interagency 5-year action plan on microbial genomics, including functional genomics and bioinformatics in FY 2001. In FY 2002 this working group has continued to coordinate genomic activities across Federal agencies, including those related to biodefense, and has also focused on issues related to genomic data release and usage and genomic databases. In addition, NIH participates in the Federal Bureau of Investigation-sponsored Scientific Working Group on Microbial Genetics and Forensics. Participants include Federal agency officials and scientists with expertise in genomics, bioinformatics, microbiology, and infectious diseases. The mission of the working group is to define criteria and coordinate the development and validation of microbial forensic methods that will support the attribution for criminal investigations.

PERFORMANCE TARGETS	BASELINE[1]	FY 2003	FY 2004	FY 2005
Complete the genomic sequences for at least five bacteria and two protozoa that cause infectious disease.	(FY02) Genome sequences for 29 bacterial pathogens, 1 protozoan parasite, and 1 insect completed	◆[e]		
Complete the genomic sequences of at least three fungal pathogens, five bacterial pathogens, and two protozoa that cause infectious disease.	(FY03) Genome sequences for 39 bacterial pathogens, 4 protozoan parasites, and 1 insect completed		◇	
Complete the genomic sequences of at least two fungal pathogens, five bacterial pathogens, and four protozoa that cause infectious disease.	(FY03) Genome sequences for 44 bacterial pathogens, 6 protozoan parasites, 3 fungi and 1 insect completed			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was met and exceeded, largely due to gains in efficiency in the sequencing process. Ten (rather than the target five) bacterial pathogen sequences were completed in FY 2003, including *Burkholderia mallei, Clostridium perfringens, Escherichia coli* (K1 RS218), *Streptococcus agalactiae, Rickettsia rickettsii, Rickettsia typhi, Salmonella typhi, and Wolbachia.* Three (rather than the target two) protozoan sequences were also completed in FY 2003, including *Leishmania major*, *Trypanosoma cruzi*, and *Cryptosporidium parvum* (bovine isolate). NIH has made a significant investment in large-scale sequencing projects that continue to generate an enormous amount of DNA sequence information. In FY 2003, NIH supported 36 large-scale DNA sequencing genome projects for microbial pathogens and invertebrate vectors of infectious diseases. In addition, in FY 2003, NIH initiated sequencing projects for *Burkholderia thailandensis*, different strains and clinical isolates of *Bacillus anthracis*, and another strain of *Clostridium perfringens*. Genome sequencing data are available on publicly accessible web sites, and the genome sequences of *Bacillus anthracis* (Ames), *Bacillus cereus, Coxiella burnetii, Enterococcus faecalis, Anopheles gambiae,* and *Plasmodium falciparum* were published in FY 2003.

Implementation Strategy Advances or Other Highlights

In FY 2003, NIH expanded its support for *Bacillus anthracis* genomics, and through genomic analysis, a number of genes encoding proteins that *B. anthracis* may use to enter host cells were identified. Information obtained from these efforts will aid in the design of new vaccines and treatments. In addition, genomic comparison of *B. anthracis* to two closely related *Bacillus* strains revealed remarkably little difference among the strains, highlighting the potential biodefense relevance of pathogens not associated with anthrax disease.

In FY 2003, NIH awarded a contract to support the Microbial Genome Sequencing Center (MGSC) to allow for rapid and cost-efficient production of high-quality, microbial genome sequences, including Category A, B, and C agents; clinical isolates; invertebrate vectors of infectious diseases; and microorganisms responsible for emerging and re-emerging infectious diseases. MGSC has the capacity to respond to national needs and Federal agencies' priorities for genome sequencing, including identification of forensic strains and targets for drugs, vaccines, and diagnostics.

The Pathogen Functional Genomics Resource Center (PFGRC), established in FY 2001, provides genomic resources and technologies to the broader research community for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases. In FY 2003, additional organism-specific microarrays were generated and distributed to the scientific community, including *Mycobacterium tuberculosis, Neisseria gonorrhoeae,* and *Plasmodium falciparum*. Moreover, within a month of the announcement of the SARS

[1] The baseline numbers are in some cases higher than what would be calculated by simply adding on the numbers from the targets (see "Efficiency" section).

coronavirus genomic sequence, NIH/PFGRC made freely available one of the first genomic resources for SARS, a "SARS chip." This genomic tool allows scientists to detect tiny genetic variations among the different SARS clinical strains.

In FY 2003, NIH continued to provide support for databases of genomic and postgenomic information and analysis tools on sexually transmitted pathogens (www.stdgen.lanl.gov) and poxviruses (http://www.poxvirus.org). Genomic information for 13 bacteria and viruses is now included in the STD Sequence Databases (STDGEN), which is supported in part by NIH. Additionally, the NIH-DARPA collaborative Poxvirus Bioinformatics Resource Center (http://www.poxvirus.org) serves as a resource for the scientific community.

Efficiency

Technological developments have allowed the cost of sequencing DNA to drastically decrease and efficiency to greatly increase. For example, The Institute for Genomic Research (TIGR), an international microbial sequencing center, has reported that sequencing a piece of DNA, approximately 650 nucleotides in length, has decreased from $7.70 in 1996 to $0.98 in 2002. In 2003, the cost had decreased to $0.88. Also, NIH exceeded targets or completed projects ahead of schedule on several occasions, because the genomic sequencing process has become faster and more accurate.

GOAL 8b) BY 2009, IDENTIFY AND CHARACTERIZE TWO MOLECULAR INTERACTIONS OF POTENTIAL CLINICAL SIGNIFICANCE BETWEEN BONE-FORMING CELLS AND COMPONENTS OF BONE. SUCH INTERACTIONS ARE DEFINED AS THOSE HAVING SIGNIFICANT IMPACT ON THE ACCRUAL OF BONE MASS OR THE ACTUAL MECHANICAL PERFORMANCE OF BONE (I.E., FRACTURE RESISTANCE) IN LABORATORY ANIMALS.

BACKGROUND

Both skeletal health and the maintenance of normal blood calcium levels depend on the process of bone turnover, in which small regions of bone are broken down (resorbed) and then replaced with new bone. The regulation of the balance between bone resorption and new bone formation, which can be affected by nutritional, endocrine, and pharmacological factors, is critical to maintaining bone mass and preventing fracture. An excess of resorption over formation underlies many bone diseases, such as postmenopausal osteoporosis.

Osteoblasts are the cells that form new bone during bone turnover. In addition, some osteoblasts remain embedded in the bone, becoming osteocytes. Recent work has shown that osteocyte survival is an important requirement for skeletal health. Bone is composed of mineral crystals embedded in a matrix made up of many different proteins. There is evidence that interactions between matrix proteins and proteins found at the cell surfaces of osteoblasts and osteocytes produce signals that are important for the regulation of bone turnover and the survival of osteocytes. However, the molecular details of cell-matrix interactions have been explored in only a few instances. If known, the mechanisms of these interactions could yield targets for new drugs that might act to stimulate bone formation or block bone resorption.

Rationale

Recent advances, particularly in the genetic manipulation of mice, make it possible to define the function of different matrix proteins and the cell surface proteins that interact with them. For example, mice can be created that either lack a certain matrix protein or produce abnormally large amounts of the protein. Cell surface proteins thought to interact with matrix proteins also can be tested in this way. It is important to conduct these experiments with intact, genetically modified mice, rather than in cell culture, for two reasons. First, although osteoblasts can be induced to produce bone matrix in culture, the interaction between cells and matrix in culture is not normal. For example, osteoblasts do not become osteocytes within the bone produced in culture. Second, the consequences of interfering with specific cell-matrix interactions can be assessed thoroughly by examining the bones of mice. This can even indicate the ultimate effect on the mechanical strength of the bones.

It is clear from work to date that altering cell-matrix interactions can produce changes in bone remodeling activity and bone mass. However, to accelerate progress toward this goal, there is a need to refine the understanding of known cell-matrix interactions and identify new interactions with important roles in the maintenance of skeletal health.

PLANNED IMPLEMENTATION STRATEGIES

NIH will use existing mouse strains and cell culture systems to (1) determine the effects of matrix proteins on the generation of osteoblasts from precursors and on the survival of the cells, (2) identify the biochemical pathways within cells that mediate the effects of the proteins, (3) identify the specific portions of the proteins that are responsible for the effects, and (4) identify the molecules on the surface of cells that interact with matrix proteins. This strategy is important to achieving this goal for several reasons. First, cell cultures allow for very precise measurements of biological effects, at low cost. Detailed knowledge of the effects of matrix proteins on isolated cells is the first requirement for predicting the effects of drugs that either mimic or block

the cell-matrix interactions. Second, identification of the active portions of the matrix proteins and the interacting cell proteins will allow for design of new drugs and selection of existing drugs for testing. Third, observations of genetically modified mice place the results of cell culture experiments in the context of the intact organism. This is essential because therapies would be applied in intact humans, where many factors are present that cannot be replicated in cell cultures.

NIH will also employ genetic engineering technology to generate new mouse strains: (1) mice that allow for visualization of matrix proteins in tissue samples and (2) mice in which the matrix proteins are produced in certain cells, at specific stages of development. Using new mouse strains will help determine the effects of matrix protein-osteoblast interactions at different stages of osteoblast development. This strategy adds to the information gained by the first strategy, placing the initial observations in the context of time and place. Knowing where and when the matrix proteins are produced in a normal mouse gives a rough idea of which cells must be targeted in designing a therapy and at what stage in cell development the effect is most critical. Producing the proteins at specific times and places by genetic technology establishes these parameters more precisely.

NIH will determine the physical and mechanical properties of bone from genetically modified mice. These measurements are necessary to assess the potential clinical significance of interventions based on interactions between bone cells and matrix proteins. Ultimately, therapies targeting osteoporosis are effective only if they improve the resistance of bone to fracture.

BASELINE(S)

- Skeletal health depends on the process of bone turnover, in which small regions of bone are broken down (resorbed) and then replaced with new bone. The regulation of the balance between bone resorption and new bone formation is critical to maintaining bone mass and preventing fracture. An excess of resorption over formation underlies many bone diseases, such as postmenopausal osteoporosis. Osteoblasts are the cells that form new bone during bone turnover. Understanding how the number and activity of osteoblasts are controlled could lead to new therapies for restoring lost bone, either with drugs or by tissue-engineering approaches.

- Bone is composed of mineral crystals embedded in a matrix made up of many different proteins. To date, nine relatively abundant proteins have been identified in bone matrix, in addition to collagen, the principal structural component of bone. There is evidence that interactions between matrix proteins and proteins on the surfaces of osteoblasts produce signals that are important for osteoblast function. If known in detail, the mechanisms of these interactions could yield targets for new drugs that might act to stimulate bone formation.

- Two of the noncollagen proteins, thrombospondin-2 and osteonectin, have been selected for intensive study, based on evidence that they play important roles in the generation and survival of osteoblasts. Genetically modified mouse strains lacking either thrombospondin-2 or osteonectin have been generated. Mice lacking thrombospondin-2 have increased numbers of osteoblasts, whereas osteonectin-deficient mice have fewer osteoblasts than normal mice. Using cells isolated from the genetically modified mice, cell culture systems have been developed, in which the effects of thrombospondin-2 and osteonectin on osteoblasts and their precursor cells can be determined. These mice and cell culture systems are valuable tools for the strategies outlined below.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Characterize effects of the bone protein thrombospondin-2 on the generation of bone-forming cells from precursor cells in the bone marrow and identify regions of the thrombospondin-2 molecule that are required for the effects.	(FY02) Information on the role of thrombospondin-2 in bone generation is incomplete.	◆		
Identify biochemical pathways in bone-forming cells that are responsible for extended survival of cells on interaction with the bone protein osteonectin.	(FY03) Biochemical pathways that mediate cell survival are unknown		◇	
Identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation. Generate a genetically altered mouse strain in which a fluorescent protein is produced under the control of the same genetic elements that control the production of thrombospondin-2.	(FY03) Information incomplete on where thrombospondin-2 is produced; mouse model can provide this data			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

During the first year of the project, it was demonstrated that thrombospondin-2 acts early in the process of cell growth to promote the generation of bone-forming cells. The region of the molecule that is responsible for the effect has been distinguished from the region that inhibits the formation of fat cells, another aspect of thrombospondin-2 function. Investigators exposed marrow precursor cells to both normal thrombospondin and genetically engineered versions of thrombospondin that lacked specific regions of its structure. The presence of thrombospondin was required only at early stages of cell differentiation to promote bone formation. This is in contrast to the inhibition of fat cell formation, which occurs late in the process. Tests of the truncated thrombospondin molecules showed that the promotion of bone formation requires elements in the carboxy-terminal half of the protein, whereas the inhibition of fat cell formation requires elements in the amino terminal half.

Implementation Strategy Advances or Other Highlights

A collaboration has been established with the University of Wisconsin that will help develop new molecular tools that refine the analysis of the region of thrombospondin-2 that promotes bone formation. Results to date point to a region with a structure similar to that of proteins that interact with cellular components called integrins. If this is confirmed, existing tools for analysis of integrin function could be brought to bear on this project.

GOAL 8c) BY 2006, BUILD A PUBLICLY ACCESSIBLE COLLECTION OF REFERENCE SEQUENCES (REFSEQ COLLECTION) TO SERVE AS THE BASIS FOR MEDICAL, FUNCTIONAL, AND DIVERSITY STUDIES. A COMPREHENSIVE REFSEQ COLLECTION WILL SERVE AS A FOUNDATION FOR GENOMIC RESEARCH BY PROVIDING A CENTRALIZED, INTEGRATED, NONREDUNDANT SET OF SEQUENCES, INCLUDING GENOMIC DEOXYRIBONUCLEIC ACID (DNA), RIBONUCLEIC ACID (RNA) TRANSCRIPT, AND PROTEOME (PROTEIN PRODUCT) SEQUENCES, INTEGRATED WITH OTHER VITAL INFORMATION FOR ALL MAJOR RESEARCH ORGANISMS.

BACKGROUND

The Reference Sequence (RefSeq) Collection will provide a unified view of the genetic knowledge of organisms. A single, high-quality collection of reference sequences for multiple species that is richly annotated and highly connected to other information sources will make it possible to undertake large-scale comparative analyses. The ability to make discoveries in one organism (such as mouse models of a human disease) and immediately apply them to another organism (such as humans) is one of the most powerful aspects of molecular biology. The academic and pharmaceutical research communities use reference sequences in this way to investigate basic molecular biological processes and medical problems, such as different disease susceptibilities for individuals or targeted individual drug treatment approaches. The availability of a RefSeq Collection means that time once spent identifying resources, gathering data, and reviewing its quality is freed for research.

Rationale

Hundreds of millions of dollars have been invested by Federal agencies, international governments, and charitable foundations to obtain genomic and transcript sequence data for organisms, from human to viruses. Although a wealth of sequence data is now available, these data exist in multiple formats, and locations and are not connected to other information; furthermore, the data produced by different groups are often redundant, inconsistent, or partially overlapping. Without a cohesive representation of the data, it is difficult to reap the full benefit of the massive public investment in obtaining the data. The RefSeq Collection will serve as a foundation for genomic research by providing a centralized sequence set integrated with other information, including publications, phenotypes, and disease catalogs. This collection must be built and maintained through both computational and expert analysis to integrate large quantities of disparate data while also providing a high-quality resource. Both the computational and expert tasks must be ongoing so that (1) the collection stays current as new data become available, (2) quality is ensured, and (3) new opportunities that add value are identified.

PLANNED IMPLEMENTATION STRATEGIES

The RefSeq project will expand and enhance its access to the general biomedical research community. RefSeq is intended as the most comprehensive and stringently reviewed collection of gene sequences publicly available with a broad domain of applications, from investigating the function of single genes to assisting in the conduct of large-scale comparative analyses of genes across multiple organisms. With the introduction of the Web-based Genes database, NIH will be providing the 20,000 users who daily search for sequence information with a highly interactive and powerful means of accessing a unified and richly annotated view of sequence and gene data.

To facilitate more sophisticated and specialized uses of RefSeq, the database will be available for complete downloading to allow commercial or academic groups to generate value-added versions of the database to target specialized or species-specific audiences and allow them to perform exhaustive analyses across the entire data set. Through extended development of the suite of RefSeq analytic tools, NIH intends to increase

by many times the number of scientists who will be able to carry out computationally sophisticated analyses on the RefSeq Collection without the need for programming skills.

Finally, methods will be developed to foster collaborations with outside groups to augment the public data. These collaborations will include whole-genome annotation, functional annotation of multigene families, expert review of single genes, and annotation of single records from multiple sources. Related resources at NIH for functional gene information include the Comparative Toxicogenomics Database, the Encyclopedia of DNA Elements and Mammalian Gene Collection, the Cancer Genome Anatomy Project, and the database of eye-related genomic information.

BASELINE(S)

- The initial phase of the RefSeq project focused on developing infrastructure for processing and accumulating data. At the end of FY 2002, the RefSeq Collection included approximately 446,000 protein records from numerous organisms. Data accumulation continues.

- One goal of the RefSeq project is to provide expert analysis, either through collaboration or by review of the sequence data by the in-house staff, to ensure data quality and accuracy as well as to add functional information. RefSeq "status" codes are provided to track this progress; records that are marked as "reviewed" or "validated" have been checked for sequence accuracy. At the end of FY 2002 there were approximately 34,000 human RefSeq protein records, 6,800 of which had undergone curation. Curation figures are not available for the full collection for this time period.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Make the RefSeq Collection database available for downloading to enable commercial or academic groups to perform exhaustive analyses across the entire RefSeq Collection data set.	(FY02) At the end of FY02, the RefSeq collection included 446,000 proteins and was not available for FTP	◆[e]		
Develop the infrastructure to support wider access to the RefSeq Collection via the Internet to provide users with a centralized set of annotated sequence information.	(FY03) RefSeq collection includes sequence data from 2124 species; only a limited database is available		◇	
Expand the project to include outside groups to increase the amount of sequence and functional information in the database. Collaborations will provide additional reference sequence records, whole-genome annotation, functional annotation of multigene families, and expert review of single genes.	(FY03) About 40 collaborations in place for obtaining annotated RefSeq records and other functional data			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

NIH has implemented the database and software infrastructure to provide the RefSeq collection for file transfer protocol (FTP) download in a regular release cycle. The RefSeq release includes quality control measures, extensive documentation, and user support in addition to the reference sequence records.

The first RefSeq release (RefSeq Release 1), representing the entire RefSeq collection generated at that time, was made available for anonymous FTP in July 2003; ongoing additions and updates to the RefSeq collection are also provided for FTP. FTP downloads of the RefSeq release data are monitored; over 44,000 files were downloaded after the first release, demonstrating the utility of these data.

The RefSeq FTP release provides significant support to commercial and academic groups that are interested in carrying out analysis across the entire collection or a subset of the collection or including the RefSeq collection in a commercial product. The RefSeq FTP release is structured to support groups that are interested in the complete collection as well as those interested in a smaller subset. The data provided include statistics, documentation, and a catalog of the sequence records provided; the catalog supports independent quality control checks on the sequence records available for FTP.

Implementation Strategy Advances or Other Highlights

To generate a file-based distribution format for the RefSeq collection, a database, software, and a series of processing steps were developed. The content of the database was processed to produce multiple sequence files divided into different categories of interest and different file formats. A quality control procedure was established to detect and correct any errors and omissions prior to file release. Documentation was also written to accompany the files on the FTP site and for the RefSeq Web site. Users can subscribe to an e-mail announcement service to receive notices of releases and updates. As an indicator of the success of the FTP distribution format, over 44,000 files were downloaded following the first release.

Feedback from groups using the RefSeq FTP release data has been positive and has identified an area where additional support would be advantageous. Therefore, additional software development is planned to provide more specific downloads of user-defined subsets of the collection.

At the end of FY 2003, the RefSeq collection included 831,287 proteins and 2,124 species; the number of proteins included nearly doubled over a 1-year period. The RefSeq collection continues to expand both in terms of the number of sequences included in the collection and the number of organisms. Significant growth is expected to continue apace with the numerous genome sequencing projects planned for the next several years. The table below shows the growth in the database during a 1-year period.

	NUMBER OF SPECIES	NUMBER OF RECORDS	NUMBER OF PROTEINS
As of October 2002	Not tracked	Not tracked	446,000
As of October 2003	2,124	1,097,404	831,287

Efficiency

The archival sequence database, GenBank, contains millions of records representing the accumulation of sequence data over many years. In contrast, the RefSeq collection provides an organized distillation of the current state of genomic sequence knowledge. In using the RefSeq collection, scientists can quickly identify and compute on the best available data and only drill down to the archival sequence data available in GenBank. Thus, the availability of the RefSeq collection by FTP provides a way for thousands of U.S. scientists to use their valuable research time more efficiently.

GOAL 8d) BY 2009, ASSESS THE IMPACT OF TWO MAJOR INSTITUTIONAL DEVELOPMENT AWARD (IDEA) PROGRAMS ON THE DEVELOPMENT OF COMPETITIVE INVESTIGATORS AND THEIR CAPACITIES TO COMPETE FOR NIH RESEARCH FUNDING.

BACKGROUND

The Institutional Development Award (IDeA) Program was authorized by the NIH Revitalization Act of 1993 to foster health-related research and increase the competitiveness of investigators at institutions located in States with historically low grant awards from NIH. An institution's eligibility to participate in the IDeA Program is determined by the aggregate level of NIH grant funds collectively received by all research institutions within its State over the preceding consecutive 5-year period and/or the average success rate of research applications over that same time span. Between 1997 and 2001, States that received on average less than $75 million in NIH grant awards and/or had a success rate of less than 20 percent were eligible for the IDeA Program.

The IDeA Program was established in FY 1993 at a funding level of $750,000, which slowly increased to $10 million in FY 1999. This limited funding precluded development of major initiatives. However, in FY 2000, funding increased to $38.5 million, which allowed for the development and implementation of a more comprehensive initiative, the Centers of Biomedical Research Excellence (COBRE). The COBRE initiative was specifically designed to enhance the pool of well-trained investigators who could successfully compete for NIH grant awards. This initiative augments and strengthens institutional biomedical research capacities by expanding or modifying research facilities, equipping laboratories with modern research equipment, mentoring of promising candidates, and developing research faculty through support of a multidisciplinary center, led by a peer-reviewed, funded investigator with expertise central to the research theme of the center.

The FY 2001 appropriation for the IDeA Program increased to $100 million and this allowed for the development of a second initiative, the Biomedical Research Infrastructure Network (BRIN). BRIN enhances the pipeline for outstanding students and bolsters the quality of science faculty at baccalaureate and other participating institutions. The BRIN is intended to network research intensive and undergraduate institutions in IDeA states to prepare students for graduate and professional schools as well as for careers in the biomedical sciences.

In FY 2003, the appropriation for the IDeA Program was $209 million. It is anticipated that future funding will remain at or above this level.

Rationale

Strong congressional interest in the IDeA Program, along with significant increases in funding, has led to questions about whether the biomedical research capabilities of institutions in IDeA-eligible States will be enhanced and whether this will lead to increased competitiveness of investigators to obtain either NIH research grants or other Federal or non-Federal support. An evaluation will assess the impact of the IDeA Program on the acquisition of NIH research funding as a percent of total NIH funding by the cohort of eligible States and will determine the factors that have had the greatest impact on enhancing investigator competitiveness.

PLANNED IMPLEMENTATION STRATEGIES

A database will be developed for the annual progress report to collect potential indicators based on previous related NCRR evaluations and the pre-COBRE analysis findings.

Two separate evaluations, one for COBRE and another for BRIN, will be conducted to assess the IDeA Program. Each will consist of an evaluation design study followed by the full-scale evaluation. The evaluation design studies will include an assessment of data needs, site visits, data collection, data analysis, and a final report. Expert panels will provide advice throughout the evaluations.

Step 1 of the Assessment Methodology for the IDeA Program will consist of completing the evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact and developing a data collection system for BRIN. Step 2 will consist of completing the evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact and assessing the results of the COBRE evaluation design study.

Since the COBRE began before BRIN, the two evaluations will be conducted at different intervals. The evaluation design study for COBRE will be completed in FY 2004 and that for BRIN will be completed in FY 2005. The full-scale evaluation for COBRE will be completed in FY 2008 and that for BRIN will be completed in FY 2009.

The purpose of each evaluation design study will be to determine the best strategy for evaluating the program. Consideration will be given to determining the indicators that optimally assess whether the research competitiveness and research capacity of the institutions has increased. Some target indicators have been proposed:

INDICATOR	INDICATOR
Publications	Biomedical/behavioral grant submissions and awards
Presentations	NIH biomedical/behavioral grant submissions and awards
Recruited Faculty	Research personnel and research administration staff
Newly Constructed Laboratory Space	Investigators whose research has become independent of COBRE

The extent to which these indicators provide a sound measure of research competitiveness and research capacity will be assessed, and the availability and reliability of such data will be determined. Further, the annual progress reports that collect potential indicator data will be used to validate the list of indicators developed through the evaluation design study. Whether or not these indicators should be measured at the state, institutional, and/or center level will be determined by the design studies.

Following completion of these evaluation design studies, the full-scale evaluations of COBRE and BRIN will be conducted to determine the impact of the IDeA program.

BASELINE(S)

- Previous evaluations of NCRR programs that address the needs of non-research intensive institutions identified target indicators which are available for use in the IDeA evaluation.

- In FY 2002, an assessment of the initial IDeA Program was conducted to determine its impact from FY 1993–1999. Despite the relatively small amount of funding provided during those years, this pre-COBRE analysis identified indicators that demonstrated the program impact. However, these potential indicators will be assessed through the development of the data collection and management system.

- A review of the NIH IMPAC system data, grant applications, summary statements, and annual progress reports provides other potential target indicators for consideration.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Develop a data collection and management system to allow for the retrieval of potential target indicators to evaluate the impact of the IDeA/Centers of Biomedical Research Excellence (COBRE) Program.	(FY02) Indictors from Pre-COBRE analysis and previous evaluations.	◆		
Assessment Methodology for IDeA Program (Step 1): • Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact. • Develop a data collection system for BRIN.	(FY03) Data collection and management system to evaluate impact of IDeA/COBRE in place. (FY04) Indicators from IDeA/COBRE evaluation design.		◇	
Assessment Methodology for IDeA Program (Step 2): • Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact. • Assess results of COBRE evaluation design study.	(FY04) Data collection and management system to evaluate impact of IDeA/BRIN in place. (FY04) COBRE evaluation design completed but not evaluated.			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

A data collection and management system was designed, tested, implemented, and launched in May 2003. This database captures the following potential target indicators: number of presentations, publications, NIH grant submissions and awards, other grant submissions and awards, investigators whose research has become independent of COBRE support, recruited faculty, research personnel and research administrative staff members, and amount of newly constructed laboratory space. The evaluation design, when completed, will refine these indicators, and the database will be revised accordingly. This database will be used to monitor the IDeA Program's progress toward increasing the capacities of institutions to conduct research and expanding the pool of NIH-supported investigators. The success of this program, as demonstrated by the indicators, will serve as a building block toward increasing the research potential of the Nation.

Implementation Strategy Advances or Other Highlights

To assist in measuring the impact of IDeA/COBRE on the development of competitive investigators and their capacities to compete for NIH research funding, two contracts have been put in place. One contract deals with design and maintenance of a data collection and management system; the second focuses on conducting an initial COBRE evaluation design, which will identify the data needed to conduct the IDeA/COBRE full-scale evaluation. Using the database, NIH will be able to confirm the validity of potential target indicators needed to determine their impact on research competitiveness and research capacity. The COBRE evaluation design is anticipated to be completed in FY 2004 and will be followed by a full-scale evaluation that is anticipated to be completed in FY 2008. The BRIN evaluation design is anticipated to be completed by FY 2005 and will be followed by a full-scale evaluation that is anticipated to be completed by FY 2009.

GOAL 9a) BY 2010, DEMONSTRATE THROUGH RESEARCH A CAPACITY TO REDUCE THE TOTAL YEARS LOST TO DISABILITY (YLDS) IN THE UNITED SATES BY 10% BY (1) DEVELOPING TREATMENT ALGORITHMS TO IMPROVE THE MANAGEMENT OF TREATMENT-RESISTANT AND RECURRENT DEPRESSION AND (2) ELUCIDATING THE MECHANISMS BY WHICH DEPRESSION INFLUENCES AT LEAST TWO COMORBID PHYSICAL ILLNESSES (E.G., HEART DISEASE, CANCER, PARKINSON'S DISEASE, OR DIABETES).

BACKGROUND

Disease Burden

Mediated through the brain, mood disorders disrupt every facet of a person's life: emotions, thought processes, behavior, and physical health. In addition to the inherent effects of depression on health through sleep and appetite dysregulation, self-medicating substance abuse, and physiologic disturbances (e.g., sticky platelets) that are just beginning to be understood, major depression can significantly influence the outcome of comorbid general medical illnesses (illnesses that may be due to diseases other than the disease under study). Depression is seen frequently among people with coronary heart disease (CHD) and other cardiac illnesses; for example, among patients with congestive heart failure (CHF), estimates of the prevalence of major depression range from 17 to 37 percent. Untreated depression increases the risk of dying from heart disease by as much as six-fold. People with comorbid diabetes and depression have an eight times greater relapse rate than those with depression but without other medical conditions. The prevalence of major depression in patients after a stroke is approximately 20 percent, and estimates of lifetime rates of depression among persons living with HIV range from 22 to 45 percent.[1]

Rationale

The premise of this goal is that targeted research on these topics will have a significant impact on the overall reduction of YLDs associated with depression in two ways. First, although effective treatments benefit millions of persons with major depression, a significant proportion (50%) of persons are not helped or do not fully recover when given a standard pharmacological or psychosocial intervention. Treatments for depression occurring in the context of other general medical illnesses would benefit from refinements to clarify possible subtypes of depression and how treatments affect multiple disease processes. The quality of care available to persons with resistant depression, as well as treatments for persons with depression comorbid with other medical illnesses, will improve as (1) knowledge of the causes and processes of depression expands, including the genetic, environmental, behavioral and cultural risk and protective factors; (2) treatments—both psychosocial and pharmacological—become more refined and targeted, with initial treatments increasingly effective in reducing residual symptoms and maintenance treatments characterized by fewer adverse effects; and (3) strategies are developed for protecting individuals from relapse and recurrence.

Second, achievement of this goal will contribute to a capacity for reducing YLDs as research addresses questions about the close association between depression and physical illnesses, such as CHD, stroke, and diabetes, to name a few. This research is particularly critical since most individuals seek treatment for depression in the primary care setting. Despite the increased risk of depression in the presence of a number of other medical illnesses (e.g., CHD, diabetes), depression is not sufficiently recognized and inadequately treated, particularly over the chronic course of the illness. To prevent depression, research is under way to try to understand the relationship between this brain disorder and physical illnesses such as stroke and CHF.

[1] The Strategic Plan for Mood Disorders Research of the National Institute of Mental Health. NIH Publication No. 02-5121.

Although effective depression treatments are currently available, only an estimated 51.6 percent of patients received health care treatment for major depressive disorder, and of those receiving treatment, only 41.9 percent obtained adequate treatment.[1] Rates of underutilization are higher for persons of color, elderly persons, youth, and young and middle-age males.[2] Although several models of care have proven effective in delivering adequate depression treatment, the uptake and maintenance of this delivery of care remain poor. A major Men and Depression awareness campaign is under way to increase public and health care provider knowledge of symptoms of depression and the availability of treatment.

PLANNED IMPLEMENTATION STRATEGIES

Several strategies are planned. First, NIH seeks to identify predictors of treatment response at various points throughout the course of illness. Second, NIH plans to test interventions that produce longer recovery periods for those most at risk for relapse in community populations. Third, NIH plans to identify five factors that have an impact on effective and sustainable dissemination and implementation of scientific findings at multiple environmental levels. Fourth, NIH plans to identify three genes that produce vulnerability to depression and study gene-environment interactions. Finally, NIH anticipates identifying the mechanisms and processes by which depression has a relatively large influence on the course or outcome of a comorbid disorder associated with disability or premature mortality.

BASELINE(S)

- It is now understood that a single gene does not cause any mental disorder or determine any behavioral variant. The concept of the causative gene has been replaced by that of genetic complexity, in which multiple genes act in concert with environmental factors to produce a risk of mental disorder. Discoveries in genetics and neuroscience can be expected to lead to better models that provide improved representation of the complexity of the brain and behavior and the development of both. Knowledge of the timing of the expression of risk genes during brain development and of their function should not only contribute to an understanding of gene action and the pathophysiology of disease but also help direct the search for modifiable environmental risk factors that convert risk into illness. The function of risk genes can become comprehensible only in the context of advances at the molecular, cellular, and systems levels in neuroscience and the behavioral sciences. Genetics should yield new therapies aimed at not only symptoms but also pathogenic processes, thus permitting the targeting of specific therapies to individual patients.

- Depression is seen frequently among people with CHD and other cardiac illnesses. For example, the prevalence of depression among patients with CHF ranges from 17 to 37 percent; cardiac and vascular illnesses also have a high prevalence among depressed persons (approximately 20% for people with stroke). To unravel the riddle of whether depression causes heart disease or heart disease causes depression, scientists are starting with a suggested common link—changes in the blood vessels of people as they age. Evidence for causation will be identified if studies show a correlation between vascular changes and subsequent depression.

- The failure of depressed patients to respond satisfactorily to an adequate clinical trial of antidepressant medication or psychotherapy (an estimated 50%) and the frequency with which patients are left with unresolved symptoms or impairments (an estimated 20%) are important issues, because residual symptoms are associated with significant functional impairment and substantially increase the risk of relapse and recurrence. Estimates from clinical populations indicate that patients with major depression will experience an average of four lifetime episodes of 20 weeks each in duration, with the risk increasing with each episode. Those with at least three prior episodes show relapse rates of 70 to 80 percent. Thus, it is extremely important to find the most effective treatment for the individual. A series of clinical trials are currently under way that match patients' responses to different treatments. Correlating the biological

[1] Kessler R et al. The epidemiology of major depressive disorder. JAMA. 2003 Jun 18; 289(23):3095-105.
[2] *The Strategic Plan for Mood Disorders Research of the National Institute of Mental Health*. NIH Publication No. 02-5121.

and psychological characteristics of patients with differential responses to treatment allows for customizing treatment and decreasing the likelihood of recurring depression.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Identify at least one biological (gene-environment) interaction that has high probability of contributing to depression.	(FY02) Known that stress linked to depression but interaction not known	◆		
Determine whether vascular changes related to aging contribute to depression.	(FY03) Subcortical lesions, common in elderly with depression and in vascular disease, are being studied as potential cause of depression		◇	
Determine at least four characteristics that help identify subgroups of people with depression who respond differentially to existing treatments.	To be determined			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target has been met because of an exciting breakthrough in depression genetics research. NIH-funded researchers, studying conduct disorder and depression in young adults, found a link between a specific gene and the development of depression. They discovered the connection because they examined an environmental factor—the stress history of the study participants. The gene is a chemical transporter called 5-HTT, which regulates transmission of serotonin, the neurotransmitter affected by Prozac and other SSRI-type medications. The gene comes in two versions: the long allele and the stress-sensitive short allele. Previous studies in mice and monkeys, as well as brain imaging studies in humans, indicated that, in stressful situations, those with two "long" alleles were better able to handle stress than those with two "short" alleles. The gene has been a prime suspect in mood and anxiety disorders, but its link to depression eluded detection in eight previous studies. It was only when the researchers compared short and long alleles of the genes with the stress histories (psychosocial traumas in peoples' lives) that they made an exciting breakthrough. The 17 percent with two short alleles (one inherited from each parent) and increased number of life stressors were more likely to develop depression and to have thought about or attempted suicide. People possessing two long alleles (31%) were more resilient to stressful events and much less likely to develop depression or contemplate suicide.

This clear interaction between genetic vulnerability and environmental events holds great promise for developing treatments that can manipulate the gene's activity and behavioral interventions that decrease the environmental influence. This finding also will have a major impact on research in other psychiatric diseases and the search for their causes.

Planned Implementation Strategies

The three large NIH-supported research centers that focus on the study of mood and anxiety disorders and the multi-site Collaborative Study on Depression are instituting programs to collect genetic data that can be compared with environmental risk factors. Other studies are looking at nonhuman primate behaviors that parallel behavioral and temperamental traits linked to anxiety and depressive disorders in humans, such as fearfulness, behavioral inhibition, propensity toward distress, and reactivity. These studies will advance the understanding of the various genes and gene-environment interactions that may influence vulnerability to depression.

Major depression is associated with significant changes in neuroendocrine and autonomic activity. Such changes can place depressed people at increased risk for physical diseases. Conversely, some physical diseases may contribute to the onset of depression. Investigators are using various approaches to study the

mechanisms involved: imaging studies examine whether decreased flow of blood to specific areas of the brain may be a risk factor for late-life depression; other studies explore the possibility of chronic stress causing atrophy in the hippocampus (memory center) and the effect of stress on the vascular and immune systems; prevention clinical trials test patients at risk for depression (e.g., coronary artery bypass patients) to determine whether early drug treatment forestalls the development of postsurgical depression;and treatment trials study patients with comorbid conditions (a physical illness and depression) to determine which specific classes of drugs and/or psychosocial therapies are most effective for which comorbid diseases.

NIH is funding several large multisite clinical trials to help answer these treatment questions. For example, one long-term study will help decide which treatments work best for major depression if the first medication does not produce an acceptable response. Other trials will help establish whether genetic factors account for differences in response to medications in various subpopulations. Another study focuses on how best to treat adolescents who fail to respond to the first SSRI antidepressant they have tried and includes a test group receiving cognitive behavioral therapy combined with medications. The overall goal is to develop customized treatments that will enable durable recovery from depression.

GOAL 9b) BY 2010, IDENTIFY CULTURALLY APPROPRIATE, EFFECTIVE STROKE PREVENTION PROGRAMS FOR NATIONWIDE IMPLEMENTATION IN MINORITY COMMUNITIES.

BACKGROUND

Disease Burden

Although stroke remains the third leading cause of mortality in the United States and the leading cause of adult disability, the burden of stroke is greater among minority racial/ethnic groups by virtue of its higher incidence and mortality in these populations. The incidence of ischemic and hemorrhagic stroke is disproportionately high in the African American population and occurs at younger ages; moreover, these disparities may be increasing.[1] Mortality from stroke among African Americans is nearly twice that of Caucasian Americans.[2] Moreover, among several minority racial/ethnic groups (including African Americans, Hispanic Americans and Native Americans), the disparity in stroke mortality (both ischemic and hemorrhagic) is especially evident among younger individuals ages 45 to 64 years.[3] However, the burden may be even greater than the stroke incidence and mortality rates indicate. Initial evidence suggests that African Americans may experience more severe strokes and greater residual physical deficits, although these deficits may not be fully reflected in impairment of the ability to perform activities of daily living.[4] It remains to be determined whether other minority racial/ethnic groups also experience more severe and disabling strokes than Caucasians.

Rationale

There is a wide range of hypothesized causes of the excess stroke mortality in the southeastern United States (the "Stroke Belt") and among African Americans. The prevalence of stroke risk factors and the potential impact of reducing those factors vary among racial/ethnic groups, with potentially greater impact associated with reduction or elimination for minorities.[5] Patterns of accessing the existing health care system for acute stroke also vary among racial/ethnic groups; for example, minorities are less likely to use the emergency medical system when experiencing a stroke.[6] The reasons for these racial/ethnic variations in stroke-related risk factors and utilization of health care are not fully understood, but they should be to identify the most effective stroke prevention and treatment programs for minority communities. Prevention programs are a preferred strategy for reducing or eliminating the observed racial/ethnic disparities in stroke and include both primary and secondary prevention approaches. Primary prevention programs target stroke risk factors to reduce the occurrence of stroke. Secondary prevention programs seek to improve access to timely acute stroke care, thereby reducing mortality and morbidity, and target the use of interventions to prevent recurrent stroke in stroke survivors.

The DHHS Research Coordination Council (RCC) has identified the research theme Understanding Health Disparities—Closing the Gaps as a priority for FY 2004 and, in its stated priority areas, has recognized the need to understand factors contributing to disparities in the development of diseases, injuries, and disabilities; improve detection and diagnosis of diseases that contribute to health disparities, such as stroke; improve

[1] Kennedy BS, Kasl SV, Brass LM, VAccarino V. Trends in hospitalized stroke for blacks and whites in the United States, 1980-1999. Neuroepidemiology. 2002 May-Jun; 21(3):131-41; Sacco RL et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. Am J Epidemiol. 1998 Feb 1;147(3):259-68.
[2] Ayala C et al. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995-1998. Am J Epidemiol. 2001 Dec 1;154(11):1057-63.
[3] Ayala C et al. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995-1998. Am J Epidemiol. 2001 Dec 1;154(11):1057-63.
[4] Kuhlemeier KV, Stiens SA. Racial disparities in severity of cerebrovascular events. Stroke. 1994 Nov;25(11):2126-31; Jones MR et al. Racial variation in initial stroke severity. Stroke. 2000 Mar;31(3):563-7; Horner RD, Matchar DB, Divine GW, Feussner JR. Racial variations in ischemic stroke-related physical and functional impairments. Stroke. 1991 Dec;22(12):1497-501.
[5] Sacco RL et al. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. Stroke. 2001 Aug;32(8):1725-31.
[6] Lacy CR, Suh DC, Bueno M, Kostis JB. Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). Stroke. 2001 Jan;32(1):63-9.

approaches to delay onset or prevent diseases, injuries, and disabilities that contribute to health disparities; improve treatments for diseases and disabilities that contribute to health disparities; expand research using bioinformatics and genomics, including pharmacogenomics, in addressing health disparities; and enhance research on the intersection between nongenetic and genetic factors in health disparities. In addition, eliminating health disparities is one of the two stated goals of *Healthy People 2010*, the disease prevention agenda for the Nation.

PLANNED IMPLEMENTATION STRATEGIES

NIH will establish a program to create Nursing Partnership Centers to reduce health disparities. These Centers will establish collaborations between research-intensive schools of nursing and minority-serving university schools of nursing to address health disparities, including stroke. The Centers will focus on influential factors that reduce health disparities, such as ways to promote healthy behaviors, reduce risks that contribute to chronic diseases, and develop ethnically and culturally sensitive health care interventions. Qualifying minority-serving institutions, either in the United States or in territories under U.S. jurisdiction, are those in which students of minority groups who are underrepresented in nursing research (e.g., African American, Hispanic American, Native American, Alaska Native, Native Hawaiian, Pacific Islander, Asian American, and Philippine nurses) constitute a significant proportion of the enrollment and have a track record of commitment to the special encouragement of minority faculty, students, and investigators. It is expected that 6 to 7 partnerships, 12 to 14 5-year awards, will be funded.

To develop sustainable, replicable, and culturally appropriate prevention and intervention research programs targeted to minority populations and designed to decrease the incidence and prevalence of stroke, NIH will establish a Stroke Prevention/Intervention Research Program (SPIRP) at a minority institution. The Program will identify more effective methods of implementing, within diverse communities, stroke prevention programs that are based on current and new knowledge. Over a 2-year period, the first phase of the program will establish an infrastructure for the SPIRP, including recruitment of the SPIRP director; create mechanisms of support and evaluation activities; establish collaborations with recognized external programs in stroke; and initiate pilot studies of stroke prevention/intervention programs. The second phase will establish collaborative stroke prevention research projects to include community-based interventions, epidemiology, and/or outcome measures; and, ultimately, the SPIRP will identify effective, community-based stroke prevention and intervention strategies for export to and adaptation in other diverse communities.

Building on several years of experience with an acute stroke research and care center in the Washington, D.C., metropolitan area, another hospital, which serves predominantly nonwhite, Hispanic, and Latino populations, will be recruited to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and the effectiveness of treatments and quality of care within the specific racial/ethnic communities served by the hospital. The study also will address how to tailor stroke prevention and intervention programs to those populations. After contracting with the hospital and developing the infrastructure to recruit and treat patients, subprojects will be initiated to assess barriers to acute care and risk factor profiles of stroke patients from the minority community served and design prevention/intervention activities to address those barriers. The last phase to be implemented will determine the feasibility of and establish protocols for using community patterns to identify points of intervention and intervention strategies and evaluate the effectiveness of the intervention strategies.

NIH will establish an Alaska Native Stroke Registry to monitor stroke incidence, prevalence, mortality, and risk factor data that could be used to improve stroke prevention and the quality of stroke care provided to Alaska Natives. This multiyear, long-term project will develop and implement a pilot stroke registry, targeting Yupik Eskimos living in the Yukon-Kuskokwim Delta and Bristol Bay service units, to establish registry infrastructure and data gathering methods. If successful, the registry will be expanded statewide. Ultimately, strategies will be identified to reduce risk factors and develop statewide prevention intervention programs.

BASELINE(S)

- Numerous clinical studies and trials focusing on stroke in minority communities are under way, including Stroke Surveillance in a Biethnic Community in southern Texas; Stroke Incidence and Risk Factors in a Tri-Ethnic Region in northern Manhattan; Arch Plaques and Stroke in an Ethnically Mixed Community in northern Manhattan; Hemorrhagic and Ischemic Stroke Among Blacks and Whites in a metropolitan population; MRFASS: Minorities, Risk Factors, and Stroke Study in blacks and Hispanics; Recurrent Stroke Risk in Minorities, which will follow blacks and Hispanics for 2 years poststroke; Secondary Prevention in Small Subcortical Strokes, a small pilot trial on subcortical strokes in Mexican Americans; and a large, 5-year epidemiological study of the Stroke Belt, a region where the occurrence of stroke is exceptionally high, especially among African Americans.

- Much is already known about modifiable risk factors, but the development and testing of programs targeted to modifiable risk factors (e.g., hypertension prevention, smoking cessation) in specific populations (e.g., improving exercise among minority groups, secondary prevention among diabetics) are needed. NIH has recently launched an initiative to stimulate research utilizing community-partnered research interventions to reduce health disparities by building on existing community resources, knowledge, skill, and attributes; engaging community members in actively identifying and addressing key health issues and concerns; facilitating the building of trusting relationships between the research community and the target population; and enhancing the likelihood of long-term sustainability.

- NIH supports several centers that focus on health promotion and stroke prevention in targeted populations, including the understanding, development, and testing of self-management nursing care strategies that promote health and enhance quality of life for individuals and families at risk, such as smoking cessation and exercise promotion for low-income women and strategies for reducing cardiovascular risk in children.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Establish a 5-year program to create about 12 to 14 Partnership Centers to Reduce Health Disparities that will focus on influential factors that reduce health disparities.	(FY02) Piloted programs to build nursing center research capacity focused on health disparities	◆[e]		
Establish a minority-focused, acute stroke research and care center to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and quality of care within the specific racial/ethnic communities being served by the care center.	(FY03) Acute stroke center exists but is not focused on stroke disparities or in a minority community		◇	
Establish the infrastructure for a Stroke Prevention and Intervention Research Program (SPIRP) at a minority institution.	(FY03) Minority institution research /training programs exist but not on stroke prevention/intervention			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

NIH has established a 5-year program to create Nursing Partnership Centers (NPCs) to reduce health disparities. Seventeen Partnerships Centers have been set up linking research-experienced nursing schools with minority-serving nursing schools across the Nation. The establishment of these Centers was announced in November 2002 with funding commencing in FY 2003. The establishment of these Centers moves NIH toward accomplishing the overall stroke prevention goal by establishing a national network of NPCs, which can be used to develop and test culturally appropriate, effective stroke prevention interventions that can ultimately be implemented in minority communities nationwide.

Implementation Strategy Advances or Other Highlights

Progress has been made on the FY 2004 target for establishing a minority-focused, acute, stroke research and care center. A RFP for this program was issued by NIH in January 2003, and a contract was awarded to the Washington Hospital Center on September 30, 2003. The hospital is currently recruiting medical staff members for the program and developing the infrastructure to recruit and treat patients.

In support of the FY 2005 target NIH awarded a cooperative agreement grant to the Morehouse School of Medicine in Atlanta, Georgia, in June of 2003 to establish a Stroke Prevention and Intervention Research Program (SPIRP).

Progress toward achieving the overall Goal 9b has been shown by the Nursing Partnership Centers, which have initiated pilot intervention studies devoted to preventing, reducing, or ameliorating health behaviors associated with stroke mortality in the United States among racial/ethnic minority populations. These studies aim to reduce the incidence or delay the onset of diabetes in Mexican-Americans and American Indians, improve the physical activity of older African American adults with chronic health conditions, determine what values and beliefs are associated with African American women seeking treatment when they have signs and symptoms of heart disease, and map the sources of tobacco and its utilization among native Hawaiians.

Another notable achievement relevant to the overall goal is the establishment of six prevention and education outreach projects, called Enhanced Dissemination and Utilization Centers (EDUCs), to improve cardiovascular health in high-risk communities (defined as communities whose coronary heart disease and/or stroke death rates rank in the top 15% nationwide). The EDUCs were established to address the growing health disparities in cardiovascular disease by involving strong community-based organizations as well as health systems.

Finally, two additional program highlights of relevance to the overall goal were 1) the release of a Program Announcement in August, 2003 on “Reducing Health Disparities Through Risk Factor Self-Management,” which encourages research aimed at identifying effective, culturally acceptable interventions involving self-management of risk factors for first and recurrent stroke for members of minority populations, and 2) the release of a Request for Applications in September 2003 on “Interventions to Improve Hypertension Control in African Americans,” which encourages grant submissions to evaluate clinically feasible interventions to effect changes in medical care delivery leading to an increase in the proportion of treated hypertensive African American patients whose blood pressure is controlled.

Efficiency

The NIH initiative soliciting applications for the Partnership Centers anticipated funding 12 to 14 Centers, with a total annual budget of $3 million. However, NIH was able to fund 17 Centers for the same amount because of the development of more efficient budget requests from the funded Centers than were originally anticipated.

IV.B.2.b.2. Communication and Transfer of Results

Without the flow of information, important scientific findings would languish at the researcher's bench. The fruits of NIH's research activities—new knowledge about the causes and courses of diseases and the means to prevent, diagnose, and treat them—cannot affect human health unless that knowledge is disseminated. Scientific knowledge is the bedrock of evidence-based prevention and treatment programs. Thus, a core NIH function is to facilitate the communication of research findings to clinicians, the public health system, voluntary health organizations, and the public. Equally important is transferring knowledge to the private sector so that it can be used to develop products and technologies that benefit health. NIH's technology transfer program is one of the most active in the Federal Government.

The Public Health Service Act of 1944 authorized NIH and the other U.S. Public Health Service (PHS) agencies to collect and make available, through publications and other appropriate means, information relevant to the practical applications of research [Title III, Sec. 301 (1)]. In addition, the legislation that enables and directs the development of NIH programs emphasizes the important role NIH plays in informing the public about the results of health-related research. Similarly, the authorizing legislation for the NIH Institutes and Centers (ICs) includes "dissemination of health information" as an integral part of each IC's basic mission.

All of the NIH ICs conduct programs to collect, disseminate, and exchange information on medical and biological science, medicine, and health. The National Library of Medicine (NLM), the world's largest medical library, is a component of NIH and works closely with the ICs to ensure the effective communication of research results. NLM has a broad congressional mandate, not only to collect and organize the literature of the health sciences and to provide information services, but also, to develop programs to transfer the latest scientific findings to the scientific community, health professionals, researchers, and the general public worldwide.

The broad purpose of NIH's technology transfer activities is to facilitate and enhance the development of new drugs, other products, and methods of treatment that benefit human health by promoting the efficient transfer of new technologies resulting from NIH research to the private sector. Federal legislation empowers NIH to interact directly with industry to expedite the transfer of technological discoveries into commercial products that will benefit the public. In addition to improving public health, technology transfer contributes to the global competitiveness of the Nation's businesses and to the Nation's economic prosperity.

NIH patents technologies invented by its intramural scientists and issues licenses to organizations in the private sector that are willing and able to commercialize these inventions. To protect the public's research investment, NIH oversees licensee progress and the receipt of royalties from licensees. NIH has forged numerous partnerships with industry and other external research organizations, thereby enhancing its capacity to expedite the commercial application of these new technologies with the ultimate goal of improving the public health and advancing the research enterprise.

To achieve its full potential in this area, NIH faces a number of challenges, including (1) developing and communicating effective, well-articulated technology transfer policies, (2) building the organizational structure and partnerships necessary to facilitate technology transfer for NIH-supported investigators and measure outcomes, and (3) monitoring licensee activities and taking appropriate action against those who would infringe on NIH intellectual property rights.

NIH is proud that its first GPRA goal for technology transfer—to increase the number of scientists who have received training in technology transfer—was met 2 years earlier than planned. By 2001 almost two-thirds of NIH scientists had attended training seminars, and within the next fiscal year, the remaining two targets were met—to train approximately one-third of NIH scientists via a new Web-based training module and to incorporate the training module as a standard requirement for all new scientists at NIH.

Partnerships are as crucial to the communication and transfer of results as they are to generating new knowledge. Community-based and international partnerships are especially featured in the goals that follow, and these partnerships are important vehicles for gathering as well as for disseminating information.

GOAL a) BY 2008, REDUCE THE DISPARITY BETWEEN AFRICAN AMERICAN AND WHITE INFANTS IN BACK SLEEPING BY 50% TO FURTHER REDUCE THE RISK OF SUDDEN INFANT DEATH SYNDROME (SIDS).

BACKGROUND

The national "Back to Sleep" public health education campaign was launched in 1994 after the American Academy of Pediatrics (AAP) recommended back sleeping as the safest sleep position for infants younger than 1 year of age to reduce the incidence of SIDS. The campaign promotes placing babies on their backs to sleep and is led by NIH in collaboration with campaign sponsors AAP, Maternal and Child Heath Bureau (MCHB), SIDS Alliance, and the Association of SIDS and Infant Mortality Programs.

Rationale

Since the launch of the campaign, the SIDS rate has dropped by 50 percent. However, despite the overall success of the campaign, African American infants are placed on their stomachs to sleep much more often than white infants. Stomach sleeping is a major risk factor for SIDS, and the SIDS rate among African American infants is double that of white infants.

In September 1999 and April 2000, NIH and other campaign sponsors hosted a meeting of experts to identify strategies for reaching African American communities with "Back to Sleep" messages. Participating were representatives from various organizations, including the Alpha Kappa Alpha Sorority, Inc. (AKA), Women in the National Association for the Advancement of Colored People (WIN), the National Medical Association, the National Coalition of 100 Black Women (NCBW), and the Congress of National Black Churches, Inc.

The group was presented with general information on SIDS, and statistics illustrating the racial disparities in SIDS incidence and prevalence rates. Meeting participants proposed outreach and education strategies aimed at eliminating the racial disparity in SIDS rates. As a result, organizations developed the *Resource Kit for Reducing the Risk of SIDS in African American Communities* to help these organizations initiate SIDS risk reduction programs in their local communities. The kit contains culturally appropriate materials such as fact sheets and brochures to encourage people to lead discussion groups in various community settings on ways to reduce the risk of SIDS.

The first national training workshop on SIDS risk reduction using the resource kit was held on January 27, 2001, in Atlanta, Georgia. Approximately 50 participants convened to learn about ways to reduce SIDS.

Since then, these organizations have used their regional meetings to train colleagues on how to most effectively use the resource kit in each of their local communities. Regional trainings have been completed across the United States. Over 40 train-the-trainer sessions have been completed, with approximately 1,050 individuals trained. Once trained, chapter representatives returned to their regions to train other individuals on SIDS and the resource kit. Over 10,000 regional chapter or affiliate members have been trained to date.

PLANNED IMPLEMENTATION STRATEGIES

Three separate strategies have been developed to satisfy the overall goal of SIDS reduction in the African American community. First, regional summits will be held across the country to raise awareness and increase approaches to reducing SIDS incidence. Representative organizations will attend to ensure that appropriate guidance is delivered. A "train-the-trainer" approach will be used so that participants can transfer knowledge to their local settings. Culturally appropriate promotional materials will be developed that are targeted to African American communities. Second, after the last regional summit, NIH will conduct 250 participant

telephone interviews to determine outreach strategies that developed as a result of their participation. Feedback will steer decision-making on future summits, as well as assess effectiveness of strategic messages. Third, NIH will identify a minimum of six additional national organizations that can promote the "Back to Sleep" campaign in local communities. NIH will promote the collaboration of the new organizations with prior organizations to ensure that the most useful strategies are employed and targeted.

BASELINE(S)

- At the beginning of FY 2003, no large-scale summit meetings were known to exist that trained or motivated members of the African American community to reduce SIDS risk.
- Interviewing summit participants is an initiative that will capture the level of outreach activities that resulted from the summits. No interviews have been conducted to date.
- The three organizations currently participating in the SIDS reduction activities (i.e., AKA, NCBW, and WIN) will be used as a springboard to identify other similar organizations.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
In collaboration with African American organizations, community health and other local officials, and faith-based organizations, conduct regional summit meetings to train and motivate individuals who will implement SIDS risk reduction activities in their communities.	(FY02) No regional summit meetings were held prior to 2003	◆ e		
Conduct 250 interviews among the approximately 1,500 participants who attended the three summit meetings held in FY 2003 to determine that each summit resulted in a minimum of 50 outreach activities.	(FY03) No interviews have been conducted for this purpose		◇	
Continue to extend "Back to Sleep" campaign messages to African American populations through community-based collaborations/partnerships by involving a minimum of six national organizations in SIDS training and educational activities.	(FY03) Three participating national organizations			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The FY 2003 target was met. The summits were held in three regions of the United States that have both high rates of SIDS and large African American populations. The following is a list of the summit locations:

- NCBW as Host: Tuskegee, Alabama (January 31-February 1, 2003)
- WIN as Host: Los Angeles, California (March 14-15, 2003)
- AKA as Host: Detroit, Michigan (May 30-31, 2003)

A total of more than 1,300 people were trained on SIDS risk reduction techniques. The trainees, including parents, grandparents, childcare providers, health care providers, State health departments, community organizations, Partner members, city mayors and other local officials, and faith-based leaders, made a commitment to conduct SIDS risk reduction activities in their communities.

Implementation Strategy Advances or Other Highlights

In conjunction with Alpha Kappa Alpha Sorority, Inc. (AKA), the National Coalition of 100 Black Women (NCBW), and the Women in the NAACP (WIN), NIH formed the Partnerships for Reducing the Risk of SIDS in African American Communities to achieve this target. The leaders of these three organizations made a commitment to sponsor three summits featuring the NIH SIDS risk reduction campaign information and materials. Leaders and members of the AKA, NCBW, and WIN, participated in all three regional summits. The purpose of the summit meetings was to encourage the health and community leaders in each region to engage in SIDS risk reduction activities, build alliances within communities to assist in SIDS risk reduction activities, educate those with the power to make a change in policy or behavior, and create collaborative models and resources that can remain within communities.

Efficiency

Other African American outreach projects have emerged as a result of the Partnerships project. The National Coalition of 100 Black Women, Indianapolis Chapter in conjunction with the Indiana Black Expo held a SIDS-awareness campaign in Indianapolis, July 2003. The workshops were divided into two segments-community advocates including clergy, social service providers, county health departments, community health centers, child care providers; and medical/first response personnel including emergency medical technicians, law enforcement, fire fighters, health care providers. Approximately 100 participants attended.

Also in response to the summits, two additional events occurred in September 2003. The Sudden Infant Death Network of Ohio in conjunction with the Ohio Department of Health, the CJ Foundation for SIDS, the National Coalition of 100 Black Women, the Alpha Kappa Alpha Sorority, Inc., and the Women in the NAACP hosted a meeting in Cleveland and Columbus, Ohio. The meetings served as catalysts to encourage participants to conduct local SIDS risk reduction activities in African American communities. In total, nearly 200 participants attended.

GOAL b) **INCREASE AWARENESS AMONG THE GENERAL PUBLIC ABOUT THE SYMPTOMS OF STROKE AND THE NEED TO SEEK TREATMENT RAPIDLY BY PARTNERING WITH PROVIDERS AND VOLUNTEERS IN AT LEAST FIVE COMMUNITIES AND EXTENDING THE IMPACT OF THE CAMPAIGN, "KNOW STROKE.KNOW THE SIGNS.ACT IN TIME."**

BACKGROUND

Stroke places a major health burden on U.S. society in death, disability, and economic costs. About 700,000 new strokes (first and recurrent) are reported every year in the United States.[1] Stroke is the third leading cause of death[2] and is a leading cause of serious, long-term disability among adults. Stroke costs the United States $51.2 billion per year in direct and indirect costs.[3] To bring important health messages to the public and in response to the mandate by Congress in the FY 2001 House and Senate Appropriations Committee reports, the National Institute on Neurological Disorders and Strokes (NINDS) created the multifaceted communication effort "Know Stroke.Know the Signs.Act in Time." The campaign aims to increase awareness of the symptoms of stroke and the need for urgent action. Next year, NINDS will focus its campaign resources in at least five communities where the impact of stroke is particularly great.

In addition, NINDS will begin an outreach program targeted specifically to African Americans because the need for stroke information is especially important among this population. African Americans suffer strokes at a disproportionate rate and are more likely to die from them than other racial groups.

Stroke is a medical emergency. Rapid identification of a stroke is essential to treatment and positive outcomes. When given within 3 hours of the onset of symptoms, a clot-busting drug called tissue-type plasminogen activator (t-PA) can reduce and even reverse the impact of a stroke by dissolving the blood clot that causes damage to the brain. An NINDS study found that patients who received t-PA were at least 30 percent more likely to recover with little or no disability after 3 months. Without t-PA, stroke patients often suffer disabilities that require extensive rehabilitation. The window of opportunity to start treating stroke patients is 3 hours from the onset of symptoms, but to be evaluated, patients should arrive at the hospital within 60 minutes.

PLANNED IMPLEMENTATION STRATEGIES

The "Know Stroke" campaign is a multiphase effort. In the first phase, NIH developed materials in collaboration with key stakeholders in the stroke community, and focused efforts on reaching health care providers. In the second phase, NIH developed and executed transit public service advertising in communities across the country where stroke has a particularly negative impact.

In FY 2004, NIH will continue to cultivate its partnership with ASA to extend the "Know Stroke" campaign. NIH is organizing a strategy session with ASA Operation Stroke program directors from 20 communities across the country. Using the "Know Stroke" materials and information, ASA program directors will work within their communities to educate providers and the public about the importance of rapid treatment for stroke. Five of these communities will receive special focus in FY 2004.

During FY 2004, 3,000 "Know Stroke" community education kits will be distributed within local communities with at least 15 percent African American population, and 100,000 "Know Stroke" brochures will be distributed (of which 25,000 will be distributed to African American audiences).

[1] American Heart Association. *Heart Disease and Stroke Statistics—2003 Update*, p. 15.
[2] Centers for Disease Control and Prevention. *National Vital Statistics Reports.* Sept 16, 2002;50(15):7.
[3] American Heart Association. *Heart Disease and Stroke Statistics—2003 Update.* p. 40.

In addition, NIH will initiate strategic activities to reach African Americans. Using a phased approach, NIH will participate in and disseminate materials at large cultural events within the African American community in Washington, D.C. NIH will then seek to build partnerships through ASA and African American organizations in targeted areas with large African American populations to disseminate materials and messages and extend the reach of the "Know Stroke" campaign into communities most affected by stroke. During FY 2005, NIH will distribute an additional 5,000 kits (of which 1,000 will be through African American partners).

BASELINE(S)

- NIH has developed national partnerships (e.g., American Stroke Association, National Stroke Association) to extend the "Know Stroke" campaign. No substantive partnerships have been developed at the local level.
- The partnerships developed in FY 2004 serve as the springboard for additional community partnerships.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Work with partners in five communities with at least 15 percent African American audiences to extend the "Know Stroke" campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 "Know Stroke" community education kits and 100,000 "Know Stroke" brochures (25,000 will be distributed to African American audiences).	(FY03) National partnerships developed; no current comprehensive local partnerships		◇	
Extend the outreach program to an additional five communities nationwide, arming community leaders with tools and information to distribute an additional 5,000 "Know Stroke" community education kits (1,000 will be through African American partners).	(FY03) Five partnerships developed in FY 2004			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Performance results will be reported in February 2005.

GOAL c) THROUGH EDUCATION AND TECHNICAL ASSISTANCE, STRENGTHEN THE CAPACITY OF DEVELOPING COUNTRIES TO IDENTIFY TECHNOLOGIES AND PURSUE THEIR DEVELOPMENT INTO PRODUCTS.

BACKGROUND

NIH has a longstanding tradition of promoting science with the ultimate goal of improving the public health on a global scale. One manner in which this is accomplished is by ensuring the availability of new therapeutic drugs, vaccines, devices, and other products that improve human health by linking technologies resulting from NIH intramural research with the private sector through the Agency's technology transfer activities. In this regard, NIH is one of the most active agencies in the Federal Government, participating in infrastructure and policy-building workshops hosted in foreign countries. Meetings are held both domestically and overseas with foreign delegations interested in replicating the successful partnerships among government, industry, and academia occurring within the United States.

To more fully utilize these partnerships to meet the NIH mission, there is a need to educate members of developing countries on adapting and building the infrastructure for transferring laboratory discoveries to the bedside. Capacity building within countries is best achieved with active participation by local experts. Sometimes, however, local expertise first must be developed. This can be achieved by establishing a program for providing technical assistance and specific information to scientific and administrative personnel in developing countries on technology transfer activities and operations. This program first can be carried out with countries identified through previous collaborations as having the foundation (e.g., manufacturing capability, pool of scientific experts, and government interest) necessary to establish technology transfer offices.

PLANNED IMPLEMENTATION STRATEGIES

Establishing an in depth and long-term technology transfer assistance program to provide guidance and information related to technology transfer to scientific and administrative personnel in the appropriate institutions within developing countries will require extensive preparation. NIH plans to establish a working group in the Office of Technology Transfer (OTT) that will formulate recommendations. The recommendations will serve as the basis for a proposal for a needs assessment study that can be supported through the NIH One Percent Evaluation Set-Aside Program. This formal needs assessment will systematically detail the nature and extent of issues that the technical assistance program should address and determine appropriate program goals and outcomes. The strategy for program design (including selection of training personnel) is dependent on the outcome of the needs assessment, but NIH expects to initiate that process in FY 2005. Lastly, NIH will identify appropriate institutions in developing countries that are in need of targeted technical assistance, and administer appropriate capacity-building activities.

BASELINE(S)

- To date, no known needs assessment studies have been conducted to create technical assistance programs in developing countries. This strengthens the need for an assessment of necessary TA approaches.
- Selection and recruitment of personnel will be completed based on the findings of the needs assessment study from FY 2004.
- Although the needs assessment study will characterize specific TA gaps, it generally known that developing countries at best have very limited access to targeted training.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	(FY03) No known needs assessment studies exist for developing technology TA program		◇	
Based on results of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	(FY03) No personnel			◇
Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside.	(FY03) Limited access to targeted training in developing countries			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Performance results will be reported in February 2005.

GOAL d) INCREASE THE PERCENTAGE OF SMALL BUSINESS INNOVATION RESEARCH (SBIR) PROGRAM AWARD RECIPIENTS WHO ARE SUCCESSFUL IN IDENTIFYING THE RESOURCES AND/OR PARTNERS NECESSARY TO FURTHER THE DEVELOPMENT OF THEIR SBIR PROJECTS TOWARD COMMERCIALIZATION.

BACKGROUND

Established under the Small Business Innovation Development Act of 1982 (Public Law 97-219),[1] the Small Business Innovation Research (SBIR) program was initiated to stimulate technological innovation, use domestic small businesses to meet Federal research/research and development (R/R&D) needs, foster and encourage participation by socially and economically disadvantaged persons and women-owned small businesses in technological innovation, and increase private sector commercialization of innovations derived from Federal R/R&D.

The SBIR program is a highly competitive, three-phase award system. In Phase I, the objective is to establish the technical merit and feasibility of the proposed R/R&D efforts and determine the quality of performance of the small business awardee organization prior to providing Federal support. In Phase II, the objective is to continue the R/R&D efforts. In Phase III, the objective is for the small business to pursue, with non-SBIR funds, the commercialization objectives resulting from the research conducted in Phases I and II. Early-stage financing of innovation through public-private sector partnerships, such as those in the SBIR program, plays an instrumental role in supporting the development of new technologies and is an effective means for accelerating the progress of the technology from the laboratory to the market.

The small business research community often lacks the expertise, contacts, and funds necessary to support the commercialization of products/processes/services that are developed with NIH SBIR funds.

Rationale

To facilitate the translation of SBIR innovations into commercially viable products that will have societal benefit, NIH will develop a program of technical assistance services. These services will assist SBIR awardees in their transition from the "test tube to the medicine cabinet" and will serve as a means for leveraging NIH resources (SBIR funds) to foster new public-private sector partnerships.

Because areas of need are varied and numerous, NIH envisions providing a "menu" of services from which SBIR awardees can choose to address their individual needs. Through the development of technical assistance programs, NIH will be able to catalyze the matching of SBIR recipients with the resources/partners needed for them to bring their concepts to commercialization.

By consolidating the funds available through individual awards, NIH can create a program to assist SBIR awardees as they address the technical challenges that arise during the conduct of SBIR projects.
NIH has already conducted a pilot technical assistance program and plans to solicit proposals for contracts to provide other services/programs focused on technical and commercialization issues. The recently completed pilot was for a Commercialization Assistance Program (CAP). This program offered Phase II awardees business planning assistance and opportunities to "marry" their technologies with potential targeted strategic alliances and investors.

[1] The SBIR program was subsequently reauthorized by Public Law 102-564 in 1992 and again by Public Law 106-554 in 2000 (through September 30, 2008).

PLANNED IMPLEMENTATION STRATEGIES

Several activities will occur in order to satisfy the SBIR goal. NIH will use the results of the successful CAP Pilot to develop the NIH CAP Program. The program will include one-on-one business counseling; development of a business plan; and identification of key customers, investors, and business partners. In addition to the CAP pilot, NIH will pilot other technical assistance programs in order to expand availability of business planning assistance to small businesses. Programs that are successful in the pilot phase will be introduced to the greater pool of SBIR awardees. During FY 2005, NIH will track the progress of SBIR participants in the CAP pilot in order to measure the level of technical solutions resulting from the program. Finally, NIH will increase the number of SBIR awardees who identify appropriate resources through the technical assistance services. This will be accomplished by soliciting proposals for contracts to provide comprehensive technical assistance services including: business planning, identifying strategic partners/alliances, technology valuation, marketing and risk assessments, investigational new drug [IND] application filings, manufacturing, and licensing.

BASELINE(S)

- An evaluation of 1,052 NIH Phase II SBIR awardees from 1992 through 2001 found that 576 awardee respondents (75% of the 768 respondent awardees) expected sales on completion of their projects. Of those expecting sales, 39 percent (225) have already realized sales, and an additional 59 percent (340) anticipate sales.
- Pilot was completed for CAP in FY 2003, where Phase II SBIR awardees were offered business planning assistance. The pilot serves as the foundation upon which the CAP program will be designed.
- Fifty CAP pilot participants benefited from solutions of technical problems or commercialization. NIH seeks to increase the number of persons who benefit from the CAP.
- To date, only one pilot has been created for additional technical assistance services.
- There exists a need to increase the number of SBIR awardees who benefit from multiple technical assistance programs.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Implement the trans-NIH Commercialization Assistance Program (CAP) based on the recent CAP pilot.	(FY03) CAP Pilot completed		◇	
Initiate pilots for additional programs of technical assistance services.	(FY03) 1 pilot to date		◇	
Achieve higher than baseline indication of progress toward solution of technical problems or commercialization for participants in CAP pilot.	(FY03) 50 participants			◇
Increase by 5 percent the SBIR awardees who successfully identify appropriate resources and partners through the programs of technical assistance services.	(FY03) 50 awardees			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Summary of performance results will be reported in February 2005.

Implementation Strategy Advances or Other Highlights

Two assistance programs are being pursued: (1) Commercialization Assistance Program (CAP), and (2) a pilot Technology Assessment and Valuation Services Program (TAVSP). A Statement of Work has been drafted for a trans-NIH CAP that will be offered to all NIH-SBIR Phase II awardees. Based on a previous pilot, this program will assist SBIR Phase II awardees with defining commercialization strategies. The

program will culminate in approximately 75 companies presenting their business opportunities to technology-specific targeted groups of investors. The Request for Quotations to provide these services is expected to be released in January/February 2004 to a select group of GSA vendors. Products/services relating to the pilot TAVSP are expected to be procured from a GSA vendor in mid-January 2004. This too is a trans-NIH program that will be offered to Phase I SBIR awardees, with the goal of providing enough information to assist with business planning by assessing market opportunities and identifying new markets for possible entry.

IV.B.2.b.3. Capacity Building and Research Resources

Developing a research infrastructure is essential for continual scientific observation, discovery, and advancement. The NIH infrastructure encompasses the appropriate combination of trained scientific investigators, technologies, and research facilities. The productivity of the research enterprise depends in large measure on the strength of the talent pool and on technological and other research resources available for use in investigations. Collectively, NIH seeks to (1) recruit and train qualified investigators, (2) implement data automation and streamlined business processing where possible, and (3) expand the availability of resources by implementing Web-based tools, grant applications, and administrative portals.

Training and Career Development

NIH's training activities are designed to increase the Nation's ability to attract and retain the best and brightest minds and develop a cadre of well-trained, highly skilled investigators who are ready to generate the scientific discoveries of the future. Within that overarching objective, several foci are particularly important: augmenting the ranks of clinical researchers, enhancing the diversity of the biomedical research labor force, ensuring well-trained collaborators, and facilitating aptitude for multidisciplinary teamwork.

To nurture the talent base of investigators, NIH provides research training support at the pre-doctoral and postdoctoral levels, primarily through the National Research Service Award (NRSA) Program and career development support. The NRSA is authorized under Public Law 93-348, Section 487, of the Public Health Service Act. (Note: Effective with the enactment of Public Law 107-206 on August 2, 2002, the NRSA Program was renamed the Ruth L. Kirschstein National Research Service Award Program as a tribute to the exceptional contributions Dr. Kirschstein has made to NIH and the Nation.)

Pre-doctoral Training. At the pre-doctoral level, students who are beginning graduate training need to learn the conceptual and theoretical aspects of the science they hope to practice. Most NIH support at this level is provided through grants to institutions so that they, in turn, can provide broad, multidisciplinary training programs for a critical mass of students. In the first pre-doctoral years, didactic educational experiences for learning the fundamentals are supplemented with laboratory rotations that help students identify the frontiers of modern science and learn research methods. Later, once students select their dissertation projects, they operate primarily as research assistants on their mentors' research grants. NIH's approach to graduate training has been extensively praised. The widely cited 1995 report *Reshaping the Graduate Education of Scientists and Engineers*, by the National Academy of Sciences, recommended that all Federal agencies emulate this approach. Also, a recent NIH evaluation study[1] found that individuals who received at least 9 months of NRSA support during their pre-doctoral research training in the biomedical sciences were more likely to be employed by top-ranked academic institutions and more likely to have been awarded a research grant by NIH or the National Science Foundation (NSF) than their colleagues who did not receive NRSA training. NRSA recipients have also published more papers, and those papers are more highly cited compared with those of their colleagues. These NIH programs encourage academic institutions to provide high-quality research training and recipients of this support to make substantial contributions to the biomedical sciences.

Postdoctoral Training. At the postdoctoral level, NIH supports an extension and expansion of the apprenticeship approach. For individuals continuing their formal education in the biological or behavioral sciences, NIH offers training grants, fellowships, and research assistantships to fund this period of intense research activity. The primary focus at this level is on the acquisition of the knowledge and skills necessary to launch an independent research career.

[1] Pion M. *The Early Career Progress of NRSA Pre-doctoral Trainees and Fellows.* NIH Publication No. 00-4900, March 2001; Table 5.1.

Career Development. Whether a trained investigator (postdoctoral researcher) is just commencing an independent research career or is well established but looking to expand into a new area, career development awards provide support for acquiring specialized new skills.

Initiatives To Increase Diversity. Every NIH institutional training grant must have a minority recruitment plan in place prior to award. In addition, awards designed to increase the diversity of the pool of research scientists include Minority Access to Research Careers (MARC), Career Opportunities in Research Education and Training (COR), and Research Supplements for Underrepresented Minority Individuals in Postdoctoral Training. By funding research training experiences for high school students and undergraduate honor students at universities with a substantial minority enrollment, these award mechanisms serve an important role in attracting underrepresented students into careers in health-related research.

Initiatives To Augment the Supply of Clinical Investigators. The expansion and support of the clinical research workforce is a priority of the national clinical research effort. NIH uses several complementary approaches to stimulate the supply of clinical investigators. One approach is to provide incentives for medical students to gain research skills and earn a combined M.D./Ph.D. degree. Another is to supplement the training of clinicians so that they can join the ranks of investigators. For physicians and other clinicians with specialized skills and little training in health-related research, NIH offers career development awards that include competitive salaries to attract individuals who have completed training in other areas. These awards often include an initial didactic phase to provide instruction in the concepts the candidate will need as an independent researcher. The individual then proceeds to work as an apprentice on a specific project. In most cases, the candidate is ready to apply for his/her own research support by the end of the 3- to 5-year grant period.

Multidisciplinary Teams. Health science increasingly draws on a broad range of fields, including those not traditionally associated with biomedical sciences. In addition to physician-scientists, NIH will be developing creative approaches to address the supply of health science investigators in fields such as engineering, imaging, physics, nursing, mathematics, statistics, computer science, behavior, pharmacology, and epidemiology. Sweeping changes may be required as the cultural aspects of the health research enterprise is reconfigured—away from the traditional emphasis on grants performed by individual scientists to an increasing reliance on the combination of clinical, behavioral, population, and basic biomedical sciences in a collaborative team that incorporates multiple cross-disciplinary skills at multiple institutions.

Community and International Partnerships. Health research increasingly requires partnerships between investigators and indigenous personnel. Many important health questions are best addressed by going to unique populations, here in the United States and abroad, that due to geography, population structure, or disease burden, provide unique opportunities to understand disease pathogenesis, anticipate disease trends, or develop interventions. Anytime the success of research depends on interactions with non-mainstream populations, the quality of the partnership with that community will be an important success factor. Experience has taught NIH that two types of training have significant effects on partnerships. One is ensuring that there are well-trained collaborators from the target population available to participate. Another is the level of knowledge of and respect for local cultural norms on the part of the investigators.

Mechanisms of Support. Extramurally, NIH offers a flexible and varied series of high-quality training opportunities that are tailored to the career needs of recipients who are at different stages of education and career development. The Web site at the following link provides information on the various extramural training and career development awards: http://grants.nih.gov/training/extramural.htm.

Loan Repayment. NIH Loan Repayment Programs are a vital component of the Nation's efforts to attract health professionals to careers in clinical, pediatric, health disparity, or contraceptive and infertility research. In exchange for a 2-year commitment to a research career, NIH will repay scientists up to $35,000 per year of his or her qualified educational debt, pay an additional 39 percent of the repayments to cover Federal taxes, and may reimburse any State taxes that result from these benefits.

Many training and career development opportunities also are available in NIH laboratories. The Web site at the following link provides information on the different intramural training positions: http://www.training.nih.gov/.

Research Resources

The availability and accessibility of essential research tools, cutting-edge technologies, adequate facilities, animal models, reagents, and other repositories are fundamental to the productivity of the research enterprise. This is because research resources often set the boundaries as to which questions can and cannot be investigated. Within research resources, information technology (IT) requires special note. New information technologies to share, transfer, and mine vast amounts of complex data electronically are revolutionizing the conduct of science and the management, administration, and support of the research enterprise.

NIH has an active history of using IT to contribute to the success of its mission as well as to the efficiencies of all aspects of its administrative and scientific functions. For example, in February 2000 NIH launched ClinicalTrials.gov, a Web-based database that provides patients, family members, health care professionals, and members of the public with easy access to information on government- and industry-sponsored clinical trials. NIH also developed an IntraMall, a Web-based system for easily locating, ordering, and recording purchases of scientific supplies, computer equipment, and office supplies. IntraMall is the Federal Government's largest online purchasing system.

The promise of IT continues to be realized. Currently, NIH is involved in three major IT initiatives, known collectively as enterprise systems.[1] They are the NIH Business System (NBS), the Clinical Research Information System (CRIS), and electronic research administration (eRA). In addition to contributing to the NIH mission, each of these systems, in its own way, supports the President's Management Agenda (PMA) and the Secretary's One HHS initiative. For example, the eRA is playing a major role in supporting the DHHS E-Grants initiative. E-Grants are intended to put a single, simple face on the currently complex tasks of finding Federal grant opportunities and applying for Federal grants. Moreover, the eRA will create a unified electronic mechanism for grant application and administration to eliminate the redundant, paper-based processes currently required.

Expanding electronic government (e-gov) is one of the five key elements of the PMA and was initiated to make better use of IT investments to increase efficiency, reduce the paperwork burden, and improve government response time. The Secretary has embraced the PMA by moving to implement a "One Department" philosophy across DHHS, that is, a vision to help DHHS evolve from a collection of distinct and separate agencies into "One Department." To achieve his goal of managing DHHS IT on an enterprise basis, the Secretary directed the development and execution of the Draft *DHHS Enterprise Information Technology Strategic Plan, FY 2003-2008* (March 2003). The Plan outlines strategic goals and strategic objectives that will advance the best and most effective DHHS IT resources and will drive progress for public health and human services. All the NIH enterprise systems dovetail with the draft DHHS Enterprise IT Strategic Plan.

[1] Enterprise systems are broadly based IT systems that are expected to be used widely across NIH and interface with other major IT systems. At NIH, responsibility for the enterprise systems involves a partnership between the functional area manager/program official, who serves as the business owner of the system, and the chief information officer.

GOAL a) RECRUIT, TRAIN, AND RETAIN A DIVERSE POPULATION OF HIGHLY TRAINED SCIENTISTS IN BIOMEDICAL, BEHAVIORAL, AND CLINICAL RESEARCH USING RESEARCH TRAINING GRANTS, FELLOWSHIPS, CAREER DEVELOPMENT AWARDS, AND STUDENT LOAN REPAYMENT PROGRAMS.

BACKGROUND

A critical part of the NIH mission is the education and training of the next generation of biomedical and behavioral scientists. The overall goal of the training program is to maintain a population of scientists that is well educated, highly trained, and dedicated to meeting the Nation's future health-related research needs. At the same time, NIH believes strongly that training and supporting a research community that reflects the Nation's social diversity is a top priority. Accordingly, NIH has designed a number of training programs to provide support to a diverse population of graduate and postdoctoral students and to recruit them into research at all career levels. NIH also has developed programs designed to enhance the retention of women in biomedical research careers and support for individuals with disabilities. Continual monitoring of the demographics of the participants in NIH programs is an important aspect of fostering a diverse cadre of researchers able to conduct basic and applied scientific research.

This monitoring enables NIH to implement corrective actions. For instance, if application rates for a particular program fall below historical rates, NIH determines the reason and responds accordingly. Possible actions to enhance the attractiveness of a particular award include increasing applicants' probability of success (the success rate), increasing benefits for awardees, or improving outreach. Success rates affect the attractiveness of an award since applicants who think they are unlikely to receive an award may opt for other sources of support. It is, therefore, important for NIH to maintain stability in the overall success rate so that applicants know what to expect.

Success of the program can be proxied by the number of trainees that apply for and receive NIH research grants. Successful research applicants indicate retention.

PLANNED IMPLEMENTATION STRATEGIES

During the implementation of this goal, NIH staff will assess the quality and relevance of existing programs by closely monitoring: (1) applications for pre- and post-doctoral trainees and fellows to ensure that awardees exceed comparison groups; (2) Training grants to ensure that the targeted 10% receive multidisciplinary training grants; and (3) the number of K23, K24, and K30 awards. Additionally, NIH will increase the diversity of trainees by employing individuals from underrepresented populations in career development positions. Finally, NIH will increase its pool of investigators by using student loan repayment programs. Rolling cohorts of students will be continually drawn from data sources to ensure ample data for comparison groups.

BASELINE(S)

- *Pre-doctoral Trainees*–NRSA Study Group: 7,125 individuals with 9 or more months of NRSA support who earned the PhD during the period from 1981 to 1988; Comparison Group A: 9,985 individuals who earned the PhD in biomedical disciplines between 1981 and 1988 at institutions with NRSA training grants but who did not have NRSA (or less than 9 months) of NRSA support; Comparison Group B: 9,229 individuals who earned the PhD in biomedical disciplines between 1981 and 1988 at institutions without NRSA support.

	PERCENT SUBMITTING APPLICATIONS	PERCENT RECEIVING AWARDS
NRSA Study Group	66.8	46.3
Group A	55.0	34.9
Group B	47.0	26.3

Data were taken from NIH report entitled, "The Early Career Progress of NRSA Pre-doctoral Trainees and Fellows" by Dr. George Pion (1991).

- *Postdoctoral Trainees*–The number of training award recipients is the numerator for two groups: persons who applied but did not receive a training award, and persons who received training awards. The denominator for both groups is the total number of postdoctoral trainees. This applied for vs. received divided by the total number of trainees provides the FY 2003 baseline ratio for the comparison groups. Raw data were derived from IMPAC –II.

- *Multidisciplinary Training*–In FY 2003, there were 486 training grants with multidisciplinary training; 558 without multidisciplinary training. Baseline data were provided from database within the Office of Reports and Analysis, Office of Extramural Research.

- *Asymptotic Targets for K23, K24, and K30 Awards*–Baseline data provided from an implementation plan resulting from a subgroup of NIH Directors.

- *Underrepresented Racial and Ethnic Groups*–Baseline data were provided from database within the Office of Reports and Analysis, Office of Extramural Research.

- *Student Loan Repayment Program*–Two data sets provided by the NIH Loan Repayment Electronic Application System serve as FY 2003 baseline data: total number of applications received and number of contracts awarded.

PERFORMANCE TARGETS *Note: Annual targets are grouped by activity.*	**BASELINE**	**FY 2003**	**FY 2004**	**FY 2005**
Assess the quality and the relevance of existing research training and career development programs:				
Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	(FY03) NRSA Group: 7,125 Comparison Group A: 9,985 Comparison Group B: 9,229		◇	◇
Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	(FY03) Applied for but did not receive = 174 recipients; 929 trainees Received last year of training support 10 years before: 324 recipients; 808 trainees.		◇	◇
Ensure that there is multidisciplinary training on at least 10% of all training grants as evidenced by trainees reporting different Field of Training codes.	(FY03) 486 multidisciplinary grants		◇	◇
Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.	(FY03) 120 K23 awards for FY03-FY06 50 K24 awards for FY03-FY06 50 K30 awards for FY03-FY06		◇	◇
Increase the racial and ethnic diversity of the pool of trainees:				
Increase by 1% over baseline the number of research training and career development positions occupied by individuals from underrepresented racial and ethnic groups.	(FY03) White= 9,957; Asian: 1,862 African American = 1,112 American Indian = 106 Pacific Islander =52		◇	◇

PERFORMANCE TARGETS *Note: Annual targets are grouped by activity.*	BASELINE	FY 2003	FY 2004	FY 2005
Increase the cadre of highly qualified investigators with the diversity and expertise to build capacity to conduct biomedical/behavioral research:				
Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	(FY03) Applications received = 1,881 Contracts awarded = 1,193		◇	◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Performance results will be reported in February 2005.

GOAL b) PROMOTE DATA SHARING AND PROVIDE INFORMATION IN REAL TIME BY IMPLEMENTING THE NIH BUSINESS SYSTEM.

BACKGROUND

After an extensive review of its administrative processes and current information technology support, NIH began implementing an enterprise resource planning system known as the NIH Business System (NBS). The NBS will encompass seven functional areas that are currently included in the ADB: financial management, property management, research and development contracts, acquisition, service and supply funds operations, supply management, and travel management.

Rationale

The implementation of the NBS will create an integrated transaction processing system that promotes data sharing and provides information in real time, ultimately providing more efficient and cost-effective administrative support to achieve NIH's scientific mission. Beyond sheer automation, this project seeks to combine the latest technology with proven best business practices and to provide a new level of support to research.

Implementation of the NBS is one of several administrative improvements that demonstrate NIH's commitment to the principles behind the PMA, including improved financial performance and expanded electronic government. Specifically, it will (1) allow for greater integration of administrative processes with the financial system, and (2) encompass new financial systems to comply with all applicable accounting requirements and standards.

NIH is required by the Chief Financial Officers (CFOs) Act and the Government Management Reform Act (GMRA) to prepare annual financial statements covering all of its activities and to have the statements audited by independent auditors. The preparation of financial statements requires an integrated financial management system and processes that provide complete and accurate accounting data on a timely basis. With regard to the preparation and submission of audited financial statements, timeliness has been redefined by OMB from 6 months following the end of the fiscal year in FY 1996 to 6 weeks in FY 2004. Timeframes for other required financial reporting have also been shortened.

Deployment of the NBS should position NIH to meet the CFO Act and GMRA requirements and OMB's timeframes. Successful implementation of the NBS general ledger module for FY 2004 should reduce the number of adjustments required to prepare financial statements and will be critical to NIH meeting the tighter timeframes for annual financial statements and other financial reporting, while maintaining the accuracy of the reports. Implementation of the general ledger module and follow-on modules will strengthen NIH's compliance with accounting standards for recording transactions in the appropriate ledger accounts, providing subsidiary ledgers for all appropriate general ledger accounts, and for identifying intra-governmental partners. Complying with accounting standards will help facilitate the reconciliation process and provide more effective analysis of general ledger account balances.

The NBS also is an important component of the One HHS initiative. The NBS serves as a proof of concept for and is a major element of the DHHS Unified Financial Management System (UFMS). As both systems mature, the NBS will merge into the single financial management system envisioned by DHHS. NIH has provided resources to the DHHS UFMS and is working hard to ensure that the NBS will become an integral part of the UFMS. The NIH staff actively participates on a DHHS UFMS team to meet common goals and address Department-wide challenges.

PLANNED IMPLEMENTATION STRATEGIES

Implementation of the NBS will be phased to incorporate individual modules as they are completed. Modules of the NBS will serve similar functions to the legacy ADB system. During FY 2003, the following modules will be deployed: general ledger/budgeting module, property module, and travel module. Beginning in FY 2005, the contracts/acquisition/accounts payable/supply module and service and supply module will be deployed. Each module will be compatibility tested to ensure it functions as appropriate. Additional modules may be developed and implemented beyond the original seven functional areas of ADB.

BASELINE(S)

- The NBS will replace selected administrative operations of the aging legacy Administrative Data Base (ADB).
- Functional areas from the ADB will be represented in the NBS through a series of modules that will be phased in through FY 2005.
- The general framework for NBS (e.g., layout, design, table shells) has been developed. Modules will be added as they are completed.

PERFORMANCE TARGETS	BASELINE	FY 2002[1]	FY 2003	FY 2004	FY 2005
Deploy and implement modules of the NBS:					
1. Implement the EHRP.		◆			
2. Deploy the general ledger/budgeting module.	2. (FY02) NBS without general ledger/budget module		◆		
3. Deploy the travel module.	3. (FY02) NBS without travel module		◆		
4. Deploy the property module.	4. (FY02) NBS without property module		→	→	→
5. Deploy the property and contracts/acquisition/accounts payable/supply modules.	5. (FY03) NBS without contracts/acquisition/accounts payable/supply modules			◇	→
6. Deploy the service and supply fund activities module.	6. (FY03) NBS without service and supply fund activities module			◇	→

[1] ***Baselines were not required prior to FY 2003***

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Targets 2 and 3

NIH deployed the general ledger and travel modules as targeted. General ledger was deployed as the system of record beginning October 1, 2003. The travel was deployed on September 1, 2003.

Targets 4 and 5

The property and contracts/acquisition/accounts payable/supply modules are being replanned for the second quarter of FY 2005. Purchased "out-of-the-box," the software products selected for Property and Contracts/Acquisition/Supply modules were judged to need further customization for NIH. The purchased software was originally developed as a commercial off-the shelf product that needs to be updated to comply with Federal and departmental regulations and policies. NIH determined that additional time is warranted to design and configure the products in a manner that improves compliance with these Federal and departmental policies and regulations. The delay by extending the targets will mean continuing to operate legacy systems, maintaining complex interfaces with legacy systems, and delaying the full integration of the NBS system. The NBS project is adjusting the project schedule for the next modules to ensure that the new target date is met.

Implementation Strategy Advances or Other Highlights

Plans to provide formal and informal central NIH financial reporting for FY 2004 under the new NBS General Ledger are complete. All central budget tracking activities are also provided by the NBS. All FY 2004 NIH Travel Orders (over 10,000 to date) have been processed in the NBS Travel module, and it is now the system used daily by all NIH Travel administrative personnel. The General Ledger and Travel modules received written approval by the Deputy CFO and the CIO prior to their deployment.

GOAL c) STREAMLINE BUSINESS PROCESSES AND AUTOMATE DATA MOVEMENT BY IMPLEMENTING THE CLINICAL RESEARCH INFORMATION SYSTEM (CRIS).

BACKGROUND

The NIH Clinical Center has been a pioneer in the use of computer technology for the advancement of research and the improvement of care. The present Medical Information System (MIS) was implemented in 1975 and gave NIH physicians access to tools such as physician order entry and a point-and-click interface that are still not implemented in many academic health care settings. Unfortunately, the system was built around a proprietary database, and its capabilities no longer meet the needs of the institution for providing data in both the research and clinical care settings. For some functions such as pharmacy, surgical services, and consent management, no automation is currently in place.

To address the limitations of the present system and to fully automate clinical care information, NIH has embarked on the CRIS project. Specific functionality that will be provided by the CRIS includes:

- Compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and regulations of the Privacy Act of 1974
- Interfacing with ancillary systems to provide integrated data and eliminate paper-and-pencil transfer of data among systems
- Reduction of potential medical errors through the implementation of a pharmacy and surgical scheduling, management, and documentation system
- Management and display of radiologic, anatomic, pathologic, and ultrasound images and other image-based data
- Interfacing to IC research databases
- Support for standardized medical vocabularies
- Support for analyzable electronic documentation (i.e., physician notes)
- Support for protocol-based provision of care
- Provision of management information for resource allocation and cost attribution
- Provision of longitudinal patient data
- Provision of historical patient data for research analysis
- Comprehensive support for patient appointing
- Support for bed management
- Support for nurse acuity assessments

Rationale

Historically, research data have been recorded in stand-alone systems or on paper. Because these research data could not be provided directly from the hospital system, they were typically copied from hospital system computer screens into the local electronic or paper-based research record. Such a process, when multiplied over the research enterprise of NIH, represents a substantial loss of productivity and a major risk of error. Implementation of the CRIS will reduce the life-cycle costs of these clinical information technology projects and obviate the need for IC-specific systems.

PLANNED IMPLEMENTATION STRATEGIES

CRIS includes several functional modules that will be phase in once they are completed. The core hospital system will be developed to include modules that streamline business processes and automate data movement among multiple systems. Staff time for redundant data entry will be reduced with the development of scheduling and resource utilization modules and pharmacy management system during FY 2004. In FY 2005, a surgery and anesthesia management system will be implemented that facilitates records management for

Clinical Center staff. Additionally, a clinical data warehouse will be developed and used across NIH. The warehouse will directly support the PMA goals of expanded electronic government and improved financial performance. The CRIS project represents the nucleus of clinical informatics for NIH, with the goal of collecting clinical information only once for patient care and research. The completed system will serve as a model for other health care organizations.

BASELINE(S)

- The MIS is a 28-year old system that needs replacing since its usefulness is limited for NIH Clinical Center staff.
- There is a demand for more sophisticated electronic functions (e.g., surgery/anesthesia management) that reflect current clinical informatics.
- The massive volume of Clinical Center data was the impetus for developing a clinical data warehouse.

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Implement modules of the CRIS:				
Implement a core hospital system, including scheduling and resource utilization modules and pharmacy management system.	(FY03) 28 year old legacy system		◇	
Implement a surgery and anesthesia management system.	(FY03) No current system exists			◇
Implement a clinical data warehouse.	(FY03) No trans-NIH clinical data warehouse currently exists			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Performance results will be reported in February 2005.

GOAL d) PROVIDE GREATER FUNCTIONALITY AND MORE STREAMLINED PROCESSES IN GRANTS ADMINISTRATION BY CONTINUING TO DEVELOP NIH ELECTRONIC RESEARCH ADMINISTRATION (ERA).

BACKGROUND

The eRA is NIH's infrastructure for conducting interactive electronic transactions for the receipt and review of applications, and the monitoring and administration of NIH grant awards to biomedical investigators worldwide. Public Law 106-107 requires Federal agencies to migrate from paper-based to electronic systems, thus improving the delivery of services to the public. Therefore, the overall objective of the eRA is to provide a two-way electronic interface for the submission and processing of grant applications and reports in compliance with Public Law 106-107. eRA system development incorporates government wide standards and will integrate with the other NIH, DHHS, and e-grants systems. DHHS is the agency partner in the development of the government-wide Grants.gov effort. NIH eRA staff is also involved in this effort. Recently, DHHS designated eRA as the common system for all DHHS research grant processing.

Future eRA aims include the development of methodologies to electronically receive grant applications as eXtensible Markup Language (XML). XML is the next generation beyond HyperText Markup Language (HTML), and provides independence from proprietary development tools. XML enables a single data entry point, more efficient maintenance, and higher quality products. This places the NIH eRA system in a strategic position to integrate with the DHHS e-Grants storefront initiative, and ultimately to achieve the ability to execute end-to-end electronic processing between NIH and the external community using shared electronic resources.

Other future eRA aims include the transition of client/server applications to the Java 2 Platform, Enterprise Edition (J2EE) architecture. J2EE enables a component-based, multi-tier enterprise architecture, improving the reusability of eRA assets, and increasing software quality, application reliability, and security. This places the NIH eRA system in a strategic position to become the DHHS grants administration system for all research and training grants.

Existing eRA applications are being migrated to the J2EE-based technology in a systematic manner as defined by an eRA J2EE migration plan. The X-Train system, which is scheduled for migration to the new technology in FY 2004, will expand the ability to monitor training appointment information, and to establish a link to the professional profiles of all NIH trainees.

PLANNED IMPLEMENTATION STRATEGIES

First, electronic reporting will be implemented in institutions participating in the Federal Demonstration Partnership (FDP) through a Web-based progress-reporting system. A pilot of this system began in November 2002, and was tested throughout FY 2003 by making it available to FDP institutions that requested to use it. Second, after ensuring acceptable performance of the progress reporting system once all FDP institutions have been invited to use it, its availability will be expanded to all grantee institutions. This will be publicized as a formal announcement on the NIH Commons during the third quarter of FY 2004. Third, the XML language will be pilot tested by receiving simple, competing grant applications from the grantee community as XML documents. Although the XML pilot supports only a small subset of the types of grant applications received by NIH, it enables NIH to begin establishing the technology infrastructure needed for more complex services, such as those involving multi-project mechanisms. Fourth, multi-project progress reporting will be tested by expanding the grant application XML pilot to support complex services, such as the receipt of multi-project progress reports as XML documents. Finally, migration of existing client/server applications will be completed by implementing an eRA J2EE Migration Plan. This plan stages the transition

of proprietary client/server applications to a standard, multi-tier, component-based technology. The J2EE architecture compliments the XML technology, transforming eRA into an open, secure enterprise system.

BASELINE(S)

- At the beginning of FY 2003, there were no institutions using electronic reporting.
- A plan is in place to expand electronic reporting to all grantee reporting institutions who do business with NIH.
- Incorporating XML into the system will be important to support complex services, such as the receipt of multi-project progress reports.

PERFORMANCE TARGETS *Note: Annual targets are grouped by activity.*	BASELINE	FY 2000	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005
Develop methodologies to electronically receive grant applications as XML files:							
1. Implement electronic reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership.[1]	(FY99) No institutions using electronic reporting	→	→	→	◆[e]		
2. Begin pilot-testing of progress reporting for multi-project mechanisms.[2]	(FY99) 14 simple competing grant applications received	→	→	→	→	→	◇
3. Expand availability of electronic progress reporting to all grantee institutions.[3]	(FY02) 145 FDP institutions given access to electronic reporting				→	→	◇
4. Pilot-test extensible Markup Language (XML) transmission between extramural community and NIH.	(FY03) Need for system to conform with OMB/Federal Enterprise Architecture					◇	
Migrate Oracle forms applications into Java Version 2.0 Enterprise Edition (J2EE) technologies:							
5. Complete migration of existing client/server applications to Web-based technology.[4]	(FY03) Migration plan developed						◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

Target 1—This target has been met, since electronic reporting is now available to the original 65 institutions as well as to 80 additional FDP-participating institutions. Electronic reporting is enabled by the eRA e-SNAP system. The e-SNAP system began a pilot phase in November 2002. It was opened to all FDP schools at that time, although few institutions took advantage of the system initially. The e-SNAP system was tested throughout 2003, and in January 2004, a formal announcement inviting all 145 FDP institutions to use it will be issued.

Target 2—Development and pilot-testing of a system to accommodate progress reporting for multiproject mechanisms have been postponed until FY 2005. Multiproject progress reporting requires an eXtensible Markup Language (XML) infrastructure, which eRA is currently architecting for the receipt of competing

[1] Target was carried over from previous eRT goal and was met for FY 2003.
[3] Target was carried over from previous eRT goal and was extended for FY 2005.
[2] Target was carried over from previous eRT goal and was extended to FY 2004.
[4] This target was includes the deployment of the 2.0 version of X-Train, a target that is carried over from previous research training goals.

grant applications. XML will be used because it enables the exchange of information using a simple, flexible architecture that conforms to the Federal Enterprise Architecture promoted by OMB. eRA is using this technology on a small scale for the receipt of simple competing grant applications (not yet including multiproject mechanisms.) eRA expects to test this small-scale XML architecture throughout FY 2004, and expand the XML architecture to include multiproject mechanisms in FY 2005.

Target 3—This target has been postponed until the third quarter of FY 2004 because of the need to perform volume testing of the e-SNAP system. Although there has been limited use of the e-SNAP pilot by 32 institutions in FY 2003, the formal announcement in January 2004 will increase usage significantly. The second quarter of FY 2004 will be used to test the load and performance of the e-SNAP system so that its availability can be expanded to all grantee institutions in the third quarter of FY 2004.

Implementation Strategy Advances or Other Highlights

As of November 2003, eRA has received a total of 531 e-SNAP reports from 32 different FDP institutions. The e-SNAP project continues to expand the usage of the eRA system by allowing FDP institutions to register user accounts.

As of December 2003, eRA had received 14 grant applications as XML transmissions as part of a grant application pilot. This project has enabled a limited XML mapping to the NIH grant form. Although the pilot supports only a small subset of the types of grant applications received by NIH (e.g., multi-project mechanisms are not supported), it allows grantee institutions to submit simple research grant applications electronically, advancing the e-grant initiative at NIH.

Efficiency

The deployment of the e-SNAP system results in savings of time, money, and staff resources. e-SNAP provides the interchange of information from and to institutions, reducing the amount of paper NIH receives each year.

FDP membership increased from 65 institutions during Phase III of the project to 145 institutions during Phase IV. This increase in membership allowed eRA to make the e-SNAP system available to a greater number of grantee institutions during the e-SNAP pilot than originally planned.

IV.B.2.b.4. Strategic Management of Human Capital

Performance-based results have become a central theme in human capital management efforts at NIH. NIH is developing a strategic, performance-based approach to workforce management by generating performance goals and measures that will (1) align individual performance with organizational goals, (2) provide seamless leadership continuity and succession planning, and (3) appropriately allocate rewards and incentives. Efforts are being invested to develop a clearly articulated workforce plan to address strategic alignment, results orientation, performance measurements, interdisciplinary teaming, and workforce succession planning.

NIH is developing a methodical process that provides managers with a framework for making human resource decisions based on the organization's mission, strategic plan, budgetary resources, and a set of desired workforce competencies. Management is currently discussing longer range resource priorities and staffing needs based on realistic resource improvement goals and staffing requirements. Plans are being developed to allocate funding to improve operating efficiencies and improve technical skills and competencies. NIH is in the process of determining current and future workforce needs, assessing how its current workforce and anticipated future workforce compare with these needs, and developing effective strategies to fill the gaps. The successful implementation of the plan will be critical to achieving program objectives, thus providing a basis for justifying budget allocation and workload staffing needs.

NIH values employees as an essential organizational asset and strives to provide them with the tools they need to be successful. The workforce plan is designed to match the right person with the right job by ensuring more efficient and effective recruitment, training, and retention. In high-performing organizations, employees see a direct connection between their work and accomplishing the organization's mission. Toward this end, NIH places a heavy emphasis on the education, development, and training of its employees. The plan will enable employees and managers to identify training and career development needs, link training with performance goals, provide meaningful performance incentives, and foster a diverse workforce.

To meet the challenge of workforce management, NIH has delayered management levels and consolidated human resource management functions. In addition, NIH has achieved great success in reaching competitive sourcing goals in a variety of commercial areas. While all these initiatives are under way, NIH managers are confronted with the need to balance the certainty of short-term requirements with long-term planning. The workforce plan is central to achieving NIH's long-term objectives and will be the foundation for policies that reshape the workforce over time.

In April 2003 the NIH Director formed the Administrative Restructuring Advisory Committee (ARAC) in response to administration mandates to examine consolidation and restructuring as a means to provide more responsive, flexible, and efficient administrative services. Drawing on input from the ARAC, the NIH leadership prepared a restructuring plan and presented it to DHHS for consideration. Pending feedback from the Department, that plan will be the basis for a future GPRA goal.

GOAL a) IMPLEMENT A GOVERNMENTWIDE INITIATIVE ON DELAYERING MANAGEMENT LEVELS AND STREAMLINING ORGANIZATIONS.

BACKGROUND

The aim of NIH research is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability. At the same time, NIH is responsible for improving its management to further the success of its mission and research goals. To that end, NIH is working to implement five government wide PMA initiatives aimed at:

- Strategic management of human capital
- Expansion of electronic government
- Competitive sourcing
- Improvement of financial performance
- Budget and performance integration

To determine the best course of action for implementing these initiatives, the NIH Administrative Coordination Working Group was formed to make recommendations to the NIH Director. The group's deliberations focused on the DHHS Secretary's vision of "One HHS," the views of DHHS senior staff members, guidance from OMB, and the recommendations of the 1997 Arthur Andersen study of NIH administrative activities. The group's recommendations included centralizing the NIH Servicing Personnel Office, using the new NBS as the model for implementing the UFMS, and supporting the development of departmental IT and EHRP systems.

In addition, NIH developed this performance goal focused on "delayering,"—reducing the number of layers in management to streamline its organization. Reducing management layers will lessen the distance between citizens and decision makers, thereby allowing NIH to be more responsive to public health needs.

A preliminary review revealed that although NIH ICs require different organizational designs to meet their individual scientific objectives, four management layers at the IC level are likely to be sufficient in most cases. However, certain complex organizational issues may preclude some ICs from effective performance under this management model. These issues include the organization of some intramural research laboratories that provide services through widely disbursed and mobile staff members and the size and scope of organizations such as the National Cancer Institute (NCI).

The proactive NIH compliance effort will use the following process to achieve the delayering goals and targets:

- Assess current organizational reporting structures and identify the mission and support areas affected.
- Establish review groups within the Institutes and Centers.
- Review functions for impact on science or delivery of services, including review of personnel issues and supervisory ratios.
- Formulate and announce delayering plans.
- Complete organizational changes and reassignments.

BASELINE(S)

- Six organizational units identified for delayering.

PERFORMANCE TARGETS *Note: Annual targets are grouped by activity.*	BASELINE	FY 2002[1]	FY 2003	FY 2004[2]	FY 2005[2]
Identify NIH organizational units for possible delayering:					
1. Complete assessment of NIH organizational level structure and rationale for current patterns.		◆			
2. Identify organizational units for delayering.		◆			
Delayer NIH organizational units:					
3. Develop implementation plans to accomplish delayering for each organizational unit.		◆			
4. Develop specific numeric targets for the implementation plans.		◆			
5. Complete delayering for each organizational unit identified.	(FY02) Six units identified		◆[e]		

[1]Baselines not required in FY 2000–2002.

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

NIH completed the initiative on delayering management levels and streamlining organizations by delayering components in three Institutes and three components in the Office of the Director. Currently, no NIH organization is above four organizational levels. NIH also instituted a review process for all organizational changes to ensure that no future change results in organizations deeper than four levels. NIH official organizational charts reflect the changes made to the NIH organizational structure.

All targets for this goal have been achieved; NIH has implemented a governmentwide initiative on delayering management levels and streamlining organizations. This goal will be dropped from future GPRA plans/reports.

Efficiency

Reducing management layers has reduced the distance between citizens and decisionmakers, thereby allowing NIH to be more responsive to public health needs.

[2]Delayering was completed in FY 2003; the goal has been achieved.

GOAL b) **IDENTIFY AND DEVELOP POTENTIAL SUCCESSORS FOR CRITICAL LEADERSHIP POSITIONS BY (1) DEVELOPING AND IMPLEMENTING AN NIH-WIDE SUCCESSION PLANNING PROCESS THAT ASSESSES THE GAPS BETWEEN SENIOR LEADERSHIP NEEDS AND TALENT AVAILABLE; (2) IDENTIFYING LEADERSHIP COMPETENCIES THAT WILL BE CRITICAL TO THE MISSION OF NIH NOW AND IN THE FUTURE; AND (3) PROVIDING DEVELOPMENTAL OPPORTUNITIES THAT WILL PREPARE POTENTIAL SUCCESSORS TO MEET THE DEMANDS REQUIRED OF SENIOR LEADERSHIP POSITIONS.**

BACKGROUND

OPM recently identified *Human Capital Standards for Success* (http://apps.opm.gov/humancapital/standards/index.cfm), which includes an assessment of how well departments are ensuring continuity of leadership through succession planning and executive development.

Succession planning is crucial if NIH is to maintain adequate institutional knowledge and effectively carry out its mission during periods of high workforce turnover. For example, the average Senior Executive Service (SES) employee at NIH today is 60 years old with 25 years of service. Of these, 73.3 percent will be eligible to retire by the end of 2005. Although the exodus of talent will not happen overnight, NIH must plan now to maintain required levels of experience, competencies, and knowledge at all levels.

The consolidation/streamlining and competitive sourcing activities, coupled with the potential number of retirements at NIH, makes succession planning extremely critical to ensuring the recruitment, retention, and training of employees for a seamless succession of leadership. Voluntary Early Retirement Authority (VERA) was recently given to NIH for the human resources function and subsequently to those areas potentially affected by the competitive sourcing studies. In total, approximately 10,000 employees at all levels have been identified as potentially being affected. Together with normal attrition and retirements, the exodus of potential skills, competencies, and knowledge would be devastating without a plan for remedy.

A major management challenge will be to ensure that NIH has experienced employees in key positions. Careful planning and allocation of resources will be critical to NIH's success in meeting this challenge, allowing NIH to balance the need to meet its present workload demands with the need to build and train the NIH workforce of the future.

PLANNED IMPLEMENTATION STRATEGIES

Target 1—A thorough workforce assessment study was planned, entitled Comprehensive Workforce Assessment to Map Workforce Policies with the NIH Mission over the Next Five Years, until that project was subsumed into a larger NIH study being conducted at a higher level within the Office of the Director, NIH. A contract was awarded at the end of FY 2003 to the National Academy for Public Administration (NAPA) to conduct that comprehensive study entitled Review of Administrative Functions/NAPA Partnership under the guidance of the Deputy Director of the NIH. This is expected to not only determine the potential for additional restructuring opportunities as a means of further improving resource utilization and savings but also result in an evaluation of NIH's programmatic objectives and projected human resource needs. This will form the basis of a comprehensive human capital plan for improving the strategic management of NIH human resources.

Target 2—NIH has a variety of programs in place to identify and develop potential leaders, but there are questions concerning the coordination, efficacy and competency framework for these programs. NIH will benefit from a review of best practices in other agencies and industry, as will be assessed with Target 4.

Target 4—NIH will study the "tenure" system practices currently operating to ensure the quality and continuity of leadership in its intramural scientific research programs. The study will first research succession planning practices in other research organizations and compare those to NIH practices. In this benchmarking phase of the study, at least eight similar public and private research organizations will be examined. The study will then focus on the extent to which current NIH practices are effective, any changes that could make them more effective, and any opportunities for application to the extramural and administrative functional communities.

Target 5—This target is aimed at developing a succession-planning framework, including the tools/ resources needed to facilitate the process. The workgroup that has been established will address this issue. Further, NIH is currently revising its Senior Leadership Development program to align it more closely with critical leadership competencies and is co-chairing a Department-wide initiative to develop leadership competencies. These competencies are to replace the current KSA system. The concept of a pilot program, using focus groups, is being developed. A major difficulty with this target is drawing competencies from the more generic KSAs.

BASELINE(S)

- NIH Workforce Plan, June 2001
- Administrative Restructuring Advisory Committee (ARAC)
- Study questions identified
- Workgroup established to study competencies

PERFORMANCE TARGETS *Note: Annual targets are grouped by activity*	**BASELINE**	**FY 2003**	**FY 2004**	**FY 2005**
Data collection and analysis:				
1. Conduct a study and report on average age, years of service, and retirement eligibility. Assess future potential impact.	(FY01) NIH Workforce Plan, June 2001	→	◇	
2. Conduct a study and report on current state. Assess strengths, weaknesses, and needs for changes in current practices.	(FY01) NIH Workforce Plan, June 2001	◆		
Steering/oversight committee:				
3. Establish a steering committee.	(FY02) Administrative Restructuring Advisory Committee	◆		
Succession planning framework:				
4. Identify industry best practices. Develop a succession planning process to meet the needs of NIH.	(FY02) Study questions identified	→	→	◇
Leadership competencies:				
5. Conduct study to identify competencies needed by NIH leaders who will drive future development efforts.	(FY02) Workgroup established to study competencies	→	◇	

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

Target 1—This target has been extended. As part of the workforce assessment, the target addresses the data collection and analysis for determining the status of the senior leadership at NIH. The target was extended because the NIH Workforce Plan of June 2001, on review, did not have sufficient data breakdowns and multi-

level groupings to assess the potential impact of retirement on the NIH workforce, including the senior leadership, over a 5-year period. This may be due, in part, to the numerous administrative restructuring initiatives impacting NIH. A result of the latter changes is the planning of a much larger study than initially anticipated, further delaying its initiation. Also, the Workforce Plan of June 2001 was developed from an episodic survey that does not give the information needed to assess impact. OSMP is initiating discussions with CIT to consider developing an automated tool that would capture workforce information and also allow the type of analysis that Target 1 needs. A comprehensive, Web-based tool is needed to have a systematic way to collect, report, and archive data on a long-term basis. In FY 2004, the tool will be developed and the study conducted. In FY 2005, 1 percent evaluation funds will be requested to assess impact. Therefore, performance results for this target will be reported in FY 2006.

Target 2—This target has been met. It refers to the data collection and analysis for succession planning and leadership development efforts, an extension of Target 1. A study of strengths, weaknesses, and opportunities was conducted, and the report "Succession Planning Report" was issued. The report identified a significant increase in retirement eligible staff in senior-level positions by 2005. It called for an assessment of the workforce strategy to determine whether that strategy can provide for agency leadership in the future, whether current mechanisms are sufficient to develop talent for leadership positions, and whether new strategies need to be implemented to address the loss of key staff members over the next 5 years. It included a list of steps by which best practices dictated such an assessment should be done.

Target 3—This target has been met by virture of the establishment of the NIH Steering Committee that now guides the policy and direction of NIH-wide administrative efforts such as succession planning. This committee supersedes the Administrative Restructuring Advisory Committee (ARAC).

Target 4—This target has been extended. It refers to the need to ensure the quality and continuity of leadership in the NIH Intramural Research Program through studying industry best practices and by developing a succession planning process. The target was extended because the start of the planned study was delayed. The delay stemmed from very informative discussions with intramural research leaders who had reviewed the plan and found it did not cover the entire program in sufficient depth and did not address the issues of greatest concern to the current leadership. Furthermore, the process of renegotiating the study plan within the framework of Federal contracting regulations added an additional delay. However, a contractor has now been engaged (Cambria, Inc.) to carry out this study, which is expected to be completed during FY 2004.

Target 5—This target has been extended. It is aimed at developing a succession planning framework, including the tools/ resources needed to facilitate the process. A workgroup was established to review and study available information for competencies. The pace of the leadership competencies workgroup is largely beyond the control of NIH. NIH cochairs the group, but it is a departmental entity and includes representation from all the HHS OPDIVs. NIH can influence its progress to a small degree, but the group can only move ahead at a pace that all the OPDIVs agree on. The group has developed a draft statement of leadership competencies and is now entering the validation phase of the process. The current goal is to validate the draft and issue final competencies before the end of FY 2004.

Implementation Strategy Advances or Other Highlights

Formation of the NIH Steering Committee was announced in July 2003. It consists of a rotating membership of 10 directors derived from and representing the 27 NIH Institutes and Centers. It is chaired by the NIH director. The goal of this committee is to give "crisp strategic direction" to the agency and streamline its decisionmaking processes.

GOAL c) IMPROVE THE STRATEGIC MANAGEMENT OF NIH HUMAN RESOURCES BY DEVELOPING A COMPREHENSIVE HUMAN CAPITAL PLAN BASED ON THE AGENCY'S PROGRAMMATIC OBJECTIVES AND PROJECTED FUTURE NEEDS.

BACKGROUND

The first item on the President's Management Agenda (PMA) is the strategic management of human capital, which seeks to create a more effective Government that depends on attracting, developing, and retaining top-quality employees from diverse backgrounds and ensuring that they perform at high levels.

> *We must have a Government that thinks differently, so we need to recruit talented and imaginative people to public service. We can do this by reforming the civil service with a few simple measures. We [will] establish a meaningful system to measure performance. Create awards for employees who surpass expectations. Tie pay increases to results. With a system of rewards and accountability, we can promote a culture of achievement throughout the Federal Government.*
>
> ☙ President George W. Bush

Strategic human capital management is the transformation of how to employ, deploy, develop, and evaluate the workforce. It focuses on results, not processes. It places the right people in the right jobs to most effectively perform the work of the organization. OPM's Human Capital Assessment and Accountability Framework (the Framework) offers possible performance indicators and links to other resources to help make and measure improvements. OPM believes organizations that make good use of the Framework will have a valuable system of human capital management accountability.

The OPM Framework contains the elements of strategic human capital planning for Federal agencies in the form of six standards:

- **Strategic alignment.** Agency human capital strategy is aligned with mission, goals, and organizational objectives and integrated into its strategic plans, performance plans, and budgets.
- **Workforce planning and deployment.** Agency is citizen centered, delayered, and mission focused and leverages e-Government and competitive sourcing.
- **Leadership and knowledge management.** Agency leaders and managers effectively manage people, ensure continuity of leadership, and sustain a learning environment that drives continuous improvement in performance.
- **Results-oriented performance culture.** Agency has a diverse, results-oriented, high-performing workforce and has a performance management system that effectively differentiates between high and low performance and links individual/team/unit performance to organizational goals and desired results.
- **Talent.** Agency has closed gaps in most mission-critical skills, knowledge, and competency deficiencies and has made meaningful progress in hiring qualified staff.
- **Accountability.** Agency human capital decisions are guided by a data-driven, results-oriented planning and accountability system.

NIH is deeply committed to creating and sustaining a trained and motivated workforce to carry out the mission of the Agency and has taken a number of steps to improve human capital management over the past several years—developed an initial strategic workforce plan, drafted a plan for managing the employee displacements expected to result from competitive sourcing initiatives, created a leadership succession plan, consolidated human resource management functions, and implemented performance contracts for senior executives and managers. All of these steps are important and useful. These and related human capital initiatives will be incorporated into a coordinated human capital strategy that fully supports the NIH mission.

The strategic human capital management plan will capture the workforce needs based on NIH's scientific agenda over the next 3 to 5 years, identify areas of staff expansion and contraction, establish basic competencies for key leadership positions, incorporate succession planning and leadership development programs to ensure that viable candidates are available for critical positions, and fully integrate human resources policies to shape the NIH workforce according to the mission of the Agency over the coming years. In addition to the OPM Framework, all workforce planning activities will support the tenets of the PMA and DHHS management initiatives.

PLANNED IMPLEMENTATION STRATEGIES

NIH is addressing its human capital management needs on multiple fronts. Cambria, Inc, a management consulting firm, has been engaged to study key aspects of the NIH scientific workforce. Meetings to clarify the full extent of the study are ongoing, but the current set of study issues includes:

- Rotating or changing lab chiefs
- Pathways for clinical research careers
- The role of recognition in succession planning for science positions
- Recruitment and retention of women and minorities in senior scientific positions
- Retirement of senior scientific staff; retention of commissioned officers after retirement
- The role and competencies required of staff scientists who must now work in interdisciplinary groups
- General recruitment issues for potential postdoctoral fellows, tenure-track investigators, tenured investigators, and clinicians.

The scientific workforce study described above will elucidate the issues dealing with turnover from key scientific leadership positions. It will provide the foundation for developing and implementing a systematic succession plan to preserve the continuity and quality of scientific leadership. This study is still in the early stages, but is moving forward and is expected to generate results in the coming months.

Also, NIH has contracted with Research and Organization Management, Inc. to assess the effectiveness of all administrative/research support functions. The purpose of this assessment is to provide NIH with a comprehensive strategy for improving its administrative activities to ensure that it is operating as efficiently and effectively as possible. An important corollary is that the administrative improvements augment the completion of its mission. All administrative/research support functions will be reviewed, including human resources, budget, finance, grants management, general administration, acquisition, contracting, property, facilities management, etc.

In addition to developing options for the consolidation of administrative activities, the review will assess the need to increase the supervisor-to-employee ratio, improve customer service, establish performance standards, reduce overlaps, enhance the use of technology, increase contracting out, and improve overall efficiency and effectiveness. NIH has engaged the National Academy of Public Administration to assist in the assessments that will be necessary during any consolidation of administrative functions.

A preliminary analysis of NIH leadership succession planning needs has been completed. Like the entire Federal workforce, the Senior Executive Service cadre at NIH is aging. NIH faces the prospect of significant leadership gaps as the baby-boom generation approaches retirement age. NIH has a variety of programs in

place to identify and develop potential leaders, but there are questions concerning the coordination, efficacy and competency basis for these programs. The latter is one reason why NIH is co-chairing a Departmental workgroup that is developing leadership competencies for use in leadership training and development programs. Lastly, NIH could possibly benefit by adopting leadership succession best practices developed in other agencies.

Finally, work on revising the NIH Strategic Workforce Plan is scheduled to begin in January 2004.

BASELINE(S)

- NIH Strategic Workforce Plan of August 2002
- Federal Human Capital Survey, 2002
- NIH Intramural Tenure-Track Program Guide; A Guide to Training and Mentoring in the Intramural Research Program at NIH; Demographic Analysis of NIH senior executive cadre as of 2002; Succession Planning Report, November 2002; Succession Planning Proposal, November 2002
- OPM Human Capital Standards; OPM Human Capital Assessment and Accountability Framework (the Framework)

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Considering the scientific agenda, applicable DHHS management initiatives, and future workforce trends, project the NIH human capital needs for the next 3 to 5 years.	(FY03) NIH Strategic Workforce Plan of August 2002		◇	
Using the standards for success outlined in Office of Personnel Management's Human Capital Assessment and Accountability Framework (i.e., the Framework), assess where NIH strengths and weaknesses exist regarding management of human capital.	(FY03) Federal Human Capital Survey, 2002		◇	
Implement succession planning and leadership development processes for critical positions.	(FY03) Succession Planning Report and Planning Proposal, November 2002			◇
Revise the NIH Strategic workforce plan to include new projections regarding human capital requirements and expand it to include an associated system of human capital management accountability.	(FY03) NIH Strategic Workforce Plan of August, 2002; OPM Human Capital Standards; the Framework			◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Performance results will be reported in February 2005.

GOAL d) ENSURE THAT NIH COMMERCIAL FUNCTIONS ARE PERFORMED AS EFFICIENTLY AND COST-EFFECTIVELY AS POSSIBLE BY CONDUCTING COMPETITIVE SOURCING REVIEWS ON THE REQUIRED NUMBER OF FUNCTIONS WITHIN THE AGENCY'S COMMERCIAL INVENTORY.

BACKGROUND

Governed by OMB Circular A-76, the underlying goals of the competitive sourcing initiative are to:

- Increase competition, thereby generating savings and noticeable performance improvements.
- Promote innovation, efficiency, and greater effectiveness through competition.
- Provide an imperative for the public sector to focus on continuous improvement by focusing on desired results and outcomes and removing roadblocks to greater efficiency.

In support of the DHHS objectives and the President's Management Agenda (PMA), NIH began identifying commercial activities for competitive sourcing reviews in FY 2002. By 2014, NIH will have performed cost comparisons on 100% of its commercial activities; these will be completed according to the requirements provided in the future years.

The competitive sourcing program will ensure that commercial activities are subjected to the rigor and discipline of market competition. On completion of each comparison, NIH will select the source that can provide the necessary services and ensure that quality standards are met at the lowest possible price.

Consistent with the Department's commitment that affected employees will have a job, NIH will be using all tools at its disposal to retrain, counsel, and place affected employees within NIH, HHS, other federal agencies or alternate employers. Use of VERA and Voluntary Separation Incentive Payments should help reduce the number of affected employees who will need to be placed.

PLANNED IMPLEMENTATION STRATEGIES

In accordance with the PMA, NIH plans to carry out annual commercial sourcing reviews through FY 2014. The basis for the reviews are the number of full time equivalent staff in particular functional areas and the annual guidance from the Department. To accomplish this task each year, NIH carries out a preplanning step in order to identify potential functional areas for review. A subset of the identified functional areas are then deemed appropriate for review through a negotiation process with the Department and OMB and then are reviewed. The A-76 requirement is met once the reviews are conducted and awards are made.

For FY 2004, the preplanning step identified 14 potential functional areas for review, and of these, ten were deemed appropriate for review and will be reviewed.

After each review is completed, NIH will develop transition plans to move to the new organizational structures and fill positions as proposed in the respective Most Efficient Organizations (MEOs) awards.

The NIH Transition Center is currently preparing to provide services to employees who are not hired into the MEOs, such as job search assistance and outplacement assistance. Further, the NIH Transition Center web site is under development, concurrent with development of a comprehensive database aimed at tracking affected employees' progress toward finding other employment as quickly as possible.

BASELINE(S)

- Preplanning initiated for identifying functional areas

- Functional areas identified as appropriate for review
- Transition plans developed for employees

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
1. Identify annually commercial activities for competitive sourcing comparison.	(FY02) Preplanning initiated for identifying functional areas	◆[e]	◇	◇
2. Complete negotiated competitive sourcing reviews annually.	(FY02) Functional areas identified as appropriate for review	◆[e]	◇	◇
3. Implement transition services for employees annually displaced due to prior year's competitive sourcing.	(FY03) Transition plans developed for employees		◇	◇

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

Target 1—For FY 2003, preplanning identified two potential functional areas for review. These two were deemed appropriate for competitive sourcing review and were reviewed.

Target 2—The two functional areas reviewed were in the areas of extramural administrative support services and real property management. Each review resulted in the decision to award the competed service to the NIH MEO.

Implementation Strategy Advances or Other Highlights

Through preparing and submitting bids for these services, NIH has demonstrated its commitment to careful stewardship of taxpayers' resources.

IV.B.2.b.5. Program Oversight and Improvement

NIH takes its responsibility as a steward of Federal funds very seriously. Exercising careful oversight is key to demonstrating good stewardship. In addition, NIH strives to continually improve oversight procedures, policies, and systems when need or opportunity arises. Management systems must be repeatedly updated to keep pace with advances in public administration, and mechanisms to ensure proper stewardship must evolve with the development of new requirements and rising thresholds for accountability. Meeting these challenges has always been a priority for NIH, but the PMA and the "One HHS" management objectives are focusing NIH attention even more tightly on results-oriented management.

The philosophy/value of results-oriented management is beginning to permeate oversight practices for all types of NIH activities and at all levels of supervision. Examples include implementation of an Earned Value Analysis and Management System for oversight of construction projects, expansion of the use of performance-based contracting, linkage of employee performance contracts with organizational objectives, and performance of proactive, compliance site visits to grantee institutions.

Some of the NIH goals that address program oversight and improvement also pertain to other functional areas for achieving the NIH mission and thus are included in other sections of this Plan/Report. The goal to develop the NBS is one such example. The NBS not only incorporates improved financial systems but also is an "enterprise" IT goal. Accordingly, the NBS goal is grouped with the other enterprise IT goals in the Capacity Building and Research Resources section.

GOAL a) ENSURE THAT APPROVED DESIGN AND CONSTRUCTION PROJECTS ARE EXECUTED ON TIME, ON SCOPE, AND ON BUDGET BY IMPLEMENTING AN EARNED VALUE ANALYSIS AND MANAGEMENT SYSTEM (EVAMS).

BACKGROUND

NIH is committed to improving management and oversight of its real property capital projects. The Earned Value Analysis and Management System (EVAMS) provides a means to do this. The EVAMS links resource planning to schedules and to technical cost and schedule requirements so that performance goals and management processes can be monitored and compared against actual results. All work is planned, budgeted, and scheduled in time-phased "planned value" increments that permit real-time data analysis for determining contract status to generate corrective actions when problems are identified. The EVAMS will provide NIH project managers with the information they need to track project performance and intervene as necessary to keep projects on time, on scope, and on budget.

PLANNED IMPLEMENTATION STRATEGIES

In accordance with OMB Circular No.A-11, Part 7,[1] NIH will implement a project management review system based on the EVAMS and use it to monitor and manage the performance of the design, acquisition, construction, and commissioning of capital facility projects. As a first step in the implementation of the EVAMS, NIH will integrate existing project management data from Lab 33–The Center for Bio-Terrorism and Emerging Infections, and the Northwest Parking Garage, into a "proof-of-concept" version of an NIH EVAMS. NIH will use information generated by EVAMS data reports and analysis to evaluate and redesign work processes to improve the efficiency and effectiveness of its capital project delivery systems.

The NIH established preliminary EVMS policies and procedures in June 2003 as a management tool to improve the delivery of capital projects. Projects in design and proposed for construction were identified to evaluate the system and be a source for collection of data to validate its effectiveness and flag areas needing enhancements.

Evaluation and assessment of existing project management systems and their integration into a proof-of-concept version of an EVAMS are estimated to take between nine and 12 months. The first draft of the development of EVAMS policies and procedures began in late June 2003. Implementation of a revised project management system that incorporates EVAMS is expected to take place within 16 months after the evaluation and proof of concept are completed.

Further, NIH will continue review of its project management systems, benchmark with public and private sector organizations, and pursue a grant under the NIH One Percent Evaluation Set Aside Program to assist in the evaluation, assessment, and validation of proposed EVAMS methodology.

Concurrent with this action, ORF will begin initial implementation of its proposed EVAMS and beta test it using a minimum of one (1) design and up to two (2) construction projects.

The NIH will continue data analysis and collection to enhance the EVMS. The services of a consultant, recognized as an EVAMS specialist, will be obtained to review, analyze and further validate the proof of concept version. Data will be verified using information from the Office of Research Facilities Quality Management System and the earned-value analyses that are performed for pilot projects. The lessons-learned from the pilot test, the benchmark results and the observations of consultants will be used to fully launch the NIH EVAMS in FY 2005.

BASELINE(S)

- Policies and procedures in place to identify data needed for evaluations
- EVAMS proof-of-concept version

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Evaluate and assess existing project management systems and implement into a proof-of-concept version of the NIH EVAMS.	(FY03) Policies and procedures in place to identify data needed for evaluation		◇	
Implement a revised project management system that incorporates earned value analysis and management.	(FY03) EVAMS proof-of-concept version			◇

◇ Target Active	◆ Target Met	→ Target Extended	✕ Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Performance results will be reported in February 2005.

[1] Office of Management and Budget. *Planning, Budgeting, Acquisition, and Management of Capital Assets*. OMB Circular No.A-11, Part 7. Executive Office of the President, June 2002.

GOAL b) EXPAND THE USE OF PERFORMANCE-BASED CONTRACTING (PBC).

BACKGROUND

One of the major challenges for Federal Government management and administration is improving the efficiency and effectiveness of contracting and procurement activities. Historically, Government policies, regulations, and attention have been directed at acquisition of supplies rather than services. A 1997 OMB memorandum requires that all Federal agencies use PBC methods, where practicable, and match acquisition and contract administration strategies with specific requirements. In this way, PBC complements the Government's overall emphasis on managing for results by linking payments to results rather than to effort or process.

PBC involves using performance requirements that define contracted work in measurable, mission-related terms, with performance standards of quality, quantity, and timeliness tied to those requirements. PBC also requires a quality assurance plan describing how contractor performance will be measured against performance standards. In cases where a contract is either mission critical or requires a large dollar amount, incentives are tied to the quality assurance plan measurements.

PBC provides NIH with useful indicators of contactor performance and allows vendors to be innovative in responding to requirements for specific products and services. NIH is therefore strongly committed to increasing the amount of NIH contracting dollars allocated to performance-based contracts. As new contract requirements and contract renewals arise, NIH will review each situation to determine whether using PBC is appropriate.

For FY 2004 and beyond, this goal has been recast to make it more outcome oriented by focusing on percentage of eligible service contracting dollars obligated to PBC. This approach is similar to that taken by OMB and allows the NIH targets to parallel directives from OMB's Office of Federal Procurement Policy.

PLANNED IMPLEMENTATION STRATEGIES

PBC activity is tracked monthly through submission of reports from the contracting offices and through reports of PBC funding activity from the Departmental Contract Information System. IC contracting offices are aware that PBC is a NIH GPRA target and they are aware of the Government-wide move toward PBC including the objective of having 50% of the eligible service contracting dollars obligated to PBC by the end of fiscal year 2005. The planned strategy is to achieve the goal in feasible increments, as evidenced by the stated targets.

BASELINE(S)

- The baseline for FY 2003 was developed from the target of FY 2002, when it was estimated that $207 million would be allocated to contracted work with requirements tied to performance expectations.
- This estimate was based on previous and anticipated PBC obligations.

PERFORMANCE TARGETS	BASELINE	FY 2000[1]	FY 2001[1]	FY 2002[1]	FY 2003	FY 2004	FY 2005
Increase the amount of NIH contracting dollars allocated through Performance-Based Contracting (PBC):							
Allocate $19.8 million of available NIH contracting dollars to PBC-eligible contracts.		◆					
Allocate $21.2 million of available NIH contracting dollars to PBC-eligible contracts.			◆				
Allocate $207 million of available NIH contracting dollars to PBC-eligible contracts.				◆			
Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	(FY02) $207 million projected for contracted work with requirements tied to performance				◆		
Obligate 40% of eligible service contracting dollars through PBC.	(FY03) Percentage of a contract that must be performance-based meets FAR minimum requirements					◇	
Obligate 50% of eligible service contracting dollars through PBC.	(FY03) 40% of eligible service contracting dollars were PBC in 2004						◇

[1] Baselines were not required prior to FY 2003.

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

NIH substantially exceeded its PBC target for FY 2003. Obligations to PBC as reported in the Departmental Contract Information System (DCIS) were $557,899,153. These obligations were reported throughout the fiscal year as monies were committed to various contracts throughout NIH.

Implementation Strategy Advances or Other Highlights

PBC activity is tracked monthly through submission of reports from the contracting offices and through reports of PBC funding activity from the DCIS. NIH contracting offices are aware that PBC is a NIH GPRA target, and they are aware of the governmentwide move toward PBC, including the objective of having 50 percent of the eligible service contracting dollars obligated to PBC by the end of FY 2005. The funds obligated to PBC in FY 2003, $557,899,153, show considerable movement toward further implementation of PBC from FY 2002, where the amount obligated to PBC was $429,816,008.

Meeting the FY 2004 and FY 2005 targets will depend on when and how the Federal Acquisition Regulation (FAR) changes the definition of what an "eligible" service contract is for the purposes of PBC. Also, it is expected that the percentage of a contract that must be performance based for that contract to be coded as performance based will change from the current 80 percent to 50 percent.

GOAL c) IMPROVE ACCOUNTABILITY FOR ORGANIZATIONAL PERFORMANCE RESULTS AND SUPPORT FOR THE PRESIDENT'S MANAGEMENT AGENDA BY LINKING THE EMPLOYEE PERFORMANCE MANAGEMENT PLANS/CONTRACTS TO NIH'S PROGRAM AND MANAGEMENT PRIORITIES.

We must have a Government that thinks differently, so we need to recruit talented and imaginative people to public service. We can do this by reforming the civil service with a few simple measures. We [will] establish a meaningful system to measure performance. Create awards for employees who surpass expectations. Tie pay increases to results. With a system of rewards and accountability, we can promote a culture of achievement throughout the Federal Government.

☙ President George W. Bush

BACKGROUND

Inspector Generals at nine major Federal agencies have listed workforce problems among the top 10 most serious management challenges that their agencies face.

The first major government-wide initiative under the PMA is the strategic management of human capital. The underlying goals of this initiative are to:

- Focus workforce analysis on planning for retirements and resulting skill imbalances.
- Reduce layers between civil servants and the citizens that the Federal Government serves.
- Link budget to individual performance.
- Enable Government to attract, recruit, retain, develop, and reward good talent and high performers.

DHHS outlined a program in support of the PMA by delineating "One HHS" management and program objectives. One of DHHS's management objectives is to improve the strategic management of human capital. The means to accomplish this objective include:

- Conducting ongoing workforce planning to assess the skills needed to accomplish the Department's mission now and in the future
- Attracting, hiring, and retaining exceptional individuals in critical occupations throughout DHHS
- Holding employees accountable for achieving measurable results through performance objectives linked to the Department's program and management priorities
- Encouraging managers to demonstrate appreciation by recognizing performance that exceeds expectations
- Providing better access to learning opportunities for all DHHS employees so they can enhance their critical competencies
- Designing effective succession planning and career development programs to build the next generation of DHHS leaders

NIH fully supports the PMA and DHHS's One HHS management objectives as reflected in the strategic human capital goals described below.

As required by law, every Federal employee must have a performance plan or contract that clearly outlines the responsibilities and duties by which he or she will be evaluated on an annual basis. These responsibilities and duties should be directly linked to the position, which in turn supports work necessary to the immediate organization. The results of an employee's performance evaluation can influence the granting of awards for excellence, within-grade increases, performance improvement actions, and so forth.

The current performance management system has been criticized by many as ineffectual for a variety of reasons, including the lack of measurable results and the absence of clear links to the organizational mission. To remedy this, the goals outlined in the PMA link human capital strategies to organizational mission, vision, core values, goals, and objectives.

The initial step taken by DHHS to address this issue was to introduce a new contract format for the Senior Executive Service (SES) that enables executives to identify outputs and outcomes in program areas and also, identify how each would support the PMA. The intent is to use clear, carefully aligned performance outputs for individual leadership positions. The expectation is that DHHS Agencies will meet or exceed established productivity and performance goals that could be the basis for performance awards.

DHHS undertook the establishment of the new SES performance contracts that eventually would "cascade" through the organization and charged DHHS Operating Divisions and Agencies (OPDIVs) with implementing this system. Initially, the system was applied only to OPDIV heads and senior executives. NIH has expanded it to include all NIH supervisors and managers in two-grade interval professional positions (those with two-grade promotion patterns, e.g., from GS-9 to GS-11). NIH is now in the process of cascading the new performance contract methodology throughout the organization.

PLANNED IMPLEMENTATION STRATEGIES

Phase II implementation covers managers' and supervisors' performance plans. Phase III implementation, which was announced by HHS in FY 2003, covers all remaining employees. The NIH has begun the final phase but bargaining units have not yet completed this activity.

BASELINE(S)

- Measurable outputs and outcomes placed in executive plans (completion of Phase I, FY 2002).

PERFORMANCE TARGETS	BASELINE	FY 2003	FY 2004	FY 2005
Incorporate outputs and outcome methodology in managers' and supervisors' performance plans.	(FY02) Measurable outputs and outcomes placed in executive plans (completion of Phase I, FY 2002)	◆		

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

The target was met by incorporating measurable outputs and outcomes methodology into managers' and supervisors' performance plans. This effort corresponded to Phase II implementation of the new approach to performance management, in which "One HHS" program and management objectives are cascaded from the level of executives to the level of managers and supervisors. The Office of Human Resources, NIH, completed review of representative managerial contracts for quality control and quality compliance and provided detailed feedback to NIH Institutes. This process moved NIH closer to its goal of improving accountability for organizational performance results by (1) ensuring that all Institute activities flow from, and are aligned with, NIH and HHS program and management objectives and (2) promoting leadership accountability for results.

Implementation Strategy Advances or Other Highlights

In April 2003, NIH began cascading revised HHS management objectives to all remaining employees to meet the Department's deadline of June 16, 2003.

GOAL d) ENSURE PROPER STEWARDSHIP OF PUBLIC FUNDING FOR RESEARCH.

BACKGROUND

With the receipt of NIH grant awards or other types of public funding for research, principal investigators and grantee institutions accept the responsibility to conduct scientific studies ethically and honestly and to provide proper stewardship of NIH funds. Because of the nature of the assistance relationship, which is predicated largely on trust between the sponsor (NIH) and the recipient (grantee institution), the need for effective internal and external compliance programs is essential. One of the 10 Department-wide program objectives, "Advance science and medical research," lists as one of its components the strengthening of mechanisms for ensuring the protection of human subjects and the integrity of the research process. Although these are only two of the many research compliance issues of concern to NIH, the Agency complemented the objectives of the DHHS Offices of Research Integrity and Human Subjects Research by supporting and establishing programs in these two areas. NIH support of Research on Research Integrity and the Human Subjects Research Enhancements Program are two such examples, and underpin Objective 4.5 in the DHHS Strategic Plan for FY 2003-2008.

More generally, to minimize the risks associated with noncompliance, NIH established a new goal in FY 2001 to ensure proper stewardship of public funding for research. This crosscutting goal involves ICs working in partnership with grantee institutions and national professional organizations to improve institutional compliance with NIH requirements.

PLANNED IMPLEMENTATION STRATEGIES

A significant NIH strategy for enhancing compliance is to develop a proactive grants compliance program. The program currently focuses on the following major activities: (1) enhancing administrative oversight by creating a new organizational component within NIH with the capacity to perform annual proactive compliance site visits, (2) increasing educational outreach by providing compliance seminars and providing Web-based information and tools to help grantees understand their stewardship role and improve their institutional compliance programs, and (3) creating an internal NIH compliance program to provide management control and exercise oversight for implementation of grant-related policies.

The compliance program will involve a newly established management controls compliance program. A subset of grants administration policies will be reviewed in order to assess the risk level of each policy. After this is accomplished, NIH can begin the internal compliance reviews (now planned for 2004). The latter will help to determine if the policies are correct, clear, and/or if training is needed to address any instances of noncompliance. These activities serve to enhance NIH's oversight of sponsored research.

BASELINE(S)

- Criteria in place for selecting institutions for site visits
- Framework for risk assessment in place
- Ten policies selected for compliance reviews
- Web site in place for grants compliance and oversight under the Office of Extramural Research

PERFORMANCE TARGETS *Note: Annual targets are grouped by activity.*	BASELINE	FY 2001[1]	FY 2002[1]	FY 2003	FY 2004	FY 2005
Enhance NIH's administrative oversight of sponsored research:						
1. Create an organizational component within NIH with FTEs devoted expressly to compliance-related activities.		◆				
2. Perform a minimum of 10 compliance site visits.		×				
3. Conduct eight proactive compliance site visits to grant recipient research institutions.			◆			
4. Conduct five proactive compliance site visits.	(FY02) Criteria in place for selecting institutions for site visits			◆		
5. Perform a risk assessment and develop a plan for reviews of compliance with grant-related policies.	(FY03) Framework in place for risk assessment			◆		
6. Begin internal compliance reviews.	(FY03) Ten policies selected for compliance reviews				◇	
7. Implement recommendations from the internal compliance reviews held in 2004.	TBD					◇
Increase educational outreach to improve institutional compliance with NIH requirements:						
8. Publish a compendium of observations and examples of compliance in action in the conduct and administration of sponsored programs at NIH's recipient institutions.			◆			
9. Provide Internet-accessible resource information and/or tools for implementing institutional compliance programs.	(FY02) Web site in place for grants compliance and oversight under the Office of Extramural Research			◆		

[1] Baselines were not required prior to FY 2003.

◇ Target Active	◆ Target Met	→ Target Extended	× Target Not Met

SUMMARY OF PERFORMANCE RESULTS

Target

Target 3—In FY 2003, NIH performed five proactive compliance site visits. During the site visits, NIH assessed institutional understanding of Federal requirements and expectations in the areas of roles and responsibilities and training and education, financial conflict of interest, financial management of sponsored programs, administering and overseeing clinical research, and extramural intellectual property. The site visits also included a formal program for educating the host and area institutions on these and other important compliance issues.

Target 4—NIH performed an initial risk assessment of 35 grants administration policies. To assess the relative risk level of each policy, a risk assessment instrument was developed. Certain responses to questions in the risk analysis, (e.g., concerning policies related to the welfare of humans subjects or animals in research), automatically earned a high-risk rating.

Target 5—To provide resource information and/or tools for enhancing institutional compliance programs, NIH posted on the Grants Compliance and Oversight Web page the slide presentation "A Federal Perspective on Compliance," including examples of how sponsored institutions can strengthen oversight and internal control systems.

Implementation Strategy Advances or Other Highlights

On the basis of the results of the risk analysis and its review methodology, NIH selected 10 policies for future review to assess internal compliance and determine whether the policies are correct and clear and/or whether training is needed to address any instances of noncompliance. These activities serve to enhance NIH's oversight of sponsored research.

V. APPENDICES TO THE PERFORMANCE PLAN AND REPORT

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APPENDIX 1: LINKAGE TO DHHS AND AGENCY STRATEGIC PLANS

The ways in which the NIH Performance Plan links to the DHHS Strategic Plan and other administration initiatives are indicated in the Program Performance Tables (see IV.B.2.a.). In the tables, the reference fields show indicate linkage to the DHHS Strategic Plan for FY 2003-2008, *Healthy People 2010*, and the President's Management Agenda. Here, however, the DHHS Strategic Plan is the starting point, and the NIH GPRA goals are linked to the DHHS objectives. Many of the NIH goals address more than one DHHS objective.[1] Nonetheless, to keep the NIH GPRA Plan/Report as streamlined as possible, NIH has associated each NIH goal with only one DHHS objective.

DHHS GOAL 1: Reduce the major threats to the health and well-being of Americans.

Objective 1.1 Reduce behavioral and other factors that contribute to the development of chronic diseases,

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 6c) By 2012, develop a knowledge base on Chemical Effects in Biological Systems using a "systems toxicology" or toxicogenomics approach.

Objective 1.2 Reduce the incidence of sexually transmitted diseases and unintended pregnancies.

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 3d) By 2010, develop an HIV/AIDS vaccine.

Objective 1.4 Reduce substance abuse,

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 1a) By 2005, conduct medications development with use of animal models, and begin to conduct Phase I and II trials of two potential treatments for alcoholism: cannabinoid antagonist rimonabant and corticotropin-releasing hormone antagonist antalarmin.

DHHS GOAL 2: Enhance the ability of the Nation's health care system to effectively respond to bioterrorism and other public health challenges.

Objective 2.1 Build the capacity of the health care system to respond to public health threats in a more timely and effective manner, especially bioterrorism threats.

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 3b) By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.

SRO 4a) By 2004, develop two new animal models to use in research on at least one agent of bioterror.

[1] For example, two NIH goals (the SIDS health disparity goal and the healthy hearing for life goal) are associated with the DHHS objective 7.2 to improve the development and learning readiness, as appropriate, of infants, toddlers, and preschool children. However, both goals are listed in this appendix under other DHHS objectives (3.4 and 4.4, respectively).

DHHS GOAL 3: Increase the percentage of the Nation's children and adults who have access to health care services, and expand consumer choices.

Objective 3.4 Eliminate racial and ethnic health disparities.

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 9b) By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.

NIH Communication and Transfer of Results (IV.B.2.b.2)

SRO a) By 2008, reduce the disparity between African American and white infants in back sleeping by 50 percent to further reduce the risk of SIDS.

DHHS GOAL 4: Enhance the capacity and productivity of the Nation's health science research enterprise.

Objective 4.1 Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 2a) By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.

SRO 2b) By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.

SRO 2c) By 2006, develop methods that can classify at least 75 percent of proteins from sequenced genomes according to evolutionary origin and biological structure.

SRO 3c) By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease by 2013.

SRO 4b) By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD), based on emerging scientific findings of genetic or environmental influences, or interactions of genes and the environment on the development of PD.

SRO 5a) By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens.

SRO 5b) By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE or lupus).

SRO 5c) By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medicines. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.

SRO 5d) By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.

SRO 6a) By 2012, identify the genes that control the risk for the development of age-related macular degeneration and glaucoma in humans.

SRO 6b) By 2011, assess the efficacy of at least three new treatment strategies for reducing cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease.

SRO 7b) By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarker(s) (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.

SRO 7c) By 2005, create the next-generation map of the human genome, a so-called "haplotype map" (HapMap), by identifying the patterns of genetic variation across all human chromosomes.

SRO 8a) By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.

SRO 8c) By 2006, build a publicly accessible Collection of Reference Sequences to serve as the basis for medical, functional, and diversity studies. A comprehensive Reference Sequence Collection will serve as a foundation for genomic research by providing a centralized, integrated, nonredundant set of sequences, including genomic DNA, transcript (RNA), and proteome (protein product) sequences, integrated with other vital information for all major research organisms.

Objective 4.3 Strengthen and diversify the pool of qualified health and behavioral science researchers.

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 8d) By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.

NIH Capacity Building and Research Resources (IV.B.2.b.3)

CBRR a) Recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, and career development awards and student loan repayment.

CBRR b) Promote data sharing and provide information in real time by implementing the NIH Business System.

Objective 4.4 Improve the coordination, communication, and application of health research results.

NIH Communication and Transfer of Results (IV.B.2.b.2)

CTR a) Increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the NINDS campaign “Know Stroke.Know the Signs.Act in Time.”

CTR c) Strengthen the capacity of developing countries to identify technologies and pursue their development into products through education and technical assistance.

CTR d) Increase the percentage of SBIR award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.

DHHS GOAL 5: Improve the quality of health care services.

Objective 5.1 Reduce medical errors.

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 7a) By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical-drug interactions.

DHHS GOAL 6: Improve the economic and social well-being of individuals, families, and communities, especially those most in need.

Objective 6.2 Increase the proportion of older Americans who stay active and healthy.

NIH Scientific Research Outcomes (IV.B.2.b.1)

SRO 1b) By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.

SRO 3a) By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease.

SRO 8b) By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.

SRO 9a) By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United Sates by 10 percent by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).

DHHS GOAL 8: Achieve excellence in management practices.

NIH Program Oversight and Improvement (IV.B.2.b.5)

POI b) Expand the use of Performance-Based Contracting (PBC).

POI d) Ensure proper stewardship of public funding for research.

Objective 8.1 Create a unified DHHS committed to functioning as one Department.

NIH Program Oversight and Improvement (IV.B.2.b.5)

POI c) Improve accountability for organizational performance results and support for the President's Management Agenda by linking the employee performance management plans/contracts to NIH's program and management priorities.

Objective 8.2 Improve the strategic management of human capital.

NIH Strategic Management of Human Capital (IV.B.2.b.4)

SMHC a) Implement governmentwide initiative on delayering management levels and streamlining organization.

SMHC b) Identify and develop potential successors for critical leadership positions by (1) developing and implementing an NIH-wide succession planning process that assesses the gaps between senior leadership needs and talent available, (2) identifying leadership competencies that will be critical to the mission of NIH now and in the future, and (3) providing developmental opportunities that will prepare potential successors to meet the demands required of senior leadership positions.

SMHC c) Improve the strategic management of NIH human resources by developing a comprehensive human capital plan based on the Agency's programmatic objectives and projected future needs.

Objective 8.3 Enhance the efficiency and effectiveness of competitive sourcing.

NIH Strategic Management of Human Capital (IV.B.2.b.4)

SMHC d) Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible, by conducting competitive sourcing reviews on the planned number of functions within the Agency's commercial inventory.

Objective 8.4 Improve financial management.

NIH Program Oversight and Improvement (IV.B.2.b.5)

POI a) Ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing an Earned Value Analysis and Management System.

POI b) Promote data sharing and provide information in real time by implementing the NIH Business System.

Objective 8.5 Enhance the use of electronic commerce in service delivery and record keeping.

NIH Program Oversight and Improvement (IV.B.2.b.5)

POI c) Streamline business processes and automate data movement by implementing the Clinical Research Information System (CRIS).

POI d) Provide greater functionality and more streamlined processes in grants administration by continuing to develop NIH electronic Research Administration (eRA).

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APPENDIX 2: CHANGES AND IMPROVEMENTS OVER PREVIOUS YEAR

Restructuring of the Plan

This latest NIH GPRA Plan/Report is significantly restructured from prior years' plans. This restructuring essentially is the second phase of a process that began with the shift, in February 2003, from primarily broad comprehensive research outcome goals to Scientific Research Outcome goals that are specific, that is, that have endpoints. The Scientific Research Outcome goals are representative of the NIH research program.

NIH has developed a more streamlined and forceful document. This has been achieved by (1) being more selective in deciding which measures to highlight, thus resulting in the inclusion of fewer measures; (2) making goals more outcome-oriented; and (3) increasing linkage to administration plans and initiatives. To achieve these ends, the conceptual presentation of NIH's programs transitioned from the three-program approach (research, training, facilities) to a one-program approach (research) that more fully expresses NIH's mission and clarifies NIH's activities. NIH supports one research program with multiple functional areas that provide output and process strategies to improve the program's outcomes. The report has been reorganized around these functional areas, as listed below:

- Scientific Research Outcomes
- Communication and Transfer of Results
- Capacity Building and Research Resources
- Strategic Management of Human Capital
- Program Oversight and Improvement

Each functional area provides an umbrella for a number of representative performance goals with indicators of performance (targets). To foster consistency, some of the prior, or FY 2003, goals were integrated into the new infrastructure.

The current Plan/Report has a 10 percent decrease in the number of goals and a 44 percent decrease in the number of targets compared with FY 2002. Currently, FY 2004 and FY 2005 contain 41 goals and 51 targets and 39 goals and 50 targets, respectively. The current goals are more outcome oriented than many previous goals. Also, many of the newly created goals directly address One HHS management objectives and the President's Management Agenda. The table below summarizes the number of goals and targets for FY 2003 through FY 2005.

	FY 2003		FY 2004		FY 2005	
New Plan	**Goals**	**Targets**	**Goals**	**Targets**	**Goals**	**Targets**
Scientific Research Outcomes	27	27	28	28	27	27
Communication and Transfer of Results	1	1	4	5	4	6
Capacity Building and Research Resources	2	4	4	10	3	9
Strategic Management of Human Capital	3	8	2	5	2	5
Program Oversight and Improvement	3	5	3	3	3	3
TOTAL	**36**	**45**	**41**	**51**	**39**	**50**

Summary of Goal Status – FY 2000 to FY 2005

A summary of the number of goals and targets for FY 2000 through FY 2005, and their status, is provided in the table below. This summary is provided only as a descriptive indicator of the status of our targets from one year to the next. Because goals and targets are not comprehensive, the summary data do not accurately reflect NIH's overall success. Performance information was updated through September 30, 2003. Goals and targets that were met in FYs 2000 through 2003 are included in the tally below.

Fiscal Year	Goals	Targets	LEVEL OF ACHIEVEMENT							
			Program (# of Goals)	Number of Targets	End of Targeted FY			As of September 30, 2003		
					Met	Extended	Not Met	Met	Extended	Not Met
2000	44	88	Research (32)	65	49	14	2	59	3	3
			Training (6)	14	6	5	3	10	0	4
			Facilities (6)	9	3	6	0	9	0	0
2001	36	90	Research (23)	63	52	9	2	61	0	2
			Training (6)	15	10	4	1	11	2	2
			Facilities (7)	12	5	7	0	11	0	1
2002	40	80	Research (26)	58	53	5	0	54	4	0
			Training (6)	15	8	4	2	8	4	2
			Facilities (8)	7	4	3	0	4	3	0
2003	36	45	Research (36)	45	39	8	0	3	0	0
2004	41	51	Research (41)							
2005	39	50	Research (39)							

APPENDIX 3: PARTNERSHIPS AND COORDINATION

NIH activities complement the efforts of sister DHHS agencies in many ways, and NIH participates actively in endeavors to coordinate across DHHS. In addition, many initiatives are undertaken in partnership with other DHHS agencies.

Correlation and Coordination

As a research agency, NIH's relationship with sister DHHS agencies is bidirectional; that is, NIH both receives information from and contributes information to other operating divisions/agencies (OPDIVs). Information collected by other DHHS agencies helps to inform NIH priority-setting processes in important ways. For example, the extensive data on disease prevalence and incidence collected by the Centers for Disease Control and Prevention (CDC) is a key source of knowledge about the burden of illness. In turn, NIH is often an important source of expertise for sister agencies. For example, prior to issuing regulations, the Food and Drug Administration (FDA) often seeks comment from NIH.

Research Coordination Council. In terms of coordination, the recent establishment of the RCC is a significant development. The RCC—an element of the Secretary's One HHS initiative—was established by Secretary Thompson in October 2001 to streamline research and evaluate Department-wide research priorities to ensure greater efficiencies in research, demonstration, and evaluation. The RCC will continue to provide a forum for developing new ideas to enable DHHS components, including the NIH, to take advantage of every opportunity for efficiency in the support and conduct of the Department's research programs.

Healthy People 2010. The coordination activities of the RCC build on a history of Department-wide planning. Perhaps the most significant trans-DHHS planning effort is the decadal articulation of health objectives, the latest of which is known as *Healthy People 2010*. NIH is an active participant in this process, lending expertise and vision to the Department's aims for the optimal health status of the Nation.

Additional examples of correlation and coordination include:

- *Adverse Event Reporting*. NIH is working closely with FDA to harmonize human subjects protection regulations and the handling of reports of adverse events. In this regard, NIH has developed a national database for gene transfer clinical research, which includes a reporting format accepted by both the NIH and FDA. The database is called the Genetic Modification Clinical Research Information System, or GeMCRIS. GeMCRIS provides a standardized means for reporting, organizing, and analyzing data in order to enable systematic analysis of data across all clinical studies and to enhance communication and application of knowledge gained from the studies.

- *Autoimmune Disease Research Plan*. A comprehensive research plan to fight autoimmune diseases was prepared by the NIH Autoimmune Diseases Coordinating Committee, a body of government and outside experts. This committee, established in 1998, facilitates collaboration among the NIH Institutes and Centers, other Federal agencies such as the CDC and the FDA, and private organizations. The plan will foster research to identify genetic, environmental, and infectious causes of autoimmune diseases and to develop new treatments and prevention strategies.

- *Early Notification System*. The NIH Early Notification System (ENS) facilitates the dissemination of information on upcoming research initiatives. To improve coordination of the Department's research activities, each OPDIV will identify a contact person for the ENS who will determine if their proposed solicitations should be entered into the ENS and coordinate review within their OPDIV. To assist in this effort, the NIH will offer training sessions of the ENS to the various agency contacts.

Trans-DHHS Collaborations

NIH institutes and centers collaborate with other DHHS agencies to efficiently maximize resources and expertise, advance scientific discoveries, and translate these discoveries into policies and programs that benefit the Nation. Just a few examples of these numerous efforts are described below.

Selected collaborations involving more than one other OPDIV:

- *Next-generation smallpox vaccine initiative:* The National Institute of Allergy and Infectious Diseases (NIAID) is leading a trans-DHHS initiative to develop a next-generation smallpox vaccine that can be administered to a broader population than existing smallpox vaccines, which pose substantially increased risks for people with eczema or immune deficiencies and for pregnant women. An intradepartmental task force, consisting of representatives from the Office of Public Health Policy, CDC, FDA, and NIH, is rapidly implementing a research and development plan intended to demonstrate the efficacy and safety of modified vaccinia Ankara, and then license it for use in these and other populations at risk. The work of this task force is of the very highest priority to NIH and DHHS, and represents an excellent and important example of post-9/11 collaboration.

- *HIV/AIDS Treatment Guidelines.* The Panel on Clinical Practices for the Treatment of HIV Infection meets regularly in order to make reliable up-to-date information on treatment of HIV/AIDS available to healthcare providers. The Panel is a joint effort of DHHS and the Henry J. Kaiser Family Foundation. Co-chaired by the Director of the NIH's National Institute of Allergy and Infectious Diseases, the Panel includes participants from CMS, FDA, HRSA, CDC, and SAMHSA. Initially published in 1998, the *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* was constructed as a "living document" and is updated by the Panel as new data emerge.

Selected Collaborations with the Centers for Disease Control and Prevention (CDC):

- *National Health and Nutrition Examination Survey*. Several NIH institutes and centers are collaborating with the CDC on the National Health and Nutrition Examination Survey (NHANES). NHANES is the only national source of objectively measured health data capable of providing accurate estimates of both diagnosed and undiagnosed medical conditions in the population. NHANES represents a unique collaboration among CDC, NIH, and others to obtain data for biomedical research, public health, tracking of health indicators, and policy development.

- *The National Diabetes Education Program*. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Division of Diabetes Translation of the Centers for Disease Control and Prevention jointly sponsor this initiative that involves over 200 public and private partners. The goal of the program is to reduce the illness and deaths associated with diabetes and its complications by increasing public awareness and understanding, improving the knowledge of health care providers, and promoting health care policies that improve the quality of and access to care.

Selected Collaborations with the Food and Drug Administration (FDA):

- *Rhesus Breeding Colony*. NIAID collaborates with the FDA on a colony for breeding Rhesus monkeys for research.

- *Toxicological Assessments*. The National Institute of Environmental Health Sciences (NIEHS) collaborates with the FDA on the conduct of comprehensive toxicological assessments.

- *Workshop on Antioxidants*. The National Center for Complementary and Alternative Medicine (NCCAM) is collaborating with the FDA on a workshop that will address the pros and cons of antioxidants including the role of antioxidants in cancer prevention and tumor biology, and their interactions with conventional chemotherapy and radiotherapy.

Selected Collaborations with the Indian Health Service (IHS):

- *Diabetes in Indian Populations*. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) collaborates extensively with the IHS on research and education regarding diabetes.

Selected Collaborations with SAMHSA:

- *Mental Health Services Collaboration.* The National Institute of Mental Health (NIMH) works closely with SAMHSA on a number of specific critical issues. For example, NIMH's services research program sponsors research on topics including the cost-effectiveness of specific mental health treatments, the economic impact of mental disorders, innovative models for assessing and treating mental illness in primary care settings, and research on ways to increase the adoption of appropriate mental health services in everyday clinical settings. NIMH has collaborated with SAMHSA to fund research on its demonstration projects. With this collaboration, NIMH pays for the research component while SAMHSA funds the delivery of services; this close relationship provides SAMHSA's programs with a strong research base and ensures that research findings are translated and disseminated to the field.

APPENDIX 4: DATA VERIFICATION AND VALIDATION

Types of Data Sources

Data for Quantitative and Other Goals With Definitive End Points

Most of NIH's performance goals contain quantitative or otherwise objective targets. The data for assessing objective/quantitative performance goals come from a variety of NIH sources:

Completion of Studies/Actions—Where a goal is to complete an action (e.g., respond to a recommendation), documenting evidence is provided that confirms the completion or status of the action. Studies and reports developed by and for the use of peer review and advisory councils and other distinguished independent panels and committees are examples of the information useful for this type of GPRA reporting.

Program Evaluation—Objective evaluation studies and analyses are already a well-established component of NIH's regular planning and management activities for its programs. Such studies are used to provide basic data on program performance, identify avenues for program improvement, and consider the implications of emerging issues on program operation. NIH also conducts various special evaluation studies in association with such agencies as the National Academy of Sciences and the National Science Foundation – such as large-scale, long-term studies of scientific personnel and training needs, research facilities, and research instrumentation.

Data Tracking and Collection Systems—Most performance comparisons for quantitative goals are based on data from information systems that are designed to track a particular operation. NIH has established and maintains a number of large-scale databases to meet its ongoing management needs (such as IMPAC – see below) or with other Federal agencies (such as Interagency Edison, see below). These databases play a role in the agency's GPRA performance assessment process. In general, these are public databases, created over a number of years through competitive proposals and subject to outside review by knowledgeable experts, and are maintained through standard database quality protocols. These data are widely regarded, within and outside of NIH, as providing a credible picture of various aspects of the Nation's biomedical research enterprise.

The table below identifies some of the data systems that are currently used at NIH to track and develop data for performance comparisons.

SYSTEM	PURPOSE	TYPES OF DATA	EXAMPLES OF GOALS THAT HAVE BEEN AND WILL BE VERIFIED
IMPAC (Information for Management, Planning, Analysis, and Coordination)	IMPAC is a comprehensive database system covering NIH's extramural research activities.	• Records of research contracts • Records of in-process grant applications • Interagency and intra-agency agreements	Training • FY04/05 goals B2b3 a, b
DCIS (Departmental Contracts Information System)	DCIS provides data collection and reporting capabilities needed to enable DHHS to comply with the reporting requirements mandated by Public Law 93-400.	• Contract actions for awards with an anticipated award value over $25,000	Program Oversight and Improvement • FY04/05 goal B3b6 b
CMMS (Computerized Maintenance Management System) **PIN** (Project Information Network)	Together, these systems are used to manage and monitor the acquisition, design, construction, modernization, replacement, and/or enhancement of NIH's capital assets.	• Acquisition strategy • Project status • Proposed schedules • Actual schedules • Proposed costs • Actual costs • Management reports	Intramural Modernization • FY03 goals B3b5 a, b, c,
WWW (World Wide Web**)**	Use of the WWW allows worldwide sharing of data, information, images, and sound to be posted and transmitted electronically.	• Genomic sequences • NIH policy and procedure documents • Clinical trial databases • Reports on use of Web sites	Communication and Transfer of Results • FY04/05 goal B2b2c Technology Development and Utilization • FY04/05 goal B2b5c

Data for Descriptive Goals

The "Alternative Form" assessment approach used for many of NIH's scientific research outcome goals poses some unique issues for data validation and verification. Nonetheless, virtually all of the outside advisory groups that have looked at this issue over the past several years (e.g., the White House Office of Science and Technology Policy, NAS panels and committees, the Office of Naval Research, and various other science agencies) have affirmed the centrality of peer review by technical experts in preparing findings about the productivity of basic research programs. (See, for example, the 1999 and 2001 NAS reports *Evaluating Federal Research Programs: Research and the Government Performance and Results Act* [1999] and *Implementing the Government Performance and Results Act for Research* [2001].)

The approach NIH uses to prepare these annual assessments of its research goals relies chiefly on such a peer review process (see Appendix 7 – Approach to Performance Assessment). The most prominent sources of data are science advances validated through the verification process inherent in the course of publication.

GOAL-BY-GOAL VERIFICATION AND VALIDATION

SCIENTIFIC RESEARCH OUTCOMES

Performance on the targets for each Scientific Research Outcome goal will be verified through citation of appropriate documentation. For example, verification and validation of performance on progress targets might include:

- Notices for solicitations of research applications e.g., RFAs, RFPs, PAs, and PARs, including date the solicitation was published on http://www.grants.gov
- Cooperative Research and Development Agreements
- Initiated or active clinical trials, including citation of the extramural award(s) and intramural projects
- Workshops, meetings, and conferences that could be validated by copies of agendas, proceedings, reports, or other program records
- Working groups, coordinating committees, or advisory groups that could be validated by copies of rosters, meeting agendas, minutes, and other program records
- Strategic plans and research agendas validated by citations of the documents

Verification and validation of performance on output and outcome targets might include:

- Peer-reviewed journal articles (citations including publication journal and date and/or URL)
- Annual progress reports from grants/contracts
- Reports from databases maintained by clinical trial statistical centers
- Electronic databases or resources for information (URLs)
- Patents
- Licenses

FY 2003 actual verifications

GOAL	SOURCE VALIDATION
SRO 1a	Protocol submitted for IRB approval entitled, "Clinical Trial of the Cannabinoid CB1 Receptor Antagonist, Rimonabant, to Reduce Voluntary Ethanol Drinking" to test Rimonabant in humans.
SRO 1b	Yoo K, Gibbons C, Su QT, Miles RN, Tien NC. Fabrication of biomimetic 3-D structured diaphragms. Sensors and Actuators A: Physical, Volumes 97-98:448-456, 2002.
SRO 2a	Not applicable; target has been extended
SRO 2b	MCH: Proc Natl Acad Sci USA 100:10085-10090, 2003 SCD-1: Biochem Biophys Res Comm 297:1259-1263, 2002 Ghrelin: J Clin Endo Metabol 88:1577-1589, 2003
SRO 2c	The Conserved Domain Database is described in: Marchler-Bauer A, Anderson JB, DeWeese-Scott C, Fedorova ND, Geer LY, He S, Hurwitz DI, Jackson JD, Jacobs AR, Lanczycki CJ, Liebert CA, Liu C, Madej T, Marchler GH, Mazumder R, Nikolskaya AN, Panchenko AR, Rao BS, Shoemaker BA, Simonyan V, Song JS, Thiessen PA, Vasudevan S, Wang Y, Yamashita RA, Yin JJ, Bryant SH. CDD: a curated Entrez database of conserved domain alignments. Nucleic Acids Res. 31:383-387, 2003. The conserved domain database is integrated into PubMed. Search by keywords is supported at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=cdd The "domains" links from PubMed protein sequences provide classification by protein family: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=protein Search with new sequences is provided by: http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi These PubMed database services are validated continuously by automated test procedures and the Conserved Domain Database staff are notified by email in case of any failure. Usage at the end of FY 2003 averaged 24,000 domain architecture displays per day.
SRO 3a	Verification of the Simvastatin study can be found at http://clinicaltrials.gov/ct/show/NCT00053599?order=1.
SRO 3b	Hoebe K et al. Identification of Lps2 as a key transducer of MyD88-independent TIR signaling. Nature 424:743-748, 2003. Cole AM, Hong T, Boo LM, Nguyen T, Zhao C, Bristol G, Zack JA, Waring AJ, Yang OO, Lehrer RI. Retrocyclin: a primate peptide that protects cells from infection by T- and M-tropic strains of HIV-1. Proc. Natl. Acad. Sci. U S A. 99(4):1813-1818, 2002. Wang W, Cole AM, Hong T, Waring AJ, Lehrer RI. Retrocyclin, an antiretroviral theta-defensin, is a lectin. J. Immunol. 170:4708-4716, 2003.
SRO 3c	NIH's progress in funding and implementing cooperative agreements in the area of salivary diagnostics can be confirmed through the central data systems, which track applications received and projects funded in a centralized database that includes verification and quality control measures. Selected fields of this database can be accessed by the public at http://www.crisp.cit.nih.gov/. The reference numbers for these agreements are as follows: U01DE015017; U01DE015018; U01DE014971; U01DE014950; U01DE014961; U01DE014955; U01DE014964. In addition, a web site with further information on the program can be accessed at http://nidcr.bioeng.washington.edu/index.html
SRO 3d	1. Musey L, Ding Y, Elizaga M, Ha R, Celum C and McElrath MJ. HIV-1 Vaccination Administered Intramuscularly Can Induce Both Systemic and Mucosal T Cell Immunity in HIV-1 Uninfected Individuals. Journal of Immunology 171:1094-1107, 2003 (in press). 2. Haglund K, Leiner I, Kerksiek K, Buonocore L, Pamer E, and Rose JK. Robust recall and long-term memory T-cell responses induced by prime-boost regimens with heterologous live viral vectors expressing human immunodeficiency virus type 1 Gag and Env proteins. Journal of Virology 76: 7506-7517, 2002. 3. Fitzgerald, JC, Gao, GP, Reyes-Sandoval, A, Pavlakis, GN, Xiang, ZQ, Wlazlo, AP, Giles-Davis, W, Wilson, JM, and Ertl, CJ. A simian replication-defective adenoviral recombinant vaccine to HIV-1 gag. Journal of Immunology 170:1416-1422, 2003. 4. Chakrabarti BK, Kong WP, Wu BY, Yang ZY, Friborg J, Ling X, King SR, Montefiori DC, and Nabel GJ. Modifications of the Human Immunodeficiency Virus Envelope Glycoprotein Enhance Immunogenicity for Genetic Immunization. Journal of Virology 76:5357-5368, 2002. 5. NIAID Public-Private Partnerships Seek to Develop HIV/AIDS Vaccine. NIAID News (Press Release) June 27, 2000.

	http://www.niaid.nih.gov/newsroom/releases/hvddt.htm 6. NIAID awards $81 million for HIV vaccine development. NIH News (Press Release) September 29, 2003. 7. AlphaVax receives two NIH biodefense grants. AlphaVax Press Release, September 29, 2003. http://www.alphavax.com/newalphavax/html/pr13.html 8. Epimmune awarded $16.7 million National Institutes of Health contract for HIV vaccine development. Epimmune Press Release, September 29, 2003. http://www.epimmune.com/news/showarticle.cfm?number=117 9. Novavax selected by NIAID/NIH to develop HIV vaccine. Novavax Press Release, September 29, 2003. http://www.novavax.com/news.html
SRO 4a	Results of the validation testing of human variola and monkeypox cynomolgus monkey models were presented at the meeting "Smallpox Biosecurity: Preventing the Unthinkable" in Geneva, Switzerland on October 22, 2003. The title of the presentation was "Immune response to vaccination and new developments with attenuated vaccines." (http://www.smallpoxbiosecurity.org/conference2.php?menu=conference). A password to enable download of the videoconference online or a CD/ROM of the conference can be obtained by contacting CONTACT@SMALLPOXBIOSECURITY.ORG
SRO 4b	An abstract of the NIH supplement funding this resource can be found at: http://www.ninds.nih.gov/parkinsonsweb/grants_topic_2002.htm?topic=130 (Grant Number: 3P50NS038367-04S2).
SRO 5a	http://aactg.s-3.com/ainfo.htm http://www.pactg.s-3.com/pinfo.htm
SRO 5b	Not applicable; target has been extended
SRO 5c	A press release announcing establishment of the Chemical Methods and Library Development Centers is located at: http://www.nigms.nih.gov/news/releases/CMLD2.html
SRO 5d	NIH approval for the NCDDG-MD/NA grants can be confirmed through the searchable database of federally-funded biomedical research projects located at http://www.crisp.cit.nih.gov. The relevant grant numbers for the queries are as follows: U01MH069062-01 GABA B Compounds for Depression and Smoking Cessation U19MH069056-01 Collaborative Mood Disorders Initiative U19DA017548-01 Development of Novel Treatments for Nicotine Addiction
SRO 5e	Not applicable; new goal
SRO 6a	1. NEIBank web site at http://neibank.nei.nih.gov/ 2. Wistow G et al: A project for ocular bioinformatics: NEIBank. Molecular Vision 8:161-163, 2002. 3. Wistow G et al: Grouping and identification of sequence tags (GRIST): Bioinformatics tools for the NEIBank database. Molecular Vision 8:164-170, 2002. 4. Wistow G et al: Expressed sequence tag analysis of adult human lens for the NEIBank Project: Over 2000 non-redundant transcripts, novel genes and splice variants. Molecular Vision 8:171-184, 2002. 5. Wistow G et al: Expressed sequence tag analysis of human RPE/choroid for the NEIBank Project: Over 6000 non-redundant transcripts, novel genes and splice variants. Molecular Vision 8:205-220, 2002. 6. Schultz DW et al: Analysis of the ARMD1 locus: Evidence that a mutation in HEMICENTIN-1 is associated with age-related macular degeneration in a large family. Hum Mol Genet Advance Access (Oct. 2003) 7. Tomarev SI: Gene expression profile of the human trabecular meshwork: NEIBank sequence tag analysis. Invest Ophthalmol Vis Sci 44(6):2588-2596, 2003.
SRO 6b	The results of the DCCT were published in 1993 (New Engl J Med 329: 977-986). The DCCT follow-up study, EDIC, is tracking the participants in the DCCT to determine the longer-term effects of the interventions in the original trial. The results described in response to the FY 2003 target were published in 2003 (New Engl J Med 348: 2294-2303).
SRO 6c	Sources that verify that the FY 2003 performance target was achieved include the CEBS web site at http://cebs.niehs.nih.gov/ and the publications listed below. An account to access CEBS can be provided to permit independent verification of the launching of the database. Waters, M, Boorman G, Bushel P, Cunningham M, Irwin R, Merrick A, Olden K, Paules R, Selkirk J, Stasiewicz S, Weis B, Van Houten B, Walker N, and Tennant R. Systems toxicology and the Chemical Effects in Biological Systems (CEBS) knowledge base, Environmental Health Perspectives Toxicogenomics111(1T): 15-28 (2003). Xirasagar S, Gustafson S, Merrick AB, Tomer KB, Stasiewicz S, Chan DD, Yost KJ, Yates JR, Xiao N, Waters MD, CEBS object model for systems biology data, CEBS SysBio-OM (submitted October 2003). Mattes WB, Pettit SD, Sansone A, Bushel P, and Waters MD, Database development in toxicogenomics: issues and efforts (submitted August 2003).
SRO 7a	The results of all studies cited here have been published in peer reviewed scientific journals: • St. John's wort: JAMA. 290(11):1500-1504, 2003. Clin Pharmacol Ther. 73(1):41-50, 2003 • Ginkgo biloba: J Clin Psychopharmacol. 23(6):576-581, 2003 • Garlic: Clin Pharmacol Ther. 74(2):170-177, 2003 • Siberian Ginseng: Drug Metab Dispos. 31(5):519-22, 2003 • PC-SPES: J Pharmacol Exp Ther. 306(1):187-94, 2003. Epub 2003 Apr 03 • Saw Palmetto: Clin Pharmacol Ther. 74(6): 536-42, 2003

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- North American Ginseng: Drug Metab Dispos. 30(4):378-84, 2002

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<tr><td>SRO 7b</td><td>

1. Alper J. US NCI contracts push high-risk, high-reward research. Nature (online) October 2, 2003. 10.1038/bioent773
2. Liotta LA, Ferrari M, Petricoin E. Written in blood. Nature 425:905, 2003.
3. Liu J and Ferrari M. Mechanical spectral signatures of malignant disease? A small-sample, comparative study of continuum vs. nanobiomechanical data analyses. Dis Markers 18:175-183, 2002.
4. Luk YY and Abbott NL. Surface-driven switching of liquid crystals using redox-active groups on electrodes. Science 301:623-626, 2003.
5. Majumdar A. Bioassays based on molecular nanomechanics. Dis Markers 18:167-174, 2002.
6. Park EJ, Brasuel M, Behrend C, Philbert MA, Kopelman R. Ratiometric optical PEBBLE nanosensors for real-time magnesium ion concentrations inside viable cells. Anal Chem 75:3784-3791, 2003.

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<tr><td>SRO 7c</td><td>

The University of Utah has been in charge of obtaining the reconsent for the existing DNA samples needed for this project. Following IRB approval, University of Utah researchers contacted the families first by letter then by phone to obtain their consent. All of the signed consent forms for use of these samples are housed at the University of Utah.

The International HapMap Consortium has written a paper describing the International HapMap Project that can be found in Nature, 496:789-796, 2003.

An overview of the HapMap project can be found at http://www.genome.gov/10001688

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<tr><td>SRO 8a</td><td>

ORGANISM	REFERENCE	URL FOR SEQUENCE DATA
Anopheles gambiae	Holt et al., The genome sequence of malaria mosquito *Anopheles gambia*, Science 298:129-149, 2002.	http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=agambiae.inf
Bacillus anthracis	Read TD et al., The genome sequence of *Bacillus anthracis* Ames and comparison to closely related bacteria, Nature 423:82-86, 2003.	http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=299
Burkholderia mallei		http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=5069
Clostridium perfringens		http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=5107
Coxiella burnetii	Seshadri RS et al., Complete genome sequence of the Q-fever pathogen *Coxiella burnetii*. Proc Natl Acad Sci USA 100:5455-5460, 2003.	http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=293
Cryptosporidium parvum		http://www.cbc.umn.edu/ResearchProjects/AGAC/Cp/database.htm
Enterococcus faecalis	Role of Mobile DNA in the Evolution of Vancomycin-Resistant *Enterococcus faecalis*. Science 299: 2071-2074, 2003.	http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=292
Escherichia coli (K1 RS218)		http://www.genome.wisc.edu/sequencing/rs218.htm
Leishmania major		http://www.genedb.org/genedb/leish/index.jsp
Plasmodium falciparum	Gardner M et al., Genome sequence of human malaria parasite, *Plasmodium falciparum*, Nature 419: 498-511, 2002.	http://PlasmoDB.org
Streptococcus agalactiae	Tettelin H et al., Complete genome sequence and comparative genomic analysis of an emerging human pathogen, serotype V *Streptococcus agalactiae*, Proc Natl Acad Sci USA 99:12391-12396, 2002.	http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=Genome&gi=252
Rickettsia rickettsii		http://isbmgb.systemsbiology.net/cgi-bin/welcome.cgi
Rickettsia typhi	http://hgsc.bcm.tmc.edu/microbial/Rtyphi/	ftp://ftp.hgsc.bcm.tmc.edu/pub/data/Rtyphi/
Salmonella typhi	Deng W et al., Comparative Genomics of *Salmonella enterica* Serovar Typhi Strains Ty2 and CT18, J Bacteriol 185:2330-2337, 2003.	http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=290
Trypanosoma cruzi		http://www.tigr.org/tdb/e2k1/tca1/
Wolbachia		http://www.tigr.org/tigr-scripts/CMR2/GenomePage3.spl?database=dmg

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SRO 8b	The results discussed above are described in the Grant Progress Report submitted by the University of Michigan as part of the application for continued funding of this project. The Grant Progress Report is part of the official file on grant AR49682, which is maintained by the Extramural Research Program.
SRO 8c	The existence of the RefSeq release files on the FTP site serves to verify that the FY 2003 performance target was met. In addition, the RefSeq release was announced on the RefSeq home page. Quality control measures are incorporated into the implementation plan to validate the data provided. See: ftp://ncbi.nih.gov/refseq/release/ -FTP site http://www.ncbi.nih.gov/RefSeq/ - RefSeq home page
SRO 8d	The data collection and management is done at http://aprsis.ncrr.nih.gov
SRO 9a	Caspi A, Sugden K, Moffitt TE, Taylor A, Graig IW, Harrington HL, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301: 386-389, 2003. http://www.sciencemag.org/cgi/content/full/301/5631/386: Moderation by a Polymorphism in the 5-HTT Gene http://www.nimh.nih.gov/events/prreleas.cfm: Gene More Than Doubles Risk Of Depression Following Life Stresses
SRO 9b	Sources that verify the FY 2003 target have been achieved include the Notices of Grant Award (NGA) that were issued for each of the seventeen Partnership Centers and the NIH News Release announcing the creation of the Centers (http://www.nih.gov/ninr/news-info/healthdisp.pdf The NGA is the official NIH notice to a grantee that their grant is being awarded

COMMUNICATION AND TRANSFER OF RESULTS

FY 2003 actual verifications

GOAL	SOURCE VALIDATION
CTR a	**NIH NEWS RELEASES** Summits Seek to Reduce SIDS Risk In African American Community (http://www.nichd.nih.gov/new/releases/sids_risk.cfm) L.A. Summit Seeks to Reduce SIDS in Western U.S. African American Communities (http://www.nichd.nih.gov/new/releases/reduce_sids.cfm) Detroit Summit to Bring African American Women Together to Reduce SIDS Risk (http://www.nichd.nih.gov/new/releases/detroit_summit.cfm) **NEWS ARTICLES** (http://12.31.13.115/HealthNews/reuters/NewsStory0205200317.htm) (http://www.aapms.org/MS-HBU%20Dec%20031.htm)
CTR b	Not applicable; No FY 2003 targets
CTR c	Not applicable; No FY 2003 targets
CTR d	Not applicable; No FY 2003 targets

CAPACITY BUILDING AND RESEARCH RESOURCES

FY 2003 actual verifications

GOAL	SOURCE VALIDATION
CBRR a	Not applicable; No FY 2003 targets
CBRR b	The URL for the NBS PROJECT (including modules) is http://nbs.nih.gov
CBRR c	Not applicable; No FY 2003 targets
CBRR d	Verification for the FY 2003 target will be available in January 2004 when a formal announcement inviting all 145 FDP institutions to use the Electronic Streamlined Noncompeting Award Process (e-SNAP) system will be issued.

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

FY 2003 actual verifications

GOAL	SOURCE VALIDATION
SMHC a	NIH official organizational charts reflect the changes made to the NIH organizational structure. The charts are available online at: http://oma.od.nih.gov/ms/organization/
SMHC b	**Target 2**: Succession Planning Report, November 2002, can be requested from the NIH Office of Strategic Management Planning. **Target 3**: ARAC: http://www.nih.gov/icd/od/foia/icdirminutes/icdir051503.htm NIH Steering Committee: http://www.nih.gov/news/pr/jul2003/od-25.htm
SMHC c	Not applicable; no FY 2003 targets
SMHC d	Extramural Administrative Support Services award - http://www.nih.gov/news/pr/sep2003/od-24.htm Real Property Management award - http://www.nih.gov/news/pr/oct2003/od-22.htm

PROGRAM OVERSIGHT AND IMPROVEMENT

FY 2003 actual verifications

GOAL	SOURCE VALIDATION
POI a	Not applicable; no FY 2003 targets.
POI b	The DCIS is used to determine the obligated amounts: contracting personnel enter a specific code into DCIS indicating that the monies are being obligated to requirements that are performance-based. The DCIS is accessible only to authorized users. Monthly reports from the contracting offices that are submitted to the NIH Office of Acquisition Management and Policy are available.
POI c	NIH Institute Executive Officers certified completion of the establishment of performance contracts for Phase II. These certifications are located in the NIH Office of Human Resources, Workforce Relations Division.
POI d	The proactive compliance site visit schedule, the Proactive Compliance Site Visits Compendium of Findings and Observations, and A Federal Perspective on Compliance is posted publicly at http://grants.nih.gov/grants/compliance/compliance.htm The risk assessment documentation is available upon request from the Office of Extramural Research.

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APPENDIX 5: PERFORMANCE MEASUREMENT LINKAGES
(With Cost Accounting, Information Technology Planning, Capital Planning, and Program Evaluation)

Cost Accounting
NIH develops and reports the cost of its three programs on its audited Statement of Net Costs, as required by the CFO Act, the GMRA, and the Office of Management and Budget. These reported costs are derived using an accrual basis of accounting as required by federal accounting standards and the Federal Financial Management Improvement Act. These amounts differ from the reported obligations or budgetary resources included in budget documents that use an obligation basis of accounting.

NIH includes cost measures for performance goals, as appropriate, in its service and supply fund activities. NIH finances these activities using a fee for service cost recovery method. NIH develops cost per unit of goods or services and benchmarks these unit costs with other providers of similar or complementary goods and services. Also, NIH strives to increase stakeholder value by reducing the cost per unit of goods or services wherever possible.

Information Technology Planning
Information Technology (IT) plays an important role in contributing to the success of the NIH mission to uncover new knowledge about the prevention, detection, diagnosis, and treatment of disease and disability. IT supports the research done in NIH laboratories and grantee institutions as well as supports the training of research investigators, the communication of medical information, and the management of research and administrative activities. This year's Plan/Report addresses three major IT initiatives, known as enterprise systems (see IV.B.2.b.3., goals b-d). The responsibility for the enterprise systems involves a partnership between the functional area manager/program official, who serves as the business owner, and the Chief Information Officer (CIO). The enterprise systems dovetail with the DHHS Enterprise Information Technology Strategic Plan. NIH manages its IT activities in accordance with the Secretary's vision of managing DHHS IT on an enterprise basis. In the last seven years NIH has established and strengthened a governance structure that focuses the IT activities of the agency on the NIH mission and institutionalizes a corporate-wide perspective in the management of the IT function. The accomplishment of the IT-specific goals began in 1996, when the NIH Director began activities for managing selected elements of IT from a corporate-wide perspective. His first step addressed the organizational structure by hiring a CIO and the second established the Center for Information Technology (CIT). In addition, two advisory groups were established: the NIH Director formed NIH's IT Board of Governors (BOG), composed of selected senior management from across NIH, and the NIH CIO established the NIH IT Management Committee (ITMC), composed of senior Institute and Center (IC) IT representatives. The BOG's purpose is to (1) review and make recommendations on the IT activities and priorities of the NIH and (2) assess and advocate resources to implement those priorities. These recommendations are forwarded to NIH's Funding Advisory Review Board (FARB) for final decision-making.

Since then, the CIO and the CIT advisory groups have developed a process for managing IT from a corporate-wide perspective to make it more effective in supporting the mission of NIH and in providing integrated systems that support the variety of NIH business processes. They accomplished the following:

- Strengthened the investment review process
- Established a formal project management structure for enterprise IT
- Refined and implemented the strategic, corporate "IT vision" for NIH
- Developed an NIH-wide information security program
- Developed interoperability standards

In addition, guidance was developed to assist the ICs in establishing performance measures and evaluating IT programs based on performance measures, (which can be found at http://www.cit.nih.gov/mgmt-pol.html). Discussions of performance measures were woven throughout the Investment Review process described at

http://irm.cit.nih.gov/itmra/invreview.html and were also incorporated in the IT Management Guide, http://irm.cit.nih.gov/itmra/mgtprocess.html. Now, when IC program managers conduct a business case analysis, they are advised to address IT performance measures among others. Resources and tools were made available to facilitate this process and can be found at http://irm.cit.nih.gov/itmra/perfmeasure.html. In addition, the Office of the CIO initiated a recurring class in performance measures, to increase the number of IT and program managers familiar with the creation and use of performance measures.

Having set these organizations, processes, guidelines and tools in place, NIH has focused its Information Technology planning on pursuing the mission of the NIH as described in this Plan/Report. This accomplishment has also enhanced our ability to accomplish the IT-related goals within our core programs in conformance with the performance measurement principles of GPRA.

Capital Planning
For FY 2004 and beyond, NIH is taking a new approach to representation of capital planning in the GPRA Plan/Report. In accordance with OMB Circular A-11, Part 6, for FY 2004 and beyond, the NIH Capital Asset Plan (required under Part 7 of OMB Circular A-11) is hereby incorporated in the GPRA Plan/Report.

Evaluation
Evaluation is the foundation of managing for results. Inevitably, program managers and other decision-makers gather information about a program and make judgments about its worth or value. The quality of those judgments depends on the quality of the information upon which they are based. For that reason, NIH program managers depend on two complementary evaluation activities, *performance measurement* and *program evaluation*, to establish reasonable performance goals and to accurately assess progress toward those goals.

Performance measurement refers to regular monitoring of program accomplishments. Program accomplishments include the activities conducted (process), products produced or services delivered (outputs), and the results of those products and services (outcomes). Performance measurement is conducted by program managers to gauge how well the program is progressing toward its intended goals. The information gained from such on-going tracking systems may alert program managers to emerging problems and may spur a program evaluation to provide more information on why the program is not achieving anticipated results.

Program evaluation refers to systematic investigations or studies that involve assessing the worth and/or performance of particular programs. In most cases, the underlying purpose of a program evaluation is to help program managers answer specific questions about a program, such as whether it is being implemented as planned or is achieving its intended purpose. Managers typically use the information obtained from program evaluations to understand why certain results are or are not being achieved and to make adjustments in program strategies or activities. The four types of program evaluations conducted by NIH are needs assessments, feasibility studies, process evaluations, and outcome evaluations. Needs assessments and feasibility studies are usually conducted as preliminary studies (e.g., to improve the design of a more complex process or outcome evaluation). Experts external to the program often conduct program evaluations, but program managers may also conduct them.

Purposes of Program Evaluation under GPRA
At NIH, program evaluation serves two important purposes under GPRA: to support program planning and to support program performance assessment.

Support Program Planning. Program evaluations provide useful information to NIH's program managers regarding the appropriateness of established performance goals, annual targets, and implementation strategies. For example, needs assessments are typically conducted to identify systematically whom a program is serving and the extent to which their needs are being addressed. Needs assessments also may explain why certain needs are not being met and how the program could be revised to address the unmet needs. Using the information gained from such evaluations as a foundation for program planning, NIH program managers develop and modify

performance goals and targets to more effectively direct their programs toward the desired outcomes. In addition, the strategies used to implement NIH programs are often adjusted based on evaluation findings.

Support Program Performance Assessment. Program evaluations support program performance assessment activities at NIH primarily by providing insight regarding the relationship between NIH activities and the results NIH seeks to achieve. Outcome evaluations are often conducted to obtain methodologically sound information about the effectiveness of a program and to measure the program's progress towards goal achievement. In addition, this information is critical to determining the extent to which a program's activities contributed to any measured progress toward the desired end result or outcome.

NIH managers also use process evaluations to examine program progress (as evidenced primarily by program outputs) and to determine whether programs are being implemented as planned. The information gleaned from these evaluations allows managers to make midcourse corrections and improve program administration. Finally, feasibility studies are used to develop better ways to measure program performance. Examples include developing databases to track information over time, identifying ways to more effectively access existing data sources, developing new data collection instruments, and validating/verifying data sources.

APPENDIX 6: NIH INSTITUTES AND CENTERS

INSTITUTE/CENTER	MISSION
National Cancer Institute	NCI conducts and supports programs to understand the causes of cancer; prevent, detect, diagnose, treat, and control cancer; and disseminate information to the practitioner, researcher, patient, and public. The Institute's efforts are directed at reducing the burden of cancer morbidity and mortality and, ultimately, at preventing the disease.
National Heart, Lung, and Blood Institute	NHLBI's research program is directed at diseases of the heart, blood vessels, lungs, and blood and at transfusion medicine. Its activities encompass innovative basic, clinical, population-based, and health education research.
National Institute of Dental and Craniofacial Research	NIDCR's research program is directed at understanding, treating, and ultimately preventing infectious and inherited craniofacial-oral-dental diseases and disorders that compromise millions of human lives.
National Institute of Diabetes and Digestive and Kidney Diseases	NIDDK conducts and supports research, training, health information dissemination, and other programs with respect to diabetes mellitus and other endocrine and metabolic diseases; digestive diseases and nutritional disorders; and kidney, urologic, and hematologic diseases.
National Institute of Neurological Disorders and Stroke	NINDS conducts and supports research and training on the normal and diseased nervous system to reduce the burden of neurological diseases. The research program is ultimately directed at improving the prevention, diagnosis, and treatment of the hundreds of disorders affecting the nervous system. These include stroke; epilepsy; demyelinating disorders such as multiple sclerosis; tumors; pain; traumatic injury of the brain and spinal cord; degenerative disorders such as Parkinson's disease; movement disorders; developmental disorders such as autism, the myasthenias and muscular dystrophies; and numerous autoimmune, metabolic, and genetic disorders.
National Institute of Allergy and Infectious Diseases	NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives.
National Institute of General Medical Sciences	NIGMS supports basic biomedical research that is not targeted to specific diseases, but increases understanding of life processes and lays the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS attempts to ensure the vitality and continued productivity of basic biomedical research, while producing the next generation of scientific breakthroughs and training the next generation of scientists.
National Institute of Child Health and Human Development	NICHD conducts and supports research on fertility, pregnancy, growth, development, and medical rehabilitation. The Institute's broad purpose is to ensure that every child is born healthy and wanted, and grows up free from disease and disability.
National Eye Institute	NEI conducts and supports research, training, health information dissemination, and other programs directed at blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.
National Institute of Environmental Health Sciences	NIEHS conducts and supports research on how environmental exposures, genetic susceptibility, and age interact to affect an individual's health. Its overall purpose is to reduce the burden of human illness and dysfunction from environmental causes.
National Institute on Aging	NIA conducts and supports research on the biomedical, social, and behavioral aspects of the aging process; the prevention of age-related diseases and disabilities; and the promotion of a better quality of life for all older Americans.
National Institute of Arthritis and Musculoskeletal and Skin Diseases	NIAMS conducts and supports research, training, and information dissemination directed at understanding the normal structure and function of bones, muscles, and skin, as well as the numerous and disparate diseases that affect these tissues.
National Institute on Deafness and Other Communication Disorders	NIDCD conducts and supports basic and clinical research and research training in the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. These diseases and disorders currently affect about 46 million Americans. Basic and clinical research focused on understanding the normal processes and disorders of human communication are motivated by both intrinsic scientific interest and importance to the health of the Nation.
National Institute of Mental Health	NIMH conducts and supports research on the brain and behavior – basic, clinical, epidemiological, and health services research. The Institute's activities are broadly dedicated to understanding, treating, and preventing mental illnesses.

INSTITUTE/CENTER	MISSION
National Institute on Drug Abuse	NIDA conducts and supports research across a broad range of disciplines that bear on drug abuse and addiction and disseminates information about its research findings. The Institute's broad purpose is to help reduce drug abuse and to improve the options for addiction prevention and treatment.
National Institute on Alcohol Abuse and Alcoholism	NIAAA conducts research directed at improving the treatment and prevention of alcoholism and alcohol-related problems. The Institute's broad objective is to reduce the enormous health, social, and economic consequences of this disease.
National Institute of Nursing Research	NINR has a broad mandate to sponsor research on the clinical care of individuals and their responses to health problems. Scientists supported by the Institute seek to understand and mitigate the effects of acute and chronic illness and disability, promote healthy behaviors and prevent the onset or worsening of disease, and improve the health care environment.
National Human Genome Research Institute	NHGRI supports NIH's participation in the Human Genome Project, a worldwide research effort directed at analyzing the structure of human DNA and determining the location of the estimated 100,000 human genes. At the intramural level, NHGRI develops technology for understanding, diagnosing, and treating genetic diseases.
National Institute of Biomedical Imaging and Bioengineering	NIBIB promotes fundamental discoveries, design and development, and translation of technological capabilities in biomedical imaging and bioengineering, enabled by relevant areas of information science, physics, mathematics, materials science, and computer sciences. NIBIB plans, conducts, fosters, and supports an integrated and coordinated program of research and research training that can be applied to a broad spectrum of biological processes, disorders, and diseases and across multiple organ systems.
National Center for Research Resources	NCRR advances biomedical research and improves human health through research projects and shared resources that create, develop, and provide a comprehensive range of human, animal, technological, and other resources. There are four main areas of concentration: biomedical technology, clinical research, comparative medicine, and research infrastructure.
National Center for Complementary and Alternative Medicine	NCCAM conducts and supports basic and applied research and training and disseminates information on complementary and alternative medicine to practitioners and the public.
National Center for Minority Health and Health Disparities	NCMHD serves as the focal point within NIH for planning and coordinating minority health and other health disparities research. The Center coordinates the development of a comprehensive health disparity research agenda that identifies and establishes priorities, budgets, and policy that govern the conduct and support of NIH-sponsored minority health and other health disparities research and training activities.
John E. Fogarty International Center for Advanced Study in the Health Sciences	FIC leads NIH's efforts to advance the health of the American public and citizens of all nations through international cooperation on global health threats.
Warren Grant Magnuson Clinical Center	CC is the clinical research facility of NIH. It provides patient care, services, training, and the environment in which NIH clinician-scientists creatively translate emerging knowledge into better understanding, detection, treatment, and prevention of human diseases.
Center for Scientific Review	CSR carries out initial peer review of the majority of research and research training applications submitted to NIH. Peer review is the foundation of the NIH grant and award process. The Center also serves as the central receipt point for all U.S. Public Health Service applications and makes referrals to scientific review groups for scientific and technical merit review and to funding components for potential award.
National Library of Medicine	NLM is one of three national medical libraries. It collects, organizes, and makes available biomedical science information to investigators, educators, and practitioners. It also carries out programs to strengthen medical library services in the United States. NLM's electronic databases, such as MEDLINE, are used extensively throughout the world.
Center for Information Technology	CIT provides, coordinates, and manages information technology and seeks to advance computational science.

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APPENDIX 7: APPROACH TO PERFORMANCE ASSESSMENT

NIH's Annual Performance Plans/Reports include performance goals that can be assessed through objective/quantitative measures and performance goals based on descriptive achievement criteria.

The vast majority of NIH's performance goals are objective/quantitative. In these cases performance assessment is a process, principally, of comparing data on actual achievement with the target levels stated by the Annual Program Performance Plans/Reports.

Where such quantitative measures are not available or not useful, GPRA also provides a means for an agency to define performance goals that rely on qualitative criteria. Provision for this "Alternative Form" is in the Act (Public Law 103-62) at Section 1115 (b). The use of descriptive measures has been central to the approach taken with many of the outcomes goals for NIH's research activities.

Further details on these assessment approaches are discussed below.

Objective/Quantitative Performance Goals

As noted above, most of the performance goals in NIH's Annual Plans/Reports have objective/quantitative targets. For these goals, data submitted for the assessment process permit a comparison between the actual achievement level and that targeted by the performance goal. In many cases, the performance data are quantitative, drawn from one or more of NIH's databases that support the Agency's normal management processes. Or, where the goal is to complete an action or reach an intermediate milestone, data are provided that objectively documents the status of the progress. (See Appendix 4 on Data Verification and Validation for further discussion of the data sources used for quantitative performance targets.)

In the FY 2003 Performance Plan/Report, NIH used the following codes in each performance goal chart for quantitative goals:

◇	**Target Active** – Indicates when NIH plans to meet the target.
◆	**Target Met** – Indicates that NIH's actual performance met or surpassed the stated target for quantitative/objective goals.
→	**Target Extended** – Indicates that actual performance fell short of the target and that NIH extended the timeframe for meeting the target.
×	**Not Met** – Indicates that actual performance fell short of the target and that the target was specific to a particular fiscal year. Therefore, no further action can be taken to achieve the target.
◆[e]	**Efficiently Met Target –** Indicates that the target was met sooner or greater than planned.

Descriptive Performance Goals

Agencies whose missions include basic and clinical research face unique challenges in developing the objective/quantitative performance goals preferred under GPRA. NIH has utilized representative performance measures related to both basic and applied research to capture the breadth and impact of NIH's Research Program.

As already noted, the GPRA legislation anticipated that such situations could arise for some agencies and provides the "Alternative Form" as a way for an agency to identify performance goals based on criteria that are chiefly descriptive in nature. In such situations, GPRA requires an agency to develop an assessment process that is *systematic* and *independent* and that can provide *objective evaluation* of the agency's achievements relative to the stated performance goals.

In the current Plan/Report, NIH presents a set of representative, specific scientific research outcome goals. The extent to which the goals are qualitative and thus fall under the alternative format is determined as plans for annual performance reporting on the goals are developed. The intent is to have mixed measure goals when purely quantitative is not feasible.

The Challenge of Measuring Research Performance

This continuum of scientific discovery affirms the need for a balanced portfolio with high-risk/ambitious goals as well as low-risk/probable goals and all those in between. NIH recognizes that all of its goals involve some degree of uncertainty because of the risk factor inherent in the nature of scientific discovery. NIH promotes ambitious goals because they hold promise to address a critical need and improve the health of the Nation. Goals that are ambitious and/or involve risk will by nature be difficult: The pathway to discovery may not be linear, and the building blocks needed to make a scientific breakthrough still have to be determined. Through utilizing goals that span the range of the continuum, NIH is making progress toward its mission of uncovering new knowledge leading to better health for everyone.

NIH's scientific research outcome goals in the matrix represent NIH as a whole. Almost all of the goals involve the scientific and/or financial contributions of more than one IC; most goals involve several ICs. This representative approach enables an approximate performance assessment of NIH's vast and complex research program. In laying the groundwork for reporting on prospectively defined targets, NIH presents linkages among inputs, processes, outputs, and outcomes in science as unique and nonlinear in the sense that:

- Outcomes are challenging to foresee with a high degree of accuracy, but can be captured in many cases with milestones of progress toward the end goal.

- The full value of any given research finding can be visible at the time of discovery, and often reaches a state of fruition after many years or in combination with other advances.

- Although outcomes may encompass the proposed hypothesis, unplanned results such as serendipitous discoveries and findings that narrow the avenue of the research focus (elimination discoveries) can be just as significant.

- NIH supports the discovery of scientific knowledge; knowing that the downstream impact of basic research usually is dependent on substantial further development of new knowledge by private industry, other public sector researchers, and economic factors.

Each of these factors will need to be considered in interpreting research performance reports.

Intermediate vs. Ultimate Outcomes

The ultimate outcomes of medical research are, of course, improved health, longevity, and quality of life for all Americans. Each year the NIH can document a number of major medical "culminations" that are visible as practical health benefits and are often accompanied by economic benefits. For example:

- NIH-supported research recently culminated in the discovery and development of a new drug known as Gleevec. Gleevec is the first anti-cancer drug specifically developed to target a molecular problem that causes a particular type of cancer—chronic myelogenous leukemia (CML). Clinical trials are being conducted to determine the long-term effectiveness of this drug.

- A simple means of diagnosing bladder cancer may become routine based on advances made in other NIH-supported research. Scientists knew that a protein called "survivin" is made by cancer cells and released into urine, but is not made by most normal cells. Based on this and other knowledge, scientists developed a screen for survivin in urine as a sign of cancer. During testing, this diagnostic proved very sensitive, detecting

survivin in all of the bladder cancer patients studied. It also gave very few false-positives and was simple and cost-effective.

Nevertheless, the more numerous and immediate outcomes of the Nation's investment in medical research are the incremental findings and accomplishments that increase knowledge of fundamental life processes. These "intermediate" advances or "inspirations" provide building blocks for future medical culminations. For example:

- NIH-funded researchers recently solved the crystal structure of one of the three toxic proteins produced by anthrax bacteria-lethal factor (LF)-and discovered how it interacts with the specific proteins it destroys inside the cell. This structural information can now be used to look for therapeutic agents to block LF's deadly activity.

- With NIH support, researchers sequenced the genome of a virulent strain of *Streptococcus pneumoniae*. *S. pneumoniae* kills millions of people, especially elderly individuals, worldwide each year with pneumonia, blood stream infections, and meningitis. Many *S. pneumoniae* strains have become resistant to common antibiotics. The examination of this sequence and comparison with other strains should provide targets for the development of new drugs and vaccines.

- While we do not yet know exactly how the human immunodeficiency virus (HIV) causes AIDS, NIH supported scientists have discovered that HIV must attach to cholesterol-rich regions of a cell's membrane in order to enter and infect the cell. The finding provides a more detailed view of how HIV travels into and out of cells and points to possible ways to block that travel—crucial information for continued development and improvement of therapies for patients with AIDS.

None of these intermediate accomplishments directly and/or immediately improves human health. They are, however, essential research steps that enable further work that will lead to improved understanding, diagnosis, treatment, and prevention of human disease and are the expected outcomes of NIH's mission.

Independent Review Process

To assess NIH performance on the Agency's Scientific Research Outcome goals, goals that encompass the non-linear complex activity of science, NIH drew on the Alternative Form provided under GPRA. The NIH approach has been to annually assess its descriptive research outcome goals in a way that provides an independent and objective account of the agency's scientific achievements. In brief, an independent review group, impaneled by NIH, examines current information provided by the Agency on its recent research achievements and gauges the extent to which NIH research has yielded important discoveries, new knowledge, and improved technologies that can be applied to the development of new or improved diagnostics, treatments, and preventive measures. This review/evaluation is conducted by a working group of the Advisory Committee to the Director (ACD), NIH. The Assessment Working Group is composed of members of the ACD, the Director's Council of Public Representatives (COPR), and members of Institute and Center national advisory councils.

Sources of Data for the Independent Review Process. The principal data inputs to the Assessment Working Group's review/evaluation process are narratives that document and characterize significant research accomplishments that have recently resulted from NIH-conducted or-funded research. This narrative information places a specific research advance within the context of what was previously known and unknown about the topic; the scientific and/or medical significance of the research area and the accomplishment; potential applications of knowledge from the research, if known; and potential economic implications of the advance, if known. This information provides perspective for where an advance fits in within the continuum of medical research and its potential or direct contribution to understanding and improving human health.

This narrative information is of four principal types:

- *Scientific Research Outcomes* are one-page narratives that describe a specific scientific discovery published within the past year that was supported by NIH funding. The background section of the narrative places the advance in the larger context of what is known and unknown; the advance section details the discovery; and the implications section describes the significance of the finding to science, health, and/or the economy.

- *Science Capsules* are snapshots of NIH-supported discoveries. The capsules consist of a short paragraph that succinctly describes an advance and its significance and includes citations. There are obvious limitations to the sheer number of detailed, one-page Scientific Research Outcomes that Working Group members can be expected to review and assimilate. The collection of science capsules assembled for each descriptive goal facilitates an understanding of the scope of NIH Research Program outcomes.

- *Stories of Discovery* compensate for another major limitation of traditional Scientific Research Outcomes. The one-page advances address a single, incremental finding, whereas biomedical progress usually is achieved through long-range investments in research. Progress occurs slowly with one incremental gain in knowledge gradually building on one another. Stories of discovery are narratives of approximately two pages. Each story traces the major developments in one area over several decades. Important connections between advances in science and improvements in the quality of life, health, and health care—as well as any resulting economic benefits—also are highlighted.

- *Research Awards/Honors* demonstrate outside evaluation and recognition of the value of NIH Research Program outcomes. The award write-ups are brief descriptions of national and international scientific awards/honors received by NIH scientists and grantees within the given fiscal year. The brief narratives identify the researcher(s) and the award and describe the work being honored, and the significance/purpose of the award.

Together, these kinds of information provide an extensive, but by no means exhaustive, substantiation of research outcomes with regard to specific goals.

While the Assessment Working Group drew on the narrative material as a source of data for determining performance,[1] the adequacy of performance was judged based on specific assessment criteria developed by the group (see Appendix 4 on Data Verification and Validation). As illustrated below, the conclusions rendered by the Independent Assessment Group were displayed in the Annual Performance Plans/Reports using codes similar to those for the quantitative goals.

Ú	**Target Substantially Exceeded –** Indicates that NIH met certain criteria in addition to those needed to meet the target.
◆	**Target Successfully Met –** Indicates that NIH met the criteria developed by an independent Research Assessment Working Group for that target.
◇	**Target Active –** Indicates when NIH plans to meet the target and that NIH extended the timeframe for meeting the target.
×	**Not Met –** Indicates that actual performance fell short of the target and that the target was specific to a particular fiscal year. Therefore, no further action can be taken to achieve the target.

[1] The published articles that were the basis of each narrative were not provided as part of the assessment materials, but were provided upon request and at the Working Group meeting.