DEPARTMENT of HEALTH and HUMAN SERVICES

National Institutes of Health

FY 2011 Online Performance Appendix

NATIONAL INSTITUTES OF HEALTH
FY 2011 ONLINE PERFORMANCE APPENDIX

INTRODUCTION

The FY 2011 Performance Appendix is one of several documents that fulfill the Department of Health and Human Services' (HHS) performance planning and reporting requirements to the Office of Management and Budget. HHS achieves full compliance with the Government Performance and Results Act of 1993 and Office of Management and Budget Circulars A-11 and A-136 through the HHS agencies' FY 2011 Congressional Justifications and Performance Appendix, the Agency Financial Report, and the HHS Summary of Performance and Financial Information. These documents are available at http://www.hhs.gov/budget/docbudget.htm.

The FY 2011 Performance Appendix includes all performance measures for the agency, including measures discussed in the FY 2011 Performance Budget to the Office of Management and Budget.

The National Institutes of Health Congressional Justification and Online Performance Appendix can be found at http://nihperformance.nih.gov/ and http://officeofbudget.od.nih.gov/.

Transmittal Letter

I am pleased to present the Annual Performance Plan for FY 2011. This plan supported the President's and Secretary's priority initiatives and the goals and objectives in the HHS FY 2007-2012 Strategic Plan.

The success of the Human Genome Project and several subsequent major projects provides a new level of understanding of human biology and opens a new window into the causes of disease. This includes the identification of many previously unknown risk factors for cancer, diabetes, heart disease, hypertension and a long list of other common illnesses. In cancer research, a new ability to achieve comprehensive understanding of the mechanisms responsible for malignancy is already providing insights into new diagnostics and pointing to a whole new array of drug targets. Advances in the area of stem cell research, will now move forward at an accelerated pace after the President's signing of an Executive Order in March 2009 and hold great promise for future applications to diseases like Parkinson's, type I diabetes, and spinal cord injury. New partnerships between government, academia and industry promise to revitalize the drug development pipeline. An era of personalized medicine is emerging, where prevention, diagnosis, and treatment of disease can be individualized, instead of using the one-size-fits-all approach that all too often falls short. Vigorous U.S. support of biomedical research in all these areas promises to save lives, reduce the burden of chronic illness, stimulate the economy, empower new and more effective prevention strategies, and reduce health care costs.

The development of this performance budget request is consistent with the Government Performance and Results Act (GPRA). The NIH uses GPRA and many other performance monitoring tools, such as peer review, site visits, and performance-based contracting, to continually assess program performance and to plan future research programs. This FY 2011 NIH performance data is accurate, complete, and reliable and has no material inadequacies.

The NIH is one of the world's greatest assets for progress in improving health through rigorous science and evidence-based knowledge. The NIH represents an outstanding investment in the health of the Nation and its global competitiveness in a century characterized by the need to make rapid progress in the life sciences across all of its applications.

\Francis S Collins, M.D., Ph.D. \
NIH Director

NATIONAL INSTITUTES OF HEALTH
FY 2011 ONLINE PERFORMANCE APPENDIX

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RECOVERY ACT GPRA MEASURES

OVERVIEW

The National Institutes of Health FY 2011 Online Performance Appendix contains initial FY 2009 performance details and FY 2010 and FY 2011 performance planning information for each of NIH's performance measures. It includes reporting requirements for the Government Performance and Results Act (GPRA), which includes representative trans-NIH performance measures and annual targets that are milestones in the achievement of measures. The selected measures support a balanced research portfolio of extramural/intramural and basic/clinical activities which depicts the story of scientific discovery for each measure.

TREND LINE: GENE-TREATMENT VARIANCE

In 2003, the NIH and the International Human Genome Project successfully sequenced the human genome. Since then, NIH has supported advances in sequencing science and technology and enabled an increase in the number of genes that have been identified and that may impact health and disease. Using high-throughput technologies, genetic loci associated with a variety of diseases have increased from a few in 2005 to over 500 in 2009. Scientific success in identifying potential disease causing genes highlights the importance of research to translate these findings into therapeutics.

Bringing scientific advances based on the human genome to the applied practice involves four general phases: identifying candidate genes, replicating initial findings, and validating gene functions, in order to locate targets for medicine development. These phases are necessary to validate the genetic role in disease and disorders, as well as to understand the functions in order to generate appropriate diagnostics and treatments. In the first phase, scientists analyze DNA samples to determine if similar genetic differences occur significantly more frequently in people with a disease compared to people without. These variations are said to be "associated" with the disease. One of the most efficient means of determining these associations is the use of the Genome-wide Association Study (GWAS) design, which tests hundreds of thousands of genetic variants in one experiment. The associated genetic variations can serve as a prominent pointer to the region of the human genome where the disease-causing problem resides. However, it is important to understand that the associated variants may not directly cause the disease. The variants may just be "tagging along" with the actual causal variants. For this reason, researchers often need to take additional steps, such as genotyping a dense panel of gene variants in the region, also known as re-sequencing the region to identify the exact genetic change involved in the disease. Next, scientists replicate, or unify, the genetic analyses across different populations to confirm the association. In the third phase, researchers validate the functionality of specific causal genes by determining all of the potential impacts of altering the gene. This is a critical step that can help scientists learn how diseases work and what changes occur in the cells of the body. Scientists can then determine whether the specific gene is an appropriate target for diagnostic and/or treatment development. Multiple therapeutics may then be developed for different applications.

ADVANCES BASED ON GENETIC RESEARCH

Each year, NIH researchers conduct a wide array of research involving genetics and genome sequencing across the spectrum of basic to clinical research. This research is incorporated into NIH's representative portfolio of GPRA measures. These examples highlight current research advances and the potential value of continued research to address common and rare diseases and disorders.

Coronary artery disease and cholesterol
Coronary artery disease (CAD), also called coronary heart disease, is a condition in which plaque builds up inside the coronary arteries. These arteries supply your heart muscle with oxygen-rich blood. Plaque contains fat, cholesterol, calcium, and other substances found in the blood. Genetic and environmental factors influence a person's blood fat, or lipid levels, important risk factors for coronary artery disease (CAD). While there is some understanding of the environmental contribution, the role of genetics has been less defined. Recently, NIH scientists and an international collaboration conducted a GWAS and discovered more than 25 genetic variants in 18 genes connected to cholesterol and lipid levels. Researchers compared results with a separate study of 15,000 people and confirmed the association. This study is an important, basic step in finding the genes that influence lipid levels and heart disease to improve the understanding of genetic contributions to cardiovascular risk and potential treatments.

Nicotine
Through the use of tobacco, nicotine is among the heavily used addictive drugs and the leading preventable cause of disease, disability, and death in the U.S. Each year, approximately 440,000 Americans die of smoking-related illnesses. Based on previous research that identified a cluster of genes related to nicotine dependence, scientists have identified, and confirmed, specific genetic variants associated with nicotine dependence within genes coding for several nicotinic receptor subunits. Also, this variant is associated with lung cancer, COPD, and peripheral artery disease. In addition, researchers identified genetic variants associated with the successful use of various smoking cessation programs. These findings have implications for matching smokers with the type or intensity of treatment programs that is most likely to benefit them. Utilizing the results from simple DNA tests to create personalized treatments may improve smoking cessation success rates, prevent smoking addiction and create new drug targets for treatment medications.

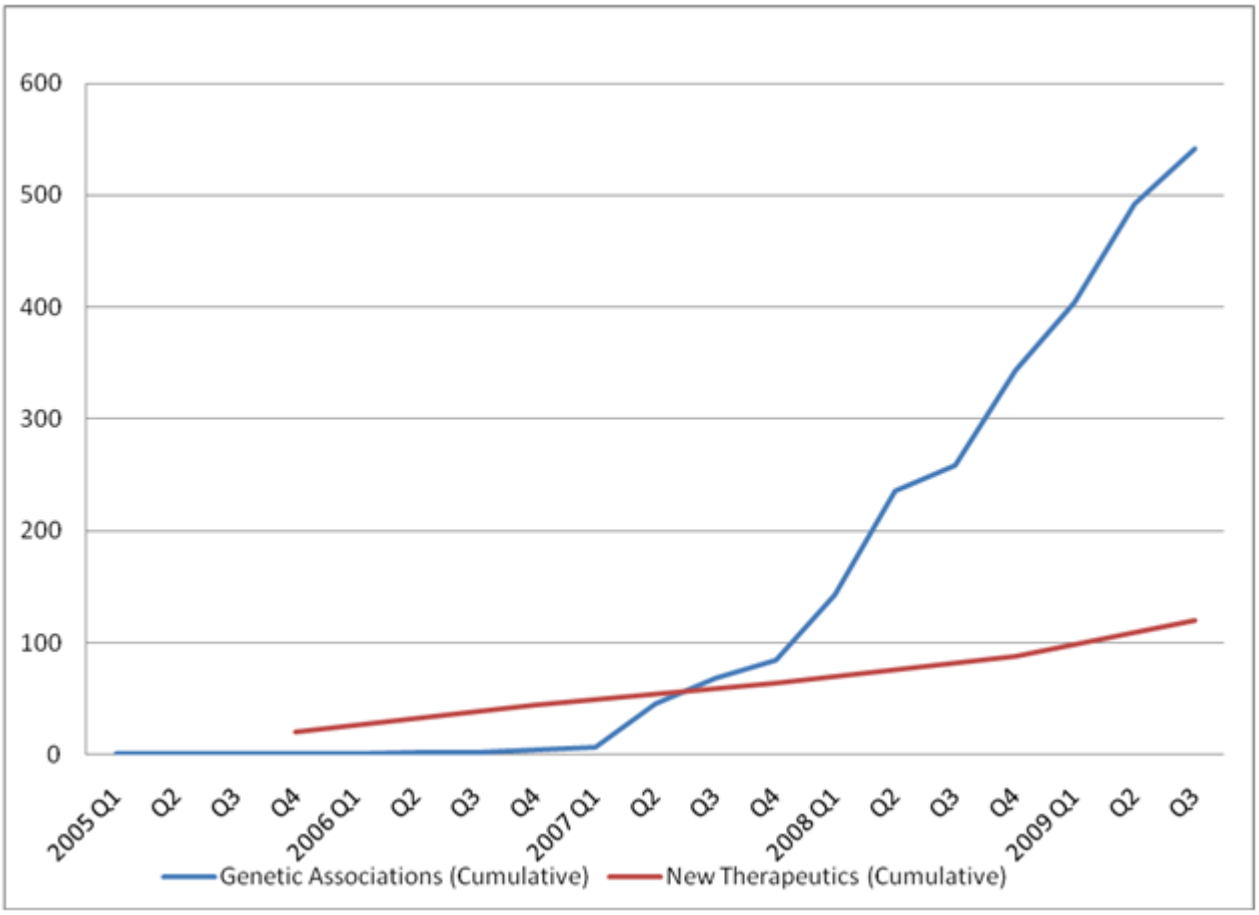
Rett Syndrome
Rett syndrome is a neurological and developmental disorder that mostly occurs in females. Infants with Rett syndrome seem to grow and develop normally at first, but then stop developing and begin to lose skills and abilities. By 6-18 months, they often stop talking and lose the ability to walk properly or make purposeful hand movements. Several factors indicate that the child often maintains a normal IQ with little ability to communicate due to the failing bodily functions. Lifetime care and assistance is needed creating a burden on the family and on the quality of life of the child. Rett syndrome has been associated with genetic mutations in a gene responsible for DNA methylation (MeCP2).Genetic mutations in MeCP2 causes epigenetic dysfunction by changing gene expression patterns caused by mechanisms other than changes in the underlying DNA sequence, such as environmental exposures. Recent studies have determined that changes in the MeCP2 gene cascade into changes in over 2600 other genes in the hypothalamus. Understanding these changes is critical to describing the pathways of effects of the mutations, and suggests that ideal therapies would aim closely at the MeCP2 gene or the genes that it directly triggers.

THERAPEUTICS

The pace of genetic research into complex diseases has accelerated over the last 5 years (see graph on next page). Complex diseases such as cancer, coronary disease and diabetes, are caused by the interaction of multiple genes and environmental factors. Advances in technology and methodology have dramatically increased the speed and reduced the cost of identifying genetic variants associated with these diseases. However, the genes identified must continue through the scientific phases described above in order to impact the prevention and treatment of disease and disorders. Currently, there is an ever growing gap between the number of identified genetic associations and number of new therapeutics. This is largely due

to the exceptional effort needed to identify the functional implications of genetic associations, and then to develop therapeutics based on these. The trend line gap in the graph indicates the potential of additional research to move identified genetic associations towards treatments that can reduce or eliminate diseases and disorders.

SIGNIFICANT OPPORTUNITIES NOW EXIST TO DEVELOP NEW THERAPIES THROUGH INCREASING GENETIC KNOWLEDGE



FUNCTIONAL AREAS FOR NIH ACTIVITIES

The NIH achieves its mission through a single overarching program—**Research**. Under this program, NIH carries out activities in five functional areas presented below. The functional area, Scientific Research Outcomes (SRO), contains representative, trans-NIH, specific scientific research performance measures. The other four functional areas include performance measures which are representative of activities that enable research and its management. The graphic below the descriptions of the five functional areas depicts the "drivers" or the components of each functional area. Each of the performance measures encompasses either intramural or extramural research activities or both, and is aligned with the agency's mission.

- *Scientific Research Outcomes (SRO).* The matrix of research measures reflects low- to high-difficulty in achieving the outcome by the number of years the program estimates that it will take to achieve results. NIH research encompasses the support and conduct of investigations across the full range of the biomedical research continuum, including basic research, observational and population-based research; behavioral research; prevention research; health services research; translational research; and clinical research. Although each area of research has unique objectives, each may benefit from findings that may be applied to transdisciplinary research.

- *Communication and Transfer of Results (CTR).* The new knowledge resulting from NIH research activities cannot benefit human health unless the information is disseminated. Thus, a core NIH function is to facilitate the communication of research findings—both in the U.S. 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, such as the internet, community outreach projects, and projects tailored to underserved populations. Equally important is transferring knowledge to the private sector to be used in the development of new interventions, behavioral strategies, medications, biomedical technologies, and devices that lead to better health.

- *Capacity Building and Research Resources (CBRR).* 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 scientists' aptitude for multidisciplinary teamwork. Capacity building also encompasses improving and maintaining the Nation's biomedical research infrastructure. 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 optimal research resources set the boundaries for what questions can be investigated. 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.

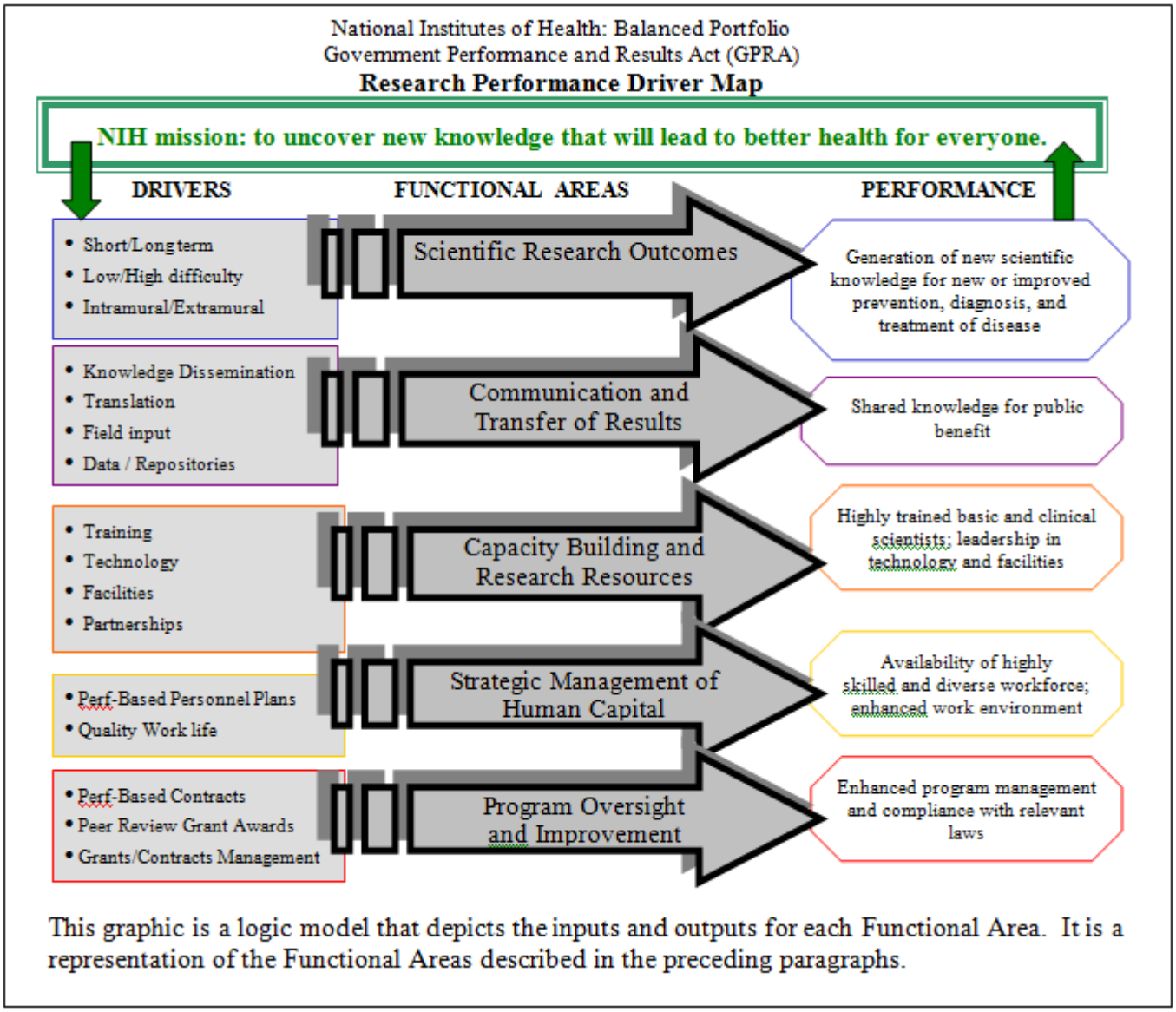
- *Strategic Management of Human Capital (SMHC).* NIH recognizes human capital as one of the most important resources of the organization. A qualified workforce, working in an environment that utilizes its strengths, fosters the effective and efficient implementation of the NIH research program. NIH aims

in this area include delayering, competitive sourcing, and developing a plan for strategic recruitment and retention, as well as planning for continuity and leadership succession.

- *Program Oversight and Improvement (POI).* 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.

SUMMARY OF PERFORMANCE MEASURES PER FISCAL YEAR BY FUNCTIONAL AREA

Functional Area	FY06	FY07	FY08	FY09	FY10	FY11
Scientific Research Outcomes	35	36	45	48	57	55
Communication and Transfer of Results	5	4	5	4	5	4
Capacity Building and Research Resources	8	7	9	11	11	9
Strategic Management of Human Capital	3	3	3	5	5	5
Program Oversight and Improvement	7	7	9	9	8	7
Totals	58	57	71	77	86	80



NIH REPORTING APPROACH

NIH categorizes performance in the GPRA Plan under five functional areas with representative trans-NIH performance measures reported for six years increments. Each measure has a narrative that describes the impetus for the measure as well as the implementation plan to achieve the measure. The narrative contains the background/state-of-the-field, rationale for the measure, target context and conditions, an annual target table, a description of target performance, other advances, and options such as a section to report retrospective efficiencies and to describe if target or measure adjustments are needed. Scientific rationales for adjusted targets are presented if applicable. To simplify reporting, completion of the measure becomes the expected annual target for the end year of the measure.

To comply with HHS reporting requirements, NIH has created a few Long-Term Objectives that aligns with science and science support, including:

- Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.
- Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

If available, FY 2009 performance summary is provided with target achievements, advances and efficiency description if a target is achieved efficiently. FY2010 and FY2011 planning performance measures are also included with supporting narrative.

Finally, at the end of the narrative, attributes related to program assessments are included. Unless stated otherwise, NIH plans to move forward with the proposed annual targets within the context of the proposed budget.

Performance and budget information for each measure is collected through a centralized online reporting system called Visual Performance Suite (VPS). The system supports e-government as it provides an electronic systematic approach of collecting performance and budget information across the Institutes and Centers (ICs) at the NIH. The system provides an anthology of performance and associated budget information to facilitate communication and can be used to support organizational annual planning.

NIH PERFORMANCE MEASURE CRITERIA

Although decisions regarding the development and implementation of performance measures are made at the NIH level, the development and administration of specific measures occur at the IC level. Consequently, budget and performance decisions are made at the IC level.

There are five factors to consider in the selection and management of GPRA performance measures: measure selection criteria, balanced portfolio of measures, the four P's (Preemptive, Predictive, Personalized, Participatory), budget/performance integration, and target adjustments.

- *Measure Selection Criteria.* NIH selects representative research measures as proxies for performance on the larger, research portfolio. As noted above, the measures were selected based on the following criteria:
  - The measures are representative, not comprehensive; that is, taken together the measures represent the breadth of NIH's portfolio. The measures address basic, prevention, diagnostic, and treatment research.
  - The measures are objective; that is, each permits a comparison between the actual achievement level and that targeted by the performance measure.
  - The measures are reportable; that is, each lends itself to annual reporting, including incremental progress.
  - The measures are not obviously attainable; that is, each must be recognized as something that *could* be achieved in the future, but may not be reachable for any number of reasons—the unpredictable progress of science, funding, and/or development of new tools needed to achieve the measure.
  - The measures are as specific (e.g., to a disease or definable problem) as possible, with reference to a metric and/or a date for progress/completion, as appropriate.

- The measures are meaningful; that is, each will be credible to the research community and the public; and the measures are important to the NIH and its research mission.

- *Balanced Portfolio of Measures (Difficulty and Time).* The continuum of scientific discovery affirms the need for a balanced portfolio of measures, ranging from low- to high-difficulty, and short- to long-term. NIH presents its scientific research outcome measures in a matrix framework (See GPRA Performance Measure Narratives by Five Functional Areas) to show the nature and extent of its portfolio.

- *The Four Ps – Preemptive, Predictive, Personalized, Participatory.* The Scientific Research Outcomes represent the continuum of scientific discovery, which support the Four Ps of the NIH Core Strategic Vision, and promote the transformation to precision medicine:
  - Transform medicine and health from a curative to a preemptive paradigm (**P**reemptive)
  - Support basic research to identify the earliest molecular stages of disease in complex biological systems (**P**redictive)
  - Accelerate translation of findings from the bench to the bedside to the community (**P**ersonalized)
  - Provide the evidence and knowledge base to allow for a rational transformation of the Nation's healthcare system (**P**articipatory)

- *Budget/Performance Integration.* The required specific scientific focus of the performance measures does not lend itself to NIH level allocation of funds. Priority setting and funding occur below the NIH level penumbra. To achieve specificity, particular performance measures are created by program staff and funded at the Institute level with multiple contributors. Often, the specificity of the measure is not captured at the level of the multiple contributing Institutes' penumbra either, since many are supported by grants and contracts. However, every performance measure is treated as a priority, performance is diligently monitored, and budgets are adjusted to facilitate the best possible outcome.

- *Target Adjustments.* The prospective target-based approach for science requires flexibility to reflect the discovery process. If an annual target is adjusted, it incorporates new knowledge and redirects performance towards achieving the best science of the measure.

Once a measure is created, the lead and contributing Institutes and Centers (ICs) coordinate on performance monitoring and funding throughout the duration of the measure. The ICs work closely with the NIH Division of Program Coordination, Planning, and Strategic Initiatives and Office of Budget to report annual performance and funding levels. Performance is monitored regularly with course corrections and the establishment of new targets occurring as needed in order to achieve the intended outcome of the measures. Programs that perform well are sustained if funding is available and the research is continued to be deemed relevant. Poorly performing programs are corrected to overcome deficiencies or funding is shifted to higher priority projects.

SUMMARY OF PERFORMANCE TARGETS AND RESULTS

NIH continues to move in the direction of increasing the number of outcome measures while decreasing the number of output measures. NIH achieves a high level of "MET" measures. Measures not met have a scientific justification for the extended or not met rating. Sound science is expected to have some extended and not met annual targets.

Fiscal Year	Total Targets	Targets with Results Reported	Percent of Targets with Results Reported	Total Targets Met	Percent of Targets Met
2006	75	70	93%	69	99%
2007	76	75	99%	66	88%
2008	80	79	99%	72	91%
2009	85	84	99%	74	88%
2010	95	N/A	N/A	N/A	N/A
2011	91	N/A	N/A	N/A	N/A

PERFORMANCE DETAIL
GPRA PERFORMANCE MEASURE NARRATIVES BY FIVE FUNCTIONAL AREAS

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. The vastness of the NIH portfolio presents a challenge in terms of articulation of measures. NIH has selected 70 specific, representative research measures as proxies for performance on the larger, research portfolio.

Central to this approach is a framework that characterizes measures on the basis of difficulty (i.e., likelihood of attaining the measure) and time. One way of visualizing this framework is to use a three-by-three matrix (see next page). Following presentation of the measures in the matrix format, the measures are presented with accompanying background information. Baseline information provides the current state of the field upon which the measure 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 measure. Since scientific discovery is complex, the annual target selected represents only one critical step in the process of achieving the final outcome.

NIH GPRA SCIENTIFIC RESEARCH OUTCOMES MEASURES MATRIX

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
High	**1.3** By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement. **1.4** By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders. **1.5** (RA) By 2012, develop a comprehensive IT platform that can facilitate evaluation of diverse behavioral interventions to promote health **1.6** (RA) By 2012, present preliminary findings from the three-pronged approach to curtail the HIV pandemic. **1.7** (RA) By 2012, incorporate scientific human development concepts, in order to develop and rigorously test at least 2 childhood learning approaches that can be integrated into science, technology, engineering and mathematics (STEM) K-12 educational programs. **1.8** (RA) By 2012, identify three research findings that will advance understanding of the biological basis underlying the heterogeneity of autism spectrum disorder (ASD) and conduct initial testing of three treatment or service delivery strategies.	**2.1** By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials. **2.2** By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. **2.4** By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life. **2.5** By 2011, identify and evaluate 5 novel molecular-targeted interventions for cancer, and determine suitability for use in early phase clinical trials. **2.6** By 2011, develop one field deployable sensor device for use in human studies and develop one biomarker to characterize the impact of environmental exposures on biological pathways. **2.7** By 2011, complete clinical testing of one candidate medical countermeasure that could be used to diagnose or treat victims of a chemical terrorist attack or accident, and complete preclinical testing for two others. **2.8** By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials. **2.9** By 2015, advance understanding of social determinants of health and health disparities using multilevel, transdisciplinary team science approaches by developing intervention models of how various factors affect individual health outcomes and their distribution in populations. **2.10** By 2014, identify three clinical candidate compounds for rare or neglected diseases. **2.11** By 2014, conduct studies of young children to determine whether the plant estrogens in soy formula produce hormone-like effects.	**3.1** By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD). **3.2** By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. **3.3** By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease. **3.4** By 2015, evaluate an HIV vaccine candidate in a test of concept (phase IIB) efficacy trial in order to move towards an HIV/AIDS vaccine. **3.5** By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies. **3.6** By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues. **3.7** By 2019, develop at least two novel therapies for immune-mediated disease. **3.8** By 2017, determine the optimal tailored treatment regimen for patients with early stage breast cancer that maximizes the benefits of chemotherapy while minimizing the side-effects of unnecessary treatment. **3.9** By 2020, identify two molecular-targeted therapies for disorders of the immune system in children. **3.10** By 2017, advance two candidate medications for treatment of substance use disorders to clinical studies in humans.

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
Medium	**4.3** By 2009, evaluate the safety and efficacy of two new treatments for nonalcoholic steatohepatitis (NASH) in adults. **4.4** By 2011, identify or study additional genes involved in communication disorders in humans and animal models. **4.5** By 2011, identify genetic and environmental factors which predispose to three complex diseases. **4.6** (RA) By 2012, develop a technology to facilitate patient-controlled, secure image sharing between medical centers and at least one clinic operating in an underserved community. **4.7** (RA) By 2011, evaluate at least one novel animal model of type 1 diabetes. **4.8** (RA) By 2011, develop and/or test at least one strategy for improving end-of-life care or palliative care. **4.9** (RA) By 2011, enhance the capacity of researchers to investigate genetic causes of disease by DNA sequencing of participants in well-phenotyped cohorts. **4.10** (RA) By 2011, accelerate progress toward identifying relevant genomic alterations in 10 tumor types. **4.11** (RA) By 2011, analyze oral cancer genomes using high throughput methods to develop a blueprint of genetic alterations. **4.12** (RA) By 2011, demonstrate the feasibility of a new therapeutic strategy in a preclinical model of a neurological disease.	**5.2** By 2010, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus). **5.3** 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. **5.6** By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction. **5.7** By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy. **5.8** By 2012, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies. **5.9** By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations. **5.10** By 2011, conduct studies of girls aged 6 through 8 years to determine the associations between the age of onset of puberty and progression through puberty with 12 environmental exposures. **5.11** By 2012, develop and test at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes. **5.12** By 2013, identify several potential targets and/or molecules that modulate or enhance the extinction of learned behaviors and conditioned associations supporting addiction, compulsion, or anxiety disorders. **5.13** By 2014, establish a process to prioritize compounds that have not yet been adequately tested for more in-depth toxicological evaluation. **5.14** By 2013, reduce tobacco prevalence among youth by preventing initiation and increasing rates of cessation.	**6.1** By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans. **6.2** 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. **6.4** By 2014, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations. **6.5** By 2014, develop and evaluate two new interventions for the prevention and/or treatment of HIV disease utilizing the newly restructured HIV/AIDS clinical trials networks. **6.6** By 2015, provide at least one new or significantly improved minimally-invasive treatment for clinical use in patients using image-guided interventions.

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
Low	**7.4** By 2009, create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis. **7.7** By 2011, assess community-based methods for facilitating cancer research and providing patients access to optimal cancer care. **7.8** (RA) By 2011, create genomic resources to identify rare genetic variants that contribute to primary open angle glaucoma. **7.9** (RA) By 2011, enhance understanding of the characteristics of differentiated heart, lung, and blood cells derived by reprogramming human embryonic and induced pluripotent stem cells. **7.10** (RA) By 2011, create a publically accessible database of novel and highly-detailed cell images, videos, and animations from a variety of organisms. **7.11** (RA) By 2012, gather sufficient data to support the development of a national standard for normal fetal growth.	**8.2** 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. **8.4** 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. **8.5** By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease. **8.6** By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES). **8.7** By 2012, identify three (3) effective implementation strategies that enhance the uptake of research-tested interventions in service systems such as primary care, specialty care and community practice. **8.8** By 2012, identify at least one candidate intervention that extends median lifespan in an animal model. **8.9** By 2014, identify 12 pathogen and/or host factors critical for understanding the molecular and cellular basis of pathogenesis of Category A-C biodefense pathogens and/or pathogens causing emerging infectious diseases.	**9.1** 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). **9.2** By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities. **9.3** By 2011, characterize the progression of normal, healthy brain development in a nationally representative sample of children in the United States by creating a database of MRI and clinical/behavioral data and analytical software. **9.4** By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life. **9.5** By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.

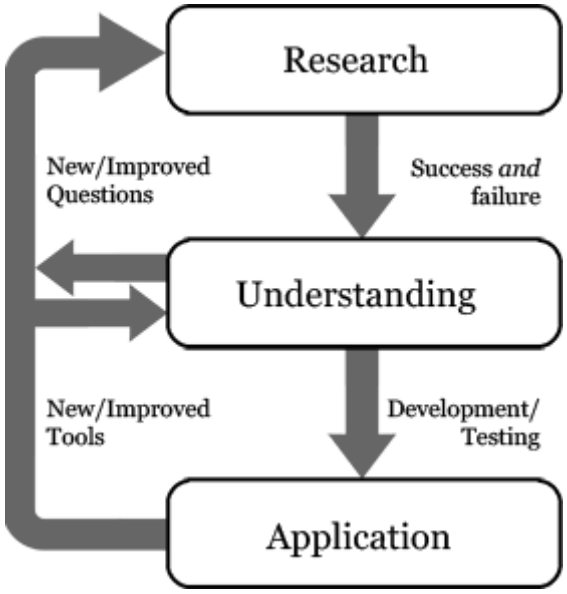
The matrix of measures selected by NIH reflects the challenges of complex biological systems. The measures range across a continuum of low to medium to high difficulty, and have a corresponding timeline for achievement (i.e., 1-3 years, 4-6 years, and 7-10 years, respectively). For example, the NIH portfolio includes high-difficulty measures 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-difficulty measure in the early stages cannot be guaranteed. In contrast, NIH low-difficulty measures usually have a long history associated with the scientific effort, and the knowledge base has known parameters. With low-difficulty measures, often only a few steps remain to translate the knowledge into an application that could lead to improved public health. NIH also utilizes performance measures that span the middle of the continuum. For the latter, a foundation of knowledge has been set but not extensively developed. Yet the measure 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-difficulty/ambitious measures as well as low-difficulty/probable measures and all those in between. NIH recognizes that all of its measures involve some degree of uncertainty because of the risk factor inherent in the nature of scientific discovery. NIH promotes ambitious measures because these measures hold promise to address a critical need and improve the health of the Nation. Measures that are ambitious and/or involve uncertainty 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 measures 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 measures in the matrix represent NIH as a whole. Almost all of the measures involve the scientific and/or financial contributions of more than one IC; most measures 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 completion of the measure.
- The full value of any given research finding may not 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 measures. 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.

Long Term Objective: (SRO-1.3) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-1.3 By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement. (Outcome)	*2010*	Complete goal of developing an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement. *(Baseline):* (FY09) Refined the device design and software using feedback from periodic clinician/patient focus groups.	N/A
	2009	Refine the device design and software using feedback from periodic clinician/patient focus groups. *(Baseline):* (FY08) Completed development of software to plan and evaluate treatment.	Controllers have been developed that can guide an upper extremity robot to assist a patient in completing a repetitive movement. (Target Met)
	2008	Develop a suite of control and assessment software to allow treatment planning and evaluation. *(Baseline):* (FY07) Current robotic aides do not have feedback mechanisms.	Developed a suite of control and assessment software to allow treatment planning and evaluation. (Target Met)

Data Source and Validation

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Milot MH, Marchal-Crespo L, Green C, Cramer S, and Reinkensmeyer D. Comparison of error amplification and haptic guidance training techniques for learning of a timing-based motor task by healthy individuals. Experimental Brain Research, published early online on September 29, 2009. http://www.springerlink.com/content/854981362u1v7r07/fulltext.pdf

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He J, Balasubramanian S, and Wei R. Designing interactive and intelligent control for rehabilitation robots. Proceedings of international conference on robot and automation. Wuhan, China, October 2008.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. Scientists have refined and developed devices and software that can be used to aid stroke patients to perform repetitive movements, such as reaching for a ball. Researchers developed controllers that can guide an upper extremity robot to repeat movements, to assist a patient in completing a movement, and based on biofeedback, to recalculate when and how much assistance is needed. The combination of these mechanisms has led to the development of controllers that can adapt to individual patients undergoing rehabilitation therapy. Preliminary data from volunteers show that the adaptive controllers can provide consistent performance for different subjects performing different reaching tasks.

Advances or Other Highlights

Researchers have developed mechanisms for the robot to quantify the amount of assistance needed, smoothness in the movement, and a way to detect fatigue. Together, these rehabilitation performance measures can be used to track the progress of a patient during the recovery period. In another study, researchers compared the effect of two techniques on learning a wrist movement task in healthy volunteers: haptic guidance (demonstrating a correct movement) and error amplification (artificially increasing errors to learn a movement). While both techniques promoted learning the wrist movement, the researchers found that for those volunteers who were more skilled initially at the task, training with error amplification led to significantly greater learning than training with haptic guidance. And for those volunteers who were less skilled at performing the task, training with haptic guidance seemed to better promote learning. The study findings suggest that both techniques help enhance performance of a task, but learning is optimized if subjects are trained with the appropriate technique based on their baseline skill level.

BACKGROUND

Often times, individuals who suffer and survive a stroke, survive with hemiparesis (muscular weakness or partial paralysis on one side of the body). Recent studies have shown that rehabilitation therapy that involves practicing a functional arm movement repeatedly can enhance recovery of arm function for certain stroke survivors. In an effort to speed the rehabilitation process to enable individuals to regain function of the arm, NIH-supported researchers are developing upper extremity exoskeleton robots—a device that patients can wear around the arm, like a brace. Such a device would help the patient move the affected arm when practicing repetitive motions. Existing robots are expensive, powered by large power sources, and are too complex for clinical or home use. Recently, researchers began making strides in overcoming the challenge of reducing the sheer size of the robot by designing devices that can be powered with compressed air (pneumatics). Further development that leads to low-cost robotic exoskeletons holds the promise of providing therapeutic activities at the clinic or at home for a range of stroke patients.

Prevalence/Incidence

Stroke is a leading cause of serious, long-term disability in the United States. The American Heart Association notes that each year about 700,000 people have a new or recurrent stroke.

Disease Burden

The American Heart Association estimates that the direct and indirect cost of stroke in the United States for 2007 is $62.7 billion.

Rationale

Rehabilitation therapy is beneficial but requires much time and energy, not only from the individual seeking to regain function in the arm, but also from the skilled physical therapists who spend many hours helping patients repeatedly move the arm. To improve this rehabilitation process, through supported research, the NIH is developing robotic devices that would enable patients to practice functional arm movements on their own. By enabling patients to practice rehabilitation exercises that have been programmed in a robotic device, not only

may the patient regain function of the arm more quickly than with conventional physical therapy sessions, but the costs of physical therapy for the patient could also decrease.

While there are preliminary research findings that suggest the robotic devices would be useful, the challenge is to develop a device in such a way so that patients will have access to it, for example at a clinic. NIH-supported researchers are now tackling this challenge by developing a portable robotic device that can be programmed to deliver aid to a patient undergoing a rehabilitative therapy program.

TARGET CONTEXT AND CONDITIONS

The NIH is developing robotic exoskeletons for clinical rehabilitation of upper extremity movement. Currently, the robotic devices can be programmed for repetitive exercises. The next steps involve engineering the device to respond to the patient's progress so that the device provides more aid and support in the beginning of the rehabilitation process and less aid as the patient regains arm function. Researchers are also developing feedback programs that will enable the device to sense the intent of the patient. For instance, when reaching for an item or when eating, the device will enable the patient to complete that particular task.

The immediate short-term and high risk goal will involve developing a device that will accommodate and control a broad range of naturalistic arm movements to enable the patient to practice functional movements needed in daily living activities. A suite of control and assessment software will be developed to allow treatment planning and evaluation, such as assessing a patient's current level of function, and to provide feedback to patients. Researchers will also refine the device design using feedback from periodic clinician/patient focus groups. These steps will lead to the development of a device to the point where researchers can execute a preliminary study to demonstrate the effectiveness of the device in retraining arm movement after chronic stroke in the clinic.

Long Term Objective: (SRO-1.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-1.4 By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders. (Outcome)	*2011*	Identify gene expression profiles for one alcohol use disorder. *(Baseline):* Cell culture standardization techniques continue to be established and/or improved.	N/A
	2010	Establish cell culture standardization techniques to enable initiation of gene expression analyses of cell lines derived from individuals with and without AUDs. *(Baseline):* Lack of cell culture standardization techniques reduces the capability for reliable analyses and cross-laboratory comparisons.	N/A

BACKGROUND

Alcohol-induced disorders, including organ damage and addiction, reflect both the genetic make-up and the cumulative responses to alcohol exposure and environmental perturbations over time (epigenetic). Each individual factor, whether genetic or environmental, generally contributes only a small fraction to the overall symptoms or phenotypes. Alcohol exerts its effects at the DNA, RNA and protein levels as well as the systems level where alterations in multiple biochemical, metabolic, or signaling pathways result in the dysfunction of many different cells and tissues. The high degree of complexity in alcohol-induced disorders limits the utility of traditional gene-by-gene studies that provide only a fragmented view of a complex picture.

Thus, global approaches such as gene expression profiling are essential to capture the full complexity of alcohol-induced disorders. Gene expression profiling surveys the whole genome and has the potential to capture alterations in expression patterns of a broad range of genes associated with susceptibility, initiation, progression, and pathogenesis of alcohol-induced disorders. Identifying variations in gene expression patterns may advance understanding of the underlying causes of these disorders could provide new avenues for diagnosis, prognosis, and therapeutic intervention of these disorders, and may support personalized medicine.

Prevalence/Incidence

Alcohol use disorders (AUDs) encompass alcohol abuse and alcohol dependence, and arise from drinking too much, too fast and/or too often. Nearly 18 million American adults (8.5% of the population age 18 and older) suffer from a 12-month alcohol use disorder, i.e., alcohol abuse and alcohol dependence (alcoholism) according to a 2004 study on trends in DSM-IV alcohol abuse and dependence for the years 1991-1992 and 2001-2002. In addition, the prevalence of drinking, especially binge drinking (i.e., drinking five or more drinks on one occasion), puts adolescents at risk for developing AUDs. For example, 26% of 9th to 12th graders report binge drinking at least one day of the previous month as reported by the CDC in 2008.

In addition to the adverse health effects that result directly from excessive alcohol consumption, AUDs often co-occur in individuals who abuse other drugs, in people with psychiatric disorders, and in people who smoke tobacco. An estimated 90% of individuals with 12-month cocaine dependence have a 12-month alcohol use disorder and as many as 60% of patients at community mental health centers have co-morbid alcohol and other drug abuse disorders. Individuals diagnosed with severe mental illness are more likely to experience a co-

occurring substance abuse disorder according to a 2005 report on a survey of alcohol and related conditions. For example, women with bipolar disorder are 7 times more likely to be alcohol dependent than women without psychiatric diagnoses. Analyses published in 2003 of data from NIH National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicate that among alcohol dependent individuals 66 % use tobacco, 51% use it daily and 45% are nicotine dependent. It appears that alcohol dependent individuals tend to become more addicted to nicotine and are less successful at quitting smoking than other smokers as noted in a 2006 update on alcohol and tobacco data from the NESARC. This puts them at a high risk for certain cancers and cardiovascular diseases that develop more readily in the presence of both alcohol and nicotine.

Disease Burden

Excessive alcohol consumption often leads to adverse health effects and medical conditions, resulting in significant economic and public health burdens to our society. These medical conditions include addiction as well as alcohol-induced organ damage such as liver disease (hepatosteatosis, inflammatory disease, alcoholic hepatitis and cirrhosis), pancreatitis, cardiomyopathy (disease of the heart muscle), fetal abnormalities, and brain damage. Excessive alcohol use is also associated with an increased risk for some types of cancer. According to a 2004 study by the CDC, in 2000, excessive alcohol consumption is the number-three cause of preventable death in the U.S., after tobacco and diet/activity patterns. In a 2009 report, the World Health Organization also ranks alcohol third among preventable risk factors for premature death in developed nations, after tobacco and hypertension. Problems related to the excessive consumption of alcohol cost U.S. society an estimated $235 billion annually due to lost productivity, medical costs and other factors based on research published in 2009 on the global burden of alcohol use and alcohol use disorders.

Rationale

Characterization of variations in gene expression patterns will provide information about how alcohol alters gene expression and will improve understanding of the mechanisms that underlie alcohol-induced disorders. The aim of this measure is to identify signature gene expression patterns that are associated with alcohol-induced disorders using peripheral tissues from individuals with and without AUDs. The rationale is three-fold. (1) Gene expression profiling is a global approach that can capture the complexity of AUDs and provide signature gene expression patterns associated with the susceptibility, initiation, progression, and pathogenesis (origin and mechanism of development) of these disorders. (2) A critical barrier for the translational research of alcohol-induced disorders is the unavailability of diseased tissues, such as brain samples from living human subjects with AUDs. The proposed studies on peripheral tissues or cell lines derived from lymphoblastoid cells, a type of immortalized white blood cell, from individuals with AUDs offer a potential solution for this problem. Immortalized cell lines consist of cells that replicate indefinitely when maintained under proper culture conditions. These cell lines provide an unlimited, renewable resource for a wide range of studies and offer the ease of experimental standardization and manipulation. Currently, there are over 145,000 immortalized lymphoblastoid cell lines available from NIH-funded cell line repositories, including cell lines derived from individuals with AUDs, and a large amount of clinical, behavioral, and genetic data is available. (3) Immortalized lymphoblastoid cell lines and peripheral tissues have been increasingly utilized successfully to identify gene expression signatures associated with complex diseases, such as autism, schizophrenia, drug dependence, and obesity, especially for those research areas where patient's diseased tissue is not available.

TARGET CONTEXT AND CONDITIONS

NIH plans to use immortalized lymphoblastoid cells and/or peripheral tissues from human subjects to identify gene expression signatures that are associated with the susceptibility, initiation, progression, and pathogenesis of alcohol-induced disorders. This measure will be achieved through a strategy implemented in four stages. In the planning stage, a workshop titled "Gene expression in immortalized cell lines: toward standardizing methodologies for GxE interaction studies" addressed various technical issues, including experimental standardization and manipulations of immortalized cell lines. Workshop results and further input from the alcohol research community and extramural staff, will be used to help guide the second stage of the program. In the second stage of this project, funded laboratories will coordinate efforts to standardize cell culture procedures and some aspects of experimentation and data analysis. In the third stage, signatures will be

obtained in immortalized lymphoblastoid cells for one alcohol-induced disorder. These signatures will be then validated using different groups of human subjects. In the last stage of this project, the signatures will be obtained for additional alcohol-induced disorders, and then validated in different groups of people.

Long Term Objective: (SRO-1.5) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-1.5 (RA) By 2012, develop a comprehensive IT platform that can facilitate evaluation of diverse behavioral interventions to promote health (Outcome)	*2011*	Develop the IT platform to facilitate evaluation of behavior interventions. *(Baseline):* Concept (design phase) completed	N/A
	2010	Complete concept (design phase) for an IT platform to facilitate evaluation of behavioral interventions. *(Baseline):* Web technologies exist to support creation of a comprehensive and reliable IT platform to facilitate evaluation of multiple behavioral interventions.	N/A

BACKGROUND

Unhealthy behaviors such as smoking, medication non-adherence, and lifestyle habits leading to obesity are major contributors to premature illness and death among older Americans. Despite the theoretical promise of behavioral economic approaches (such as reinforcement of a desired behavior with a small, immediate reward) to improve health behaviors, implementation is often costly because of the need for frequent contact and reinforcement. Furthermore, several for-profit companies have recently begun to develop and market interventions to support health-related behavior change, but these commercial entities are not generally testing interventions using randomized or careful quasi-experimental designs, and many make exaggerated claims unsupported by credible evaluations.

Rationale

Unhealthy behaviors underlie many of the chronic conditions that burden Americans. Interventions derived from theories of behavioral economics have shown promise in increasing healthy behaviors, but these interventions typically require frequent (often daily) contact, which can be expensive, challenging for investigators, and burdensome for research participants. A comprehensive information technology (IT) platform that facilitates participant tracking, monitoring using home-based devices, and participant feedback could be used to facilitate evaluation of behavioral interventions across numerous studies. The platform could promote increased efficiency and speed the pace of discovery at the intersection of health and behavioral economics – an emerging and rapidly evolving field. However, no such platform currently exists.

TARGET CONTEXT AND CONDITIONS

The primary objectives of this project are to design, build, test, and refine an IT platform that will: 1) provide investigators an easily customized web-based platform to evaluate behavioral interventions to promote health, including the use of financial incentives, frequent feedback, visual approaches to information, and social networks; 2) provide older Americans, other members of the general public, and public and private sector organizations with a web portal which can facilitate participation in innovative research on behavioral approaches to improve health behavior at low incremental cost.

NIH investigators will build a comprehensive IT platform to support the careful evaluation of the comparative effectiveness of different behavioral economic approaches to increasing the rate of healthy behaviors. This

platform will provide a state-of-the-art platform on which to build, test, and deploy large-scale behavioral intervention studies and advance the science at the intersection of behavioral economics and health. The platform will also enable linkages between this portal and a variety of home-based and hand-held health measurement devices, which could facilitate interventional studies to improve management of chronic disease among older adults. Notably, this project will enable the creation or retention of up to ten jobs in the Philadelphia area in the near term.

With Recovery Act support, NIH has established a plan to create and test a prototype platform. During the first year (FY2010), investigators will conceptualize the platform, which will consist of customized hardware and software that are fully integrated and have the built-in flexibility to connect with existing and new technologies in the areas of home health monitoring, online social networking, text messaging to cell phones, and devices with specialized health promotion applications such as advanced cell phone devices. The platform will also integrate with financial service and payment vendors. In the second year (FY2011), the platform will be developed with three layers: client, application, and database. The client layer is the public web interface of the platform. The application layer is the engine of the platform and enables randomization of participants, automated reminders, and supports the various modular elements needed of study designs. The database layer will enable the secure and reliable storage of data for studies. In the third year (FY2012), at least one pilot project will be conducted to test the functionalities of the system and their feasibility, particularly in older adults.

Long Term Objective: (SRO-1.6) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-1.6 (RA) By 2012, present preliminary findings from the three-pronged approach to curtail the HIV pandemic. (Outcome)	*2011*	Identify at least one new strategy to target residual HIV in treated patients. *(Baseline):* Basic research related to targeting residual HIV in treated patients ongoing.	N/A
	2010	Complete enrollment of two important studies that will support the "Test and Treat" approach – HPTN 061 and HPTN 064. *(Baseline):* Enrollment initiated for HPTN 061 and HPTN 064.	N/A

BACKGROUND

While there has been a decline in HIV/AIDS mortality as a result of the increased availability of antiretroviral treatment (ART) worldwide, new infections continue to impede efforts to curtail the epidemic. In the Global AIDS Epidemic 2008 report, the Joint United Nations Programme on HIV/AIDS (UNAIDS) noted that while the rate of new HIV infections has fallen in several countries, global trends are offset by the rising number of new infections in other countries. In the United States, the Centers for Disease Control and Prevention (CDC) published new data in August 2008 showing that in 2006 there were an estimated 56,300 new HIV infections - a number that is substantially higher than the previous estimate of 40,000 annual new infections. While not representing a growth in the incidence of HIV, these data more accurately reflect methods for measuring new infections. The unacceptably high level of new infections reinforces the urgent need for effective new HIV prevention tools. Existing prevention methods such as education, counseling, and condom use are important in reducing the number of HIV infections, but thus far, have been insufficient (on their own or in combination), to thwart the impact of the epidemic. Moreover, other potential prevention methods, such as a safe and effective vaccine against HIV, are still many years in the future.

Prevalence/Incidence

In 2008, there were an estimated 2 million deaths worldwide due to HIV/AIDS. That year, there were an estimated 2.7 million new HIV infections and a total of 33 million people living with HIV/AIDS globally. The number of children living with HIV/AIDS increased from 1.5 million in 2001 to 2 million, although the number of new infections per year decreased among children from 460,000 in 2001 to 430,000in 2008. According to a 2009 report by the Joint United Nations Program on HIV/AIDS (UNAIDS), Sub-Saharan Africa continues to be the most affected region, accounting for 67% of all new HIV infections globally – 68% of all new infections among adults and 91% of all new infections among children.

In the United States, the most recent statistics from the Centers for Disease Control and Prevention revealed that 56,000 people became newly infected with HIV in 2006, with African-Americans continuing to face the greatest burden of HIV/AIDS. The rate of new HIV infections among African Americans in the United States is seven times the rate among whites. There is also evidence of resurging HIV/AIDS epidemics among men who have sex with men in the United States; 53% of new HIV infections in 2006 were in men who have sex with men.

Rationale

Historically, vaccines have been our best weapon against infectious diseases. However, the human immunodeficiency virus (HIV) has unique characteristics that have greatly challenged the search for an HIV vaccine, and it is unlikely that a safe and effective vaccine will be available in the near future. Even once a vaccine is available, it is not likely to be 100 percent effective, and will need to be used in combination with other prevention approaches. There are three new approaches for controlling the HIV/AIDS pandemic – pre-exposure prophylaxis (PrEP), universal testing and treatment (test and treat), and elimination of persistent HIV reservoirs – that are being discussed in medical and public health communities. Although these approaches are still in the early stages of research and evaluation, when used in combination, their potential for curtailing the HIV pandemic is promising.

TARGET CONTEXT AND CONDITIONS

NIH is evaluating the impact of different prevention tools and pursuing basic research that could provide information critical to developing effective strategies to curb the epidemic. Two studies that are being conducted in the HIV Prevention Trials Network (HPTN), namely HPTN 064 and HPTN 061, will help determine ways to increase testing and treatment in two populations with the highest incidence of HIV in the United States – black men who have sex men (MSM) and women residing in high risk areas. Combined, these studies will help determine the feasibility and acceptability of a multifaceted intervention for preventing HIV among black MSMs, prepare for a community-level randomized trial to test the efficacy of the intervention, and determine the feasibility of novel methods for recruitment to increase testing and treatment among women believed to be at risk for HIV. These studies will also provide information that would support the "test and treat" concept. This concept involves expanding testing services so that people who are newly infected can be identified early and referred to care and treatment as needed. Not only would this help individuals with their own health and well-being, but lowering viral load among many individuals within a broader community could reduce the overall risk of HIV transmission.

Research is ongoing and will address the many factors that could impact the potential value of the test and treat strategy, including: 1) the relationship between stage of infection and transmission, 2) efficacy of antiretroviral therapy (ART) in prevention of transmission, (3) development of drug resistance, (4) behavioral disinhibition, (5) the benefit of early treatment to the individual, (6) cost-effectiveness, and (7) the ability to reach target populations and implement annual universal testing.

Pre-exposure prophylaxis (PrEP), therapy taken to prevent HIV prior to exposure, rather than treat an infection or illness, is another strategy being studied. In monkey studies, treatment with HIV antiretroviral drugs significantly reduced infections among monkeys exposed to the simian version of HIV. In humans, HIV has also been shown to be vulnerable to this type of pre-infection intervention. For example, antiretroviral treatment of an HIV-infected mother during childbirth reduces an infant's chance of contracting the virus by about 75 percent, and can significantly reduce the risk of infection when taken immediately after exposure to the virus. If PrEP is shown to help prevent infection in people, it could have an effect similar to that of a preventive vaccine. It could offer a certain degree of protection to individuals and reduce overall HIV prevalence in the larger population. As with vaccines, no HIV preventive method is expected to be 100 percent effective; therefore, PrEP would always be combined with other ongoing risk-reduction strategies such as practicing safer sex.

NIH is also supporting research that is examining ways to eliminate HIV reservoirs in HIV-infected individuals on highly active antiretroviral therapy (HAART). Reservoirs are pockets of latent and persistent HIV in people on HAART, who have undetectable levels of viral load. When these individuals stop antiretroviral treatment, they experience a rebound of viral load to levels seen prior to treatment. Research is ongoing to characterize residual HIV in treated individuals and develop techniques for its eradication. The challenge is that there may be unknown reservoirs of HIV – both cellular and anatomic – and there are no good model systems (animal models or simple assays) available to study residual HIV.

Long Term Objective: (SRO-1.7) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-1.7 (RA) By 2012, incorporate scientific human development concepts, in order to develop and rigorously test at least 2 childhood learning approaches that can be integrated into science, technology, engineering and mathematics (STEM) K-12 educational programs. (Outcome)	*2011*	Complete data collection for outcome measures for at least one study of STEM learning. Enroll 50% of participants needed for at least one additional study of STEM learning in at-risk children *(Baseline):* Several rigorous studies are planned but data collection has not begun.	N/A
	2010	Develop a rigorous study protocol, and enroll 50% of the participants needed, in at least 1 study of STEM learning in at-risk children. *(Baseline):* Several rigorous studies of STEM approaches that incorporate human development concepts are planned.	N/A

BACKGROUND

Researchers have greatly improved understanding of how people develop knowledge, skills, and reasoning ability. Brain imaging studies of children performing mathematical tasks reveal that as children mature over time, different parts of their brain are used to solve similar types of mathematical problems. Scientists are now able to characterize how young children develop the ability to draw logical inferences about groups of objects, even when some are new. Discoveries about the relationships between language development, neuro-spatial cognition, and math and science performance are among some of the key research concepts that have informed the development of educational programs. Investigators are now ready to take such evidence from human development and neuroscience research and apply it to developing, refining, and testing educational interventions. In the past, the results of neurological and developmental scientific research have not been largely transferred into real-world interventions. The most rigorous scientific approaches to translational research are needed to demonstrate efficacy in the classroom to improve education in science, technology, engineering, and mathematics (STEM). The NIH coordinates STEM education research efforts with those of other Federal agencies through the Education Subcommittee of the National Science and Technology Council. The Education Subcommittee is co-chaired by representatives from the Department of Education, the National Science Foundation, and the NIH.

Prevalence/Incidence

According to the National Assessment of Educational Progress (NAEP), less than one third of our fourth- and eighth-graders are performing at or above proficient levels in math. A closer look reveals that although overall scores have been increasing over time, the students at the lowest levels of achievement, have been making only minimal gains.

Rationale

Numerous studies have demonstrated strong correlations between mathematics achievement and subsequent economic, psychological, and health-related well being and quality of life. Reviews of the scientific literature reveal that low numeracy skills are associated with poorer health, socio-economic deprivation, social exclusion, and reduced life expectancy. Recent survey data indicate that persons with poor mathematical skills are more

likely to be receiving government financial supports and are more likely, if employed, to be working in unskilled occupations. Likewise, new data suggest that low quantitative literacy constrains treatment compliance and informed consent, and predicts 1.5 - 3.0 greater likelihood of poor treatment outcomes. Conversely, multiple studies demonstrate that good numeracy skills are associated with higher wages and greater use of preventive health care and health behaviors. Science, technology, engineering and mathematics education is fundamental to the health and well-being of the nation. Understanding scientific concepts is essential to health literacy, which in turn is required for individuals to make informed health care decisions and develop positive health behaviors. Moreover, science and mathematics performance is a strong factor supporting educational attainment, which is positively correlated with improved health outcomes, employment, longevity, and quality of life. Finally, improved STEM education is necessary to develop the next generation of the scientific research workforce. The Recovery Act program provides a unique opportunity to take advantage of the growing science base in mathematics and science cognition and learning and apply it using rigorous research designs to practical interventions for tomorrow's classrooms.

TARGET CONTEXT AND CONDITIONS

Although the results of human development research show great promise for translation into educational settings, accomplishing this will require multidisciplinary teams of individuals with scientific and educational expertise. Early intervention, during the time critical cognitive skills are developing may be needed for long-ranging benefits, thus introducing interventions to children during preschool and early elementary school is essential. Maximizing multiple developing domains (e.g., motor and perceptual, as well as cognitive) may result in even greater academic improvements. However, classroom educators and curricula are constrained by state and local requirements. As a result, educational interventions have often been tested with less rigorous approaches; researchers will need to collaborate with multiple experts and take extra steps to ensure that studies are conducted with the strongest possible methodologies. Despite these challenges, the Recovery Act program offers a great opportunity to use biomedical discoveries to inform the development and rigorous testing of interventions to improve classroom achievement.

Long Term Objective: (SRO-1.8) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-1.8 (RA) By 2012, identify three research findings that will advance understanding of the biological basis underlying the heterogeneity of autism spectrum disorder (ASD) and conduct initial testing of three treatment or service delivery strategies. (Outcome)	*2011*	Identify three research findings that will aid identification of risk factors and inform the early detection or diagnosis of ASD using research methods such as genomic analysis, neuroimaging, or behavioral screening. *(Baseline):* Genomic, neuroimaging and behavioral screening studies are currently underway.	N/A
	2010	Initiate testing of at least three novel treatment or service delivery approaches to address symptoms or improve functioning for individuals with ASD. *(Baseline):* Currently, only one behavioral intervention exists for the core social and communication symptoms of ASD and one pharmacological treatment to treat disruptive/aggressive behavior for ASD.	N/A

BACKGROUND

Autism Spectrum Disorder (ASD) is a group of neurodevelopmental disorders characterized by differences in three core domains of functioning: social behavior, communication abilities, and restricted, repetitive, or stereotyped patterns of behavior. Although these core features exist at varying degrees among all individuals with ASD, considerable heterogeneity exists within this population, which suggests there may be multiple causal factors as well as multiple developmental trajectories for these individuals. Indeed, a clear barrier to understanding the causes of ASD has been the heterogeneity within this spectrum of disorders.

In response to the heightened societal concern over ASD, Congress passed the Combating Autism Act (CAA) of 2006. Through this Act, Congress intended to accelerate the pace and improve coordination of scientific discovery in ASD research. The CAA mandated that the IACC develop and annually update a Strategic Plan for ASD Research (http://iacc.hhs.gov/reports/2009/iacc-strategic-plan-for-autism-spectrum-disorder-research-jan26.shtml), which was created with the input of the scientific community as well as advocates and advocacy organizations, including parents, providers, and individuals with ASD.

In January 2009, the Interagency Autism Coordinating Committee (IACC), a federal government advisory panel convened by HHS and consisting of federal and public members, released its first strategic plan for autism research. The IACC Strategic Plan for Autism Spectrum Disorder Research provides the scientific goals and benchmarks, and advises the Office of the Secretary on needs and opportunities for research investigating autism. The National Institutes of Health (NIH), the lead research agency on the IACC will take a major role in implementing the Plan. NIH is dedicated to supporting research that will lead to better ways to identify, treat, and even prevent the disabling symptoms of ASD and to help improve the quality of life for people with ASD and their families.

Prevalence/Incidence

Numerous studies have suggested that the prevalence of diagnosed ASD in the United States has increased dramatically in the past decades. In 2009, the CDC estimated that autism spectrum disorders affect 1 in 110 children. Increasing trends may be explained, in part, by the development of improved screening and diagnostic criteria, which may allow healthcare providers to identify more cases of ASD and at earlier ages; increased public awareness, which may encourage more parents to bring their children in for diagnosis when they suspect ASD; and increased availability of developmental disability services and providers for children with autism. However, these trends may in part be due to a rising incidence.

Disease Burden

Scientists, clinicians, and families agree that ASD is an urgent public health challenge with enormous financial and societal costs. Research data compiled in 2007 on the distribution of incremental societal costs of autism estimated the combined direct and indirect costs to care for all Americans with ASD during their lifetime will exceed $34 billion, with estimated costs for each person over his or her lifetime totaling $3 million. Families often incur large debts for medical and education services that public programs or medical insurance do not cover. Beyond financial costs, ASD often leads to profound emotional hardships for persons with the disorder and their families. As more children with ASD become adults with ASD, access to services and lack of accommodations is a growing challenge. At the same time, we need more evidence on which interventions are best for any specific individual with ASD so that there is a scientific basis to inform the choice of services provided.

Rationale

Recovery Act funds have provided an opportunity to jumpstart many of the objectives in the IACC Strategic Plan, utilizing economic recovery to support science that facilitates the best possible outcomes for individuals with ASD and their families. The Strategic Plan consists of short and long term research objectives across a range of topics, including those relevant to the heterogeneity of ASD. This includes conducting research to address the heterogeneity in autism spectrum disorders that addresses:

- the development of screening and diagnostic tools for identifying and characterizing ASD
- identification of biomarkers and biological signatures for determining risk and progression of ASD
- genomic sequencing, gene expression, and gene environment interactions
- neurobiological and behavioral treatment interventions
- pharmacological clinical trials, and
- service utilization and cost effectiveness.

Approaches to the study of ASD have evolved over time, as more is learned about these disorders. Because there are many different causal factors and trajectories for ASD, having greater knowledge of the range of ASD phenotypes may lead to more precise diagnostic and screening instruments and will increase the potential for more targeted treatment and intervention strategies. In addition, genomic studies are needed to help identify ASD subtypes; provide molecular targets for treatment development; and yield a robust strategy for the study of environmental factors (which interact with genetic risk).

TARGET CONTEXT AND CONDITIONS

In the process of gathering ideas from ASD stakeholders for the IACC Strategic Plan, certain cross-cutting themes emerged, including heterogeneity, prevention, earlier detection, community engagement of ASD research, public-private partnerships, and resources. This GPRA measure addresses one of these cross-cutting themes - the heterogeneity of ASD. In the context of ASD, the term heterogeneity refers to the spectrum of conditions and symptoms that may accompany the disorder. It means that no two children or adults with autism have exactly the same profile, behaviors, medical conditions, symptoms or developmental trajectory. The heterogeneity of ASD has profound impact on priorities of ASD research and implications for treatment and prevention.

Over the past several years, the NIH autism research portfolio has expanded significantly, ranging from basic and clinical neuroscience to treatment and services. The Recovery Act-measure represents one collaborative effort to focus, coordinate and accelerate high quality research and scientific discovery along continuum from basic science to practice. This research addresses gap areas of knowledge for ASD through robust, innovative research and intervention strategies.

The research in this measure builds on the existing ASD interventions and scientific knowledge. Currently, the only evidence-based intervention for the core social and communication symptoms of ASD is Applied Behavioral Analysis, which is efficacious for preschool-age children on the autism spectrum. In addition, risperidone is the only FDA-approved pharmacological treatment for autism, approved to treat disruptive/aggressive behavior in children with ASD, not the core symptoms.

Scientific advances using whole genome association studies have pointed to several genomic variations that may be associated with risk for ASD, but these variations require further analysis by fully sequencing target genes, regions of interest, or an individual's entire genome. Research utilizing neuroimaging techniques has made great strides in determining how brain anatomy, development and cognitive processing differ in individuals with autism. The development of new techniques and instruments in neuroimaging show promise for revealing the neural mechanisms underlying treatment effects on behavior, as well as the potential to identify biosignatures indicative of risk factors for ASD. Screening tools have been developed to identify young children at risk for autism, but further development is needed to determine their utility in large-scale, community populations; and there remains a need for screening tools for adolescents and adults at risk for ASD

These studies hold the best promise of revealing what causes autism, how it might be prevented, what treatments are effective for reducing both core and associated symptoms, and how service needs change across the lifespan. Examples of the studies include:

- A two-site study to adapt the Autism Diagnostic Interview-Revised into a brief parent interview that can be done over the phone;
- A study to expand a pilot program to identify different subtypes of autism based on behavioral, biochemical and brain imaging markers;
- A collaborative network of research labs and centers using cutting edge research to provide insight into the biology of autism and expose genes and pathways that constitute high priority targets for the development of novel treatments;
- A study to develop and test a parent-delivered intervention for high-risk infants 6-11 months focused on reducing atypical behaviors and developmental delays to help lessen or prevent the disabling symptoms associated with ASD;
- A study focusing on how race, gender, socio-economic status, family, culture and communication during clinical encounters affect the health care experiences of African American children with ASD in an urban setting;
- A study to evaluate the effects of "sensory integration treatment" on communication and social skills in children with ASD to help reduce resistance to outside stimuli and improve the integration of sensory information; and
- A study to fill a gap in scientific understanding of the effects of ASD in later life by exploring age-related changes in cognition, protective factors, changing service needs and quality of life among adults and older people with ASD.

In addition, data generated from these projects will be shared with the research community via the National Database for Autism Research (NDAR). Having this information in NDAR will allow scientists to analyze data from large numbers of individuals using similar standardized measures, providing the means to tease apart the heterogeneity of this disorder. Data sharing through NDAR is likely to advance understanding of ASD heterogeneity at a more rapid pace than would be possible through any single project.

Long Term Objective: (SRO-2.1) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.1 By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials. (Outcome)	*2011*	Reassess four pilot trials for continuation based on the safety and ability to enroll. *(Baseline):* The total number of subjects enrolled through FY10.	N/A
	2010	Continue to enroll subjects in trials, and follow enrolled subjects to endpoints. *(Baseline):* (FY09) The number of subjects enrolled in FY09 for each trial.	N/A
	2009	Continue enrollment into all trials, to reach target enrollments. *(Baseline):* (FY08) The number of subjects enrolled in FY08 for each trial.	234 subjects have been enrolled for assignment into five Phase II clinical trials and two Phase III clinical trials. (Target Met)
	2008	Initiate enrollment of individuals who have type 1 diabetes and who have severe hypoglycemic episodes and hypoglycemia unawareness into two Phase II clinical trials and one Phase III clinical trial to evaluate the effectiveness of islet transplantation. *(Baseline):* (FY07) Zero subjects accrued in each trial.	NIH initiated enrollment of individuals in five Phase III clinical trials and two Phase III clinical trials to evaluate the effectiveness of islet transplantation. (Target Exceeded)
	2007	Develop 2 clinical protocols. *(Baseline):* (FY06) Clinical protocols under development.	Seven clinical protocols were developed. (Target Exceeded)
	2006	Establish uniform cGMP manufacturing process for preparation of pancreatic islet cells across CIT centers. *(Baseline):* CIT established.	Uniform cGMP manufacturing process for preparation of pancreatic islet cells across CIT centers was developed. (Target Met)

Data Source and Validation
Patients can find out if they are eligible to participate in a CIT Consortium clinical trial at http://www.CITisletstudy.org More information on the seven trials can be found at http://www.clinicaltrials.gov using the identifiers listed below: CIT01 – "Open Randomized Multicenter Study to Evaluate Safety and Efficacy of Low-Molecular Weight Sulfated Dextran in Islet Transplantation. Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00789308 CIT02 – "Strategies To Improve Islet Survival." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00464555 CIT03 – "Peritransplant Deoxyspergualin in Islet Transplantation in Type 1 Diabetes." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00434850 CIT04 – "LEA29Y (Belatacept) Emory Edmonton Protocol (LEEP)." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00468403 CIT05 – "B-Lymphocyte Immunotherapy in Islet Transplantation." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00468442 CIT06 – "Efficacy of Islet After Kidney Transplantation." Phase III clinical trial. ClinicalTrials.gov Identifier: NCT00468117 CIT07 – "Islet Transplantation in Type 1 Diabetes." Phase III clinical trial. ClinicalTrials.gov Identifier: NCT00434811

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met as evidenced by a total enrollment of 234 subjects for assignment into the seven trials, with assignment occurring at the time that a pancreas became available for transplant. In addition, a total of 22 islet transplantations have been performed across the seven trials by the end of FY09.

The seven clinical trials are:

- CIT01 – "Open Randomized Multicenter Study to Evaluate Safety and Efficacy of Low-Molecular Weight Sulfated Dextran in Islet Transplantation," is a Phase II clinical trial to evaluate the safety and efficacy of low molecular weight dextran sulfate on post-transplant islet function in people with type 1 diabetes who have responded to intensive insulin therapy.
- CIT02 – "Strategies To Improve Islet Survival" is a Phase II clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications and medications to support islet survival, for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.
- CIT03 – "Peritransplant Deoxyspergualin in Islet Transplantation in Type 1 Diabetes" is a Phase II clinical trial. The purpose of this study is to assess the safety and efficacy of deoxyspergualin, an immunosuppressant drug, on post-transplant islet function in people with Type 1 diabetes who have not responded to intensive insulin therapy.
- CIT04 – "LEA29Y (Belatacept) Emory Edmonton Protocol (LEEP)" is a Phase II clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications, for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.
- CIT05 – "B-Lymphocyte Immunotherapy in Islet Transplantation" is a Phase II clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with the immunosuppressive medications and medications to support islet survival for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.
- CIT06 – "Efficacy of Islet After Kidney Transplantation" is a Phase III clinical trial. The purpose of this study is to compare the safety and effectiveness of islet transplantation versus intensive insulin treatment (ITT) for treating Type 1 diabetes in patients who have received kidney transplants.
- CIT07 – "Islet Transplantation in Type 1 Diabetes" is a Phase III clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications, for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.

BACKGROUND

Due to advances in immunosuppressive regimens, transplantation techniques using the body to heal internally, may be timely as a means of treating type-1 diabetes. It is difficult for patients to maintain the strict daily regimen of monitoring blood glucose levels with insulin use. A balanced approach, of treatment for the disease, as well as a focus on cures is needed.

Prevalence/Incidence

Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys the insulin-producing islets of the pancreas. According to data on prevalence and incidence published in 1995 by the NIH, 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. 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.

Disease Burden

Type 1 diabetes is a chronic, lifelong disease characterized by elevations in blood sugar that, over time, may lead to severe and life-threatening complications, including heart disease, blindness, peripheral neuropathy, foot ulcers, and kidney failure. Treatment of type 1 diabetes 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. However, even with careful attention to insulin dosing, 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 individuals with type 1 diabetes the potential for physiologic control of blood sugar as an alternative to insulin therapy. Whole-pancreas transplantation is associated with significant morbidity and even death around the time of the operation; whereas, islet transplantation is associated with considerably less morbidity and has not been associated with death in the peri-procedure period. In islet transplantation, clusters of cells from the pancreas called islets are isolated from a donor pancreas and injected into a large blood vessel that drains into 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 one 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 prospect for islet transplantation. If these results are confirmed in larger, multi-site studies, approximately 40 to 50 percent of type 1 diabetics can be expected to remain insulin independent two years following islet transplantation. Despite these advances, there is a progressive diminution in function of the transplanted islets with current approaches, and patients must remain on potent immunosuppressive drugs to prevent immune-mediated rejection of the transplanted islets. Immunosuppressive agents increase the risk of serious infection, kidney damage, 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. If successful, tolerance induction would enable life-long maintenance of islets in the absence of the drugs currently used to prevent rejection of the transplanted cells by the host immune system, many of which have deleterious side effects and associated toxicities.

Clinical and basic research conducted over the last several years through the NIH-funded Immune Tolerance Network (ITN) and elsewhere has increased understanding of the mechanisms of immune tolerance, and some initial "proof of concept" trials in highly selected patient populations have been successful. Nevertheless,

subsequent trials of tolerance-inducing agents in patients with autoimmune diseases other than type 1 diabetes indicate that the agents used are unlikely to induce total tolerance in patients with type 1 diabetes who received islet cell transplantation.

The scope of research relevant to this goal as originally written has been expanded to include multiple avenues of immune modulation research. The goal of immune modulation research is the selective modulation of the immune system through the inhibition of harmful immune responses while keeping protective ones intact. For example, in transplantation, donor-specific immune modulation — a selective blockade of immune responses directed against the graft — could enable long-term graft survival without or with less toxic systemic immunosuppressive therapy. In asthma and allergic diseases, the goal of immune modulation research is the development of methods to inhibit immune responses to allergens. In autoimmune diseases, the goal of immune modulation research is the inhibition of the immune responses that cause the body to mistakenly attack its own organs, tissues, or cells. Tolerance induction is one of the multiple immune modulation strategies that could potentially improve the safety and long-term success of islet cell transplantation in people with type 1 diabetes.

TARGET CONTEXT AND CONDITIONS

During 2005-2007, the Clinical Islet Transplantation (CIT) Consortium investigators focused on: (a) the development of clinical protocols and a manufacturing batch record, (b) submission of protocols to health authorities, (c) completion of clinical trial agreements with industry partners, and (d) solving unforeseen problems that emerged regarding acquisition of raw materials and reagents for islet manufacture. During 2008-2010, the targets are to initiate and complete enrollment in the CIT clinical trials.

The CIT is conducting 2 types of trials: (1) Phase II pilot studies of innovative interventions and (2) Phase III studies of consensus procedures. For the pilot studies, goals over the next three years will be: 1) to identify and terminate studies in which the intervention is demonstrably unsafe or less effective than consensus therapy, and 2) to continue enrolling patients in all the other studies. For those studies that achieve complete enrollment, the primary endpoint data are expected to be available for analysis in 2011. For the Phase III studies, the primary endpoint data will be available for analysis in 2012 with the caveat that the appropriate number of patients is enrolled in each trial.

Keys to achieving these goals will be:

- Timely enrollment at all sites: enrollment will be monitored on a monthly basis, and impediments to enrollment will be identified and eliminated as necessary and possible.
- Timely and accurate entry of data into the study database: all clinical sites will be monitored and where problems are identified, appropriate training/remediation procedures will be implemented.
- Maintenance of regulatory compliance: all CIT studies are carried out under IND #9336, which is held by NIH.
- Assurance of uninterrupted availability of the reagents and raw materials needed for islet manufacture: the CIT investigators and NIH will continue to evaluate alternate sources of these materials, and work with the FDA to determine where substitutions are possible without jeopardizing the integrity of the studies.

Long Term Objective: (SRO-2.2) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.2 By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. (Efficiency) (Outcome)	*2009*	Complete evaluation of the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. *(Baseline):* FY03 to FY08 results	(1) Leptin, an energy regulating protein hormone, modulates neural activity observed in response to visual food cues and may play a role in preventing weigh regain following weight loss. (2) Adults who lost weight in a six-month lifestyle change program kept more of the weight off for two years with brief, monthly personal counseling compared to a self-directed group. (Target Exceeded)
	2008	Complete delivery of the 2-year interventions being tested in the preventing obesity using novel dietary strategies (POUNDS Lost) clinical trial, which is comparing four diets of different macronutrient composition for their effects on weight loss and weight loss maintenance in overweight and obese adults. *(Baseline):* (FY06) Few trials have adequately tested the effects of diets differing in macronutrient composition.	Delivery of the 2-year interventions being tested in the POUNDS Lost trial has been completed. (Target Exceeded)
	2007	Develop and launch at least three new clinical trials to test the effectiveness of intervention programs delivered in primary care practices to treat and/or prevent obesity in children. *(Baseline):* (FY05) Few obesity intervention programs targeting children have been designed and tested to establish their effectiveness outside of small clinical settings.	Four new clinical trials were developed and launched to test the effectiveness of intervention programs delivered in primary care practices to treat and/or prevent obesity in children. (Target Exceeded)

Measure	FY	Target	Result
	2006	Enroll and randomize 240 predominantly minority pre-adolescent girls to test the efficacy of an after school dance program in reducing weight gain. *(Baseline):* (FY04) Few effective community-based interventions are available to prevent weight gain in at risk children	Two hundred forty ethnically-diverse pre-adolescent girls were enrolled and randomized to test the efficacy of an after school dance program in reducing weight gain. (Target Met)

Data Source and Validation
Rosenbaum, M. et al. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. J Clin Invest. 118: 2583-2591, 2008. Confirmation of the Weight Loss Maintenance Randomized Trial can be found at: http://www nih.gov/news/health/feb2009/nhlbi-25 htm

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and Exceeded. The Measure has been Achieved. A study was completed that demonstrated that leptin is able to modulate neural activity observed in response to visual food cues and may play a role in preventing weigh regain following weight loss. Previous work showed that low-dose administration of leptin may prevent weight regain following weight loss. The current study involved a group of obese patients who had undergone a 10 percent body weight reduction, received twice-daily subcutaneous injections of leptin or placebo, and were subjected to a functional MRI examining brain region-specific neural activity elicited by visual food cues. Maintenance of reduced body weight was associated with leptin-dependent alterations in neural activity in brain regions involved with vegetative/regulatory and hedonic aspects of energy regulation.

The Weight Loss Maintenance Randomized Trial initially enrolled 1,685 overweight or obese adults with high blood pressure or high cholesterol or both. Of those, 1,032 lost an average of 18.7 pounds during an initial six-month weight loss intervention involving 20 weekly group-counseling sessions which emphasized a heart-healthy dietary pattern and three hours per week of physical activity. The study participants were then randomly assigned to one of three strategies for weight loss maintenance: monthly personal counseling on diet and physical activity, a Web-based intervention with the same advice, and self-direction, where participants received minimal further intervention from study staff. At the end of the study, participants receiving personal counseling retained an average weight loss of 9.2 pounds, compared to an average of 7.3 pounds for those using the Web-based intervention and 6.4 pounds for those in the self-directed group.

Efficiency

The Measure was completed approximately four months ahead of time.

BACKGROUND

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and / or increased risk of type 2 diabetes, cardiovascular disease, certain cancers, and many other serious health problems. The increased prevalence of obesity in the U.S. is thought to result from the interaction of genetic susceptibility with behavior and factors in the environment that promote increased caloric intake and sedentary lifestyles. Although current approaches to

lifestyle change can reduce weight, it remains difficult to sustain weight loss. Current weight loss medications have only modest efficacy. In cases of severe obesity, bariatric surgery may be performed.

Prevalence/Incidence

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

- Approximately one-third of U.S. adults are obese(BMI $\geq$ 30).
- About 16.3 percent of children and teenagers ages 2 through 19 have a BMI $\geq$ 95th percentile, 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 American Indian women and children.

Disease Burden

A 2007 NIH report on overweight and obesity shows that obesity is associated with numerous serious diseases, including type 2 diabetes, heart disease, stroke, osteoarthritis, gallstones, breathing problems, and certain cancers. Type 2 diabetes, formerly viewed as a disease of older 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 morbidity and mortality, overweight and obesity exact enormous economic costs. In 2000 costs associated with obesity were estimated to be $117 billion.

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 (DPP) clinical trial demonstrated a substantially reduced incidence of type 2 diabetes in a high-risk population using an intervention that successfully attained moderate weight loss through decreased calorie intake and increased physical activity; 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 achievement 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 additional modalities to help individuals achieve and maintain a healthy weight.

For people who are extremely obese, expected weight loss and maintenance 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 long-term weight loss.

A major focus 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. 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.

TARGET CONTEXT AND CONDITIONS

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

The NIH is supporting research to 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, seven studies are evaluating the effects on weight control of worksite interventions that include environmental components; and at least six studies are evaluating the effects of interventions delivered in primary care settings to treat and/or prevent obesity in children and adults. Because maintenance of weight loss is a critical yet particularly difficult element of obesity treatment and prevention, NIH supported research is investigating novel ways to help individuals who have intentionally lost weight to keep the weight off. Specifically, the Weight Loss Maintenance Trial compared 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 is 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. In addition, pharmacotherapeutic strategies are being evaluated for their ability to enhance weight maintenance and/or to reverse the physiological compensatory mechanisms in response to weight loss that may contribute to weight re-gain.

Research on the effects of bariatric surgical procedures designed to restrict food intake in adults and adolescents 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 supported research has fully recruited two clinical studies to investigate the effects of two different pharmacologic agents, 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.

More broadly, the NIH is implementing the multidimensional research agenda of its Strategic Plan for NIH Obesity Research. Developed by the NIH Obesity Research Task Force with crucial input from external scientists and the public, the Strategic Plan, published in August 2004, serves as a guide for coordinating obesity research activities across the NIH and for enhancing the development of new research efforts. The NIH is supporting a spectrum of initiatives consistent with the recommendations of the Strategic Plan; these initiatives complement the NIH's strong portfolio of investigator-initiated obesity research. Additionally, the NIH continues to work with the external community on efforts to advance obesity research progress.

Long Term Objective: (SRO-2.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.4 By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life. (Outcome)	*2009*	Complete the goal of developing and testing multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life. *(Baseline):* To be determined by FY08 results.	Genetic factors coding for specific chemokines, cytokines, and other proteins were found to be associated with painful symptoms in models of tissue injury and HIV/AIDS treatment, results that could be used in developing future analgesics to reduce symptom burden in patients experiencing treatment and disease-related pain. (Target Met)
	2008	Evaluate two interventions for reducing pain, fatigue, psychological distress, or other symptoms in patients undergoing treatment for cancer or other illness/chronic disease. *(Baseline):* (FY06) Potential strategies for reducing symptom burden of patients with a chronic disease/illness identified.	Researchers completed two studies that evaluated interventions for reducing pain. Both studies explored the biological mechanisms of analgesia in oral surgery models of acute pain. (Target Met)
	2007	Contribute to the identification of potential interventions for treatment-related oral complications and associated pain by analyzing the results of two (2) clinical research protocols relevant to cancer treatment. *(Baseline):* (FY04) Two (2) IRB approved clinical research protocols addressing cancer treatment-related oral complications and associated pain are open to accrual.	Two studies on the evaluation of interventions to reduce pain and other symptoms in patients undergoing treatment for cancer were completed. (Target Met)
	2006	Contribute to the identification of potential interventions for symptom/illness burden by identifying results from one study of symptom distress/quality of life. *(Baseline):* (FY05) One study of symptom distress/quality of life completed.	Results from one study of symptom distress/quality of life were identified. (Target Met)

Data Source and Validation
Dorsey S.G., C.C. Leitch, et al. (2009). "Genome-Wide Screen Identifies Drug-Induced Regulation of the Gene Giant Axonal neuropathy (Gan) in a Mouse Model of Antiretroviral-Induced Painful Peripheral Neuropathy." Biol Res Nurs 11: 7-16. http://brn.sagepub.com/cgi/content/abstract/11/1/7 Wang X.M., M. Hamza, et al. (2009). "Up-regulation of IL-6, IL-8 and CCL2 gene expression after acute inflammation: correlation to clinical pain." Pain 142: 275-83. doi:10.1016/j.pain.2009.02.001

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and the measure was Achieved. NIH researchers identified genetic factors coding for specific chemokines, cytokines, and other proteins that are associated with painful symptoms in models of tissue injury and HIV/AIDS treatment. These results could be used in developing future analgesics to reduce symptom burden in patients experiencing treatment and disease-related pain.

In one study, scientists examined changes in biological factors that occur in response to tissue injury, and correlated these with pain intensity. These factors included chemokines and cytokines, proteins that serve as messengers between cells and that are involved in regulating inflammation. Using oral surgery as a model of tissue injury, the researchers found that injury significantly increased the gene expression of interleukin-6 (IL-6), interleukin-8 (IL-8), chemokine (C-X-C motif) ligand 1 (CXCL1), chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-X-C motif) ligand 2 (CXCL2), and annexin A1 (ANXA1). The upregulation of IL-6, IL-8, and CCL2 gene expression was positively correlated to pain intensity three hours after surgery, indicating that these three factors contribute to the development of acute inflammation and inflammatory pain. However, the pain medication ketorolac, a non-steroidal anti-inflammatory drug (NSAID), did not significantly affect expression of IL-6, IL-8, CCL2, CXCL2, and ANXA1. The factors revealed by this study to be associated with increased pain could serve as novel targets in the development of future analgesics.

In another study, researchers assessed the biological mechanisms underlying the development of painful peripheral neuropathy in some patients being treated for HIV with nucleoside reverse transcriptase inhibitors (NRTIs), components of highly active antiretroviral therapy (HAART). This debilitating neuropathy can severely reduce quality of life and limit treatment for HIV, and is resistant to conventional methods of pain management. Using genetic analysis in a mouse model of NRTI-induced neuropathy, scientists sought to determine the mechanism by which NRTIs might be contributing to the development of neuropathy. Through techniques that allowed them to detect changes in gene expression across the mouse genome, the researchers identified changes in one gene that appeared to be associated with NRTI treatment. This gene, giant axonal neuropathy 1, or Gan1, was downregulated in NRTI-treated mice compared to controls, as was its protein product gigaxonin. These results indicate that Gan1 could be a potential target in the development of new treatments for this painful condition in HIV patients.

Measure

Results of the work described here, and of those studies undertaken throughout the duration of this measure, have significantly improved our fundamental understanding of the underlying mechanisms of symptoms and symptom management, including pain management. Initial efforts established a research collaboration that allowed for multidisciplinary basic and clinical, biobehavioral studies to understand the biological basis of adverse symptoms. Subsequent studies focused on interventions to reduce symptom severity in patients undergoing treatment for cancer. For example, one study tested an intervention to reduce pain and other symptoms in patients with graft-versus-host disease (GVHD), a condition experienced by some cancer patients undergoing bone marrow transplantation. The study found that the intervention reduced pain, and it assessed a potential method for assessing symptom severity by measuring amounts of protein messengers known as

cytokines. A similar study demonstrated that cytokines might be useful in measuring pain intensity in patients undergoing chemotherapy. Further studies explored the use and mechanisms of analgesic drugs in reducing pain in surgical patients. For example, one study found that two nonsteroidal anti-inflammatory analgesics (NSAIDs) that attenuated pain in surgical patients reduced gene and protein expression of phophodiesterase type 4(PDE4D), revealing a novel mechanism which may contribute to the analgesic and anti-inflammatory effects of these drugs. Another biobehavioral study explored genetic mechanisms for explaining why some individuals respond differently to analgesic interventions than others. Researchers identified a single nucleotide polymorphism (SNP) that was associated with responses to the analgesic ketorolac. This SNP was associated with a gene that codes for a protein that binds to DNA, indicating that genetic variations in or near genes that encode DNA binding proteins may play a role in clinical responses to analgesics. Finally, recent studies revealed additional biological factors that could serve as potential biochemical targets and biomarkers for developing and assessing future behavioral pain interventions.

Taken together, the research conducted under this method has led to improved understanding of biobehavioral interventions that improve functional status and quality of life, and has expanded the knowledge-base surrounding pain and pain management. In addition to assessing interventions for reducing symptoms, this research has identified numerous potential targets to explore in developing the next generation of interventions for managing symptoms, which could lead to further improvements in symptom management, functional status, and quality of life in individuals with acute conditions or chronic illnesses who are experiencing pain and other adverse symptoms.

BACKGROUND

Across a wide range of acute and chronic disease and treatments, symptoms such as pain, fatigue, and psychological distress may arise and have an impact on the health outcome of the patient. Symptoms may impact patients in several ways: (1) symptoms may cause patients to reduce or abandon treatment, (2) symptoms may cause psychological distress, and (3) symptoms may contribute to the overall disease burden while decreasing both the functional status and the quality of life for the patient. These effects of disease- and treatment-related symptoms play an important role in health outcomes.

Disease- and treatment-related symptoms such as pain, fatigue, and psychological distress are common for diseases/conditions including cancer, acquired immune deficiency syndrome (AIDS), graft versus host disease and others. For example, persons undergoing certain chemotherapy or allogeneic bone marrow transplantation may develop stomatitis, an inflammation of the lining of the throat and mouth that may lead to ulcerations, mouth and throat pain, and decreased quality of life. Behavioral factors related to symptom burden also affect functional status and quality of life. Examples of behavioral factors include interventions used by patients and families to treat and manage physical and/or other issues resulting from symptoms. The investigation of biological mediating factors, as well as behavioral factors, need to be elucidated to provide the rationale for testing interventions targeted at increasing functional status and quality of life.

Newly established research programs addressing potential interventions of disease- and treatment-related symptoms are underway by NIH-supported scientists. Research efforts include studies of cancer treatment-related complications and associated pain, as well as symptom distress/quality of life. Through research of symptoms, NIH-sponsored scientists are identifying additional strategies to improve health outcomes.

Rationale

Elucidating interrelationships among the components of symptom experience, symptom management strategies, and symptom outcomes related to acute and chronic diseases/conditions and associated treatments is critical to providing appropriate preventative and treatment-related health care. The symptoms patients experience are often the first indicator of treatable disease, may signal disease progression, and/or may prevent optimal treatment. Understanding the biological basis or mechanisms of symptoms is a critical first step to developing and testing scientifically sound interventions that address the cause of the symptoms. NIH-

supported scientists are capable of performing research investigations, including clinical trials, to develop interventional or therapeutic strategies targeted at improving the patient's health status and quality of life.

TARGET CONTEXT AND CONDITIONS

NIH-supported scientists are addressing disease- and treatment-related symptoms that are common for diseases/conditions. The following implementation strategies or steps have been identified to provide the basis for achieving the goal: (1) forming at least one collaboration that addresses either the biological mechanisms of pain, fatigue, or psychological distress or related potential therapeutic intervention(s); (2) identifying results from at least one study of symptom distress/quality of life; (3) identifying results of clinical trials addressing cancer treatment-induced oral complications and associated oral pain; and (4) evaluating two interventions for reducing pain, fatigue, or psychological distress in patients undergoing treatment for cancer or other illness/chronic disease. As both time and science advance, other implementation strategies or steps may be identified and employed to achieve the goal.

Long Term Objective: (SRO-2.5) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.5 By 2011, identify and evaluate 5 novel molecular-targeted interventions for cancer, and determine suitability for use in early phase clinical trials. (Outcome)	*2011*	Evaluate 3 novel targeted cancer interventions using preclinical testing. *(Baseline):* Five novel targeted cancer interventions identified.	N/A
	2010	Identify 3 novel targeted cancer interventions. *(Baseline):* (FY09) Two novel interventions evaluated for use in preclinical testing.	N/A
	2009	Evaluate two targeted interventions using preclinical testing. *(Baseline):* (FY08) Two novel targeted cancer interventions identified.	NIH investigators determined that two previously identified targeted cancer interventions, novel indenoisoquinoline derivatives and a radiolabeled imaging agent, showed promising results in preclinical testing which may result in early phase clinical trials. (Target Met)
	2008	Identify two novel targeted cancer interventions. *(Baseline):* (FY07) Novel targets have been identified.	NIH investigators identified two novel targeted cancer interventions, indenoisoquinolines and 111In-Herceptin®. (Target Met)

Data Source and Validation

Antony, S. et al. Novel Indenoisoquinolines NSC 725776 and NSC 724998 Produce Persistent Topoisomerase I Cleavage Complexes and Overcome Multidrug Resistance. Cancer Res. 2007 Nov 1;67(21):10397-405 PMID: 17974983 http://www ncbi nlm nih.gov/pubmed/17974983

Xu H, et al. Toward preparation of antibody-based imaging probe libraries for dual-modality positron emission tomography and fluorescence imaging. Bioorg Med Chem. 2009 Jul 15;17(14):5176-81 PMID: 19505829 http://www ncbi nlm nih.gov/pubmed/19505829

Milenic DE, et al. Targeting of HER2 antigen for the treatment of disseminated peritoneal disease. Clin Cancer Res. 2004 Dec 1;10(23):7834-41. PMID: 15585615 http://www.ncbi nlm.nih.gov/pubmed/15585615

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. The two previously identified targeted cancer interventions, novel indenoisoquinoline derivatives and a radiolabeled imaging agent, were evaluated using preclinical methods and showed promising results in moving toward early phase clinical trials.

NIH investigators performed preclinical testing to evaluate two indenoisoquinoline derivatives, NSC 725776 and NSC 724998. Using a histone gamma-H2AX assay, investigators showed that both agents are potent and

selective Top1 inhibitors. Studies in human cells in culture showed that both agents exert antiproliferative activity at submicromolar concentrations. In addition, the studies validated histone gamma-H2AX as a potential biomarker for clinical trials.

NIH investigators also have demonstrated the strong binding capabilities of 111In Herceptin® to cancer cells measuring the amount of radioactivity (as a per cent of the total injected dose) within tumors. Ongoing studies are evaluating these agents in both subcutaneous and intraperitoneal xenograft tumor targeting model systems. Earlier results in the xenograft model have shown excellent tumor targeting by 111In Herceptin®. Investigators are also exploring combining herceptin with other radiolabels, such as Pb-212, demonstrated effective tumor killing and could be potentiated with chemotherapeutic agents.

BACKGROUND

Prevalence/Incidence

The 2006 NIH Cancer Factbook indicates that cancer is the second leading cause of death in the United States and the economic cost of cancer in 2005 has been estimated at over $200 billion As reported by the Centers for Disease Control and Prevention in 2004, managing the burden of chronic diseases and their risk factors continues to be a challenge. Although significant progress has been made toward reducing the burden of cancer in America, one of every four deaths is due to cancer. It is estimated that in 2008 there will be about 1,437,180 new diagnoses of invasive cancer and 565,650 Americans will die of cancer according to facts and figures provided by the American Cancer Society in 2008.

Recent advances in the molecular pathogenesis of cancer offer unprecedented opportunities to discover and develop novel, molecularly targeted therapeutic and preventive strategies and agents. The challenge is the definitive validation of human cancer-pertinent molecular targets. The NIH is identifying and characterizing new molecular targets important in cancer processes, diagnostics, and therapeutics. The NIH is facilitating moving novel discoveries through the development process to develop new cancer therapies by supporting the pre-clinical development of promising molecularly targeted lead compounds.

Rationale

Discovering new molecular targets through a strong basic science program will accelerate the selection and development of new treatment regimens for further validation in *in vitro* studies, preclinical models, and early phase clinical trials. By targeting specific genetic alterations that occur in cancer cells, more effective therapies can be developed to attack tumor cells while normal cells remain unharmed. This will lead to the management of cancer as a chronic condition and enhance the quality of life of cancer patients.

TARGET CONTEXT AND CONDITIONS

The NIH plans to identify 5 novel molecular-targeted interventions for cancer. Once the interventions have been identified, a number of approaches will be taken to assess the suitability of these agents for early phase clinical trials.

The agents will be evaluated using *in vitro* assays well in advance of early phase clinical trials. These assays aim to develop an understanding of the biochemical and physiological effects of a drug and how it affects cancer cell growth and division in culture.

Following in vitro testing, the agents will be tested in animal models that most appropriately recapitulate the human cancers. Such tests will validate the targets and demonstrate drug target effect in preclinical models and/or in human tissue prior to initiating the clinical trial. A molecular toxicology profile of novel agents will be developed. The NIH will develop and authenticate a variety of tests well in advance of human studies, so they can be used in early phase trials to provide information about the safety and efficacy of the agents being tested. Using the science-based evidence collected in the previous steps, the suitability of these agents for evaluation in early phase clinical trials will be determined.

Long Term Objective: (SRO-2.6) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.6 By 2011, develop one field deployable sensor device for use in human studies and develop one biomarker to characterize the impact of environmental exposures on biological pathways. (Outcome)	*2011*	Complete development of a field deployable sensor device and a biomarker to characterize the impact of environmental exposures on biological pathways suitable for initial application in human studies. *(Baseline):* Sensor performance is being improved and requires better understanding of biomarkers application to population level analysis.	N/A
	2010	Sensors and candidate biomarkers will undergo benchmark testing prior to population level analyses. *(Baseline):* Sensors and candidate biomarkers require testing and verification before human studies trials can begin.	N/A
	2009	Enhance current technologies to allow detection of multiple analytes, and use novel technologies to characterize the response in biological pathways to environmental exposures *(Baseline):* Technologies are being developed for improved assessment of exposure and biological response	The colorimetric array and novel microRNA technology were refined to quantify exposure to multiple toxic industrial chemicals and to identify exposure to tobacco smoke in minimally invasive samples. Single-cell genetic analysis is being applied to samples from studies of exposure to chemical and lifestyle exposures. (Target Met)
	2008	Refine current technologies to demonstrate analyte specificity and sensitivity in benchtop assays, and identify pathways of response for important environmental exposures *(Baseline):* Assessments of environmental exposures or biological response on a pathway level are inadequate.	Refined colorimetric array technology to improve specificity and sensitivity in detecting and measure toxic exposures. Characterized lung cell response pathways to cigarette smoke exposure, and blood cell response pathways to carcinogens. (Target Met)

Data Source and Validation
Lim SH, Feng L, Kemling JW, Musto CJ and Suslick KS. An optoelectronic nose for the detection of toxic gases. Nature Chemistry (2009)1 (7): 562 – 567 http://www nature.com/nchem/journal/v1/n7/abs/nchem.360 html Schembri F, Sridhar S, Perdomo C, Gustafson AM, Zhang X, Ergun A, Lu J, Liu G, Zhang X, Bowers J, Vaziri C, Ott K, Sensinger K, Collns JJ, Brody JS, Getts R, Lenburg ME and Spira A. MicroRNAs as modulators of smoking-induced gene expression changes in human airway epithelium. PNAS (2009) 106(7)2319-2324 http://www.pnas.org/content/106/7/2319.abstract Sterling K, Ryan J, Brody JS, and Spira A. The field of tissue injury in the lung and airway, Cancer Prev Res (2008) 1(6): 396-403 http://cancerpreventionresearch.aacrjournals.org/cgi/content/abstract/1/6/396 Beane J, Spira A, and Lenburg ME. Clinical impact of high-throughput gene expression studies in lung cancer. Journal of Thoracic Oncology (2009) 4(1):109-118 DOI: 10.1097/JTO.0b013e31819151f8

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH researchers enhanced a previously developed colorimetric array technology. Using the improved 36 element array of nanoporous pigments they have demonstrated the ability of to differentiate and quantitate a panel of 20 toxic environmental exposures at concentrations that are Immediately Dangerous to Life and Health as well as their defined Permissible Exposure Levels. In this study, the researchers also developed a statistical analysis process that is used to identify the compound, its concentration and its relationship to the other test compounds. The investigators are also beginning the development of a prototype wearable sensor device that can be used in occupational settings.

Researchers are also refining the single cell analysis system, developed in FY 2008, to detect molecular changes in key cancer-associated genes. A small pilot test of the approach is being conducted in an independent set of samples from subjects who are occupationally exposed to trichloroethylene, a chemical that has been associated with blood cancer risk.

Investigators continued development of molecular profiles of response to tobacco smoke using cells lining the nose and mouth. This year research using novel "microRNA" technologies demonstrated that small RNA molecules are altered with cigarette smoke exposure. These small RNA profiles strengthen the patterns that distinguish never, current, and former smokers. In the next step of this study, the investigators will begin to validate this approach using samples from an independent study of subjects exposed to inhaled toxicants through the burning of coal and other types of biomass burning.

BACKGROUND

Substantive evidence exists to support the concept that common human diseases, such as asthma, cardiovascular disease, and cancer, arise from a complex interplay between genes and environmental factors, including chemical toxicants and biological toxins. To understand important gene-environment interactions in these diseases, it is necessary to understand both the genetic component and the environmental component. With the human genome project, the ability to link the genetic component of human health and disease is rapidly progressing. The environmental component, however, is lagging, due in large measure to an inability to accurately measure exposures and to define the early biological consequences of those exposures.

There are currently two ways by which exposures are measured or tracked:

- Measures of what is in the environment as revealed by toxic waste reporting, air monitoring, or water assessments. These measures, however, cannot show what actual amounts of an environmental component are being taken into an individual's body.
- Individual exposure (body burden) data, such as those provided by the National Health and Nutrition Examination Survey. These data, however, have limitations for large studies both because it requires expensive blood work and because the measurement is but a single "snap shot" in time; whereas real-world exposures and the consequences of these exposures play out over a long period of time.

To move the field forward in a way that links gene-environment interactions with human health outcomes, improvements are needed in exposure assessment technology. These improvements would involve:

- Personalized exposure monitoring systems;
- Nano-scale sensing technologies that monitor personal exposures over time;
- Molecular profiling technologies that would assess important underlying biological responses to exposure such as changes in gene expression, protein levels, or metabolite formation.

The Genes, Environment and Health Initiative (GEI) aims to accelerate the understanding of genetic and environmental contributions to health and disease. It has two components: the genetic component which focuses on identifying major genetic susceptibility factors and the environmental component which focuses on development of innovative techniques to measure environmental exposures, diet, physical activity, psychosocial stress, and addictive substances that may contribute to development of disease. This measure addresses the second effort, the Exposure Biology Program (EBP), which will create new ways to assess exposures that may be used in studies which capture information about susceptibility across the entire genome. Optimally, using new bioengineering approaches, exposures that an individual comes in contact with will be measured more accurately during critical time points. This program will also develop ways to measure an individual's response to these exposures using new molecular technologies. It is envisioned that these methods will provide measures of personal exposure that are quantitative, precise, reliable, reproducible, and that can be scaled up to implement in large population studies in the near future.

Rationale

The Exposure Biology Program (EBP) arose from the recognition that current methodologies for the detection and measurement of the actual exposure sustained by a human or other organism are often limited in the number of analytes detected and the temporal, spatial, and quantitative resolution of the measurements. This is in contrast to the robust tools employed in the fields of genetics and genomics. In order to advance understanding of the gene-environment interactions underlying the majority of human disease, scientists must have personalized measures of environmental exposures and stressors that are equivalent in precision to current technology for measuring genetic variability. Fortunately, the increasing sophistication of research tools for understanding the biological pathways involved in host response to a given exposure provides new knowledge that can be applied to the development of improved methods for detecting and measuring environmental exposures and stressors. Ultimately, the information and tools generated by the EBP will be used to generate a better understanding of gene-environment interactions in disease etiology that may translate into improved health care and early, more effective, interventions.

TARGET CONTEXT AND CONDITIONS

The goals of the 4-year reporting period are to refine or enhance current technologies to improve detection or analysis of environmental exposures, and to identify and characterize pathways of response for important environmental exposures. Robust biomarkers are needed that can be reliably detected in easily obtained biological samples that reflect biological responses to environmental stressors in human population studies. This involves a continual effort by the investigators over the reporting period.

Existing technologies are being adapted to detect analytes and identify biomarkers to improve the capabilities of exposure assessments. Currently, existing sensor technologies are focused on individual analytes with little temporal and spatial resolution as opposed to 'real world' environmental exposures. Similarly, biomarkers used in current studies are limited by a focus on individual gene or protein expression changes in the absence of information on pathway behavior. These sensor and biomarker discovery methods have many known limitations such as misclassification error, individual variability, temporal uncertainty, and sequential inaccuracy. These limitations in exposure assessment methodologies have produced conflicting data and hampered our ability to prevent, predict, and treat disease.

To overcome the known limitations of current technologies, enhancement and then validation are critical. In FY 2008 and FY 2009, the NIH tested sensor devices and biomarker profiles in laboratory settings, which set the stage for later validation in larger populations. In FY 2010, sensors and candidate biomarkers will undergo benchmark testing prior to population level analyses. In FY 2011 sensors and biomarkers developed in the EBP will be validated in small cohorts to ascertain usability and potential to test novel hypotheses in environmental epidemiology including the assessment of individual exposures and the biological response to those exposures. The NIH is currently planning a follow-up research effort focused on the application of the tools developed in the EBP in population based studies.

Long Term Objective: (SRO-2.7) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.7 By 2011, complete clinical testing of one candidate medical countermeasure that could be used to diagnose or treat victims of a chemical terrorist attack or accident, and complete preclinical testing for two others. (Outcome)	*2011*	Identify one candidate medical countermeasure that could be used to diagnose or treat victims of a chemical terrorist attack or accident, and complete preclinical testing for two others. *(Baseline):* Completed preclinical tests of one chemical agent therapy.	N/A
	2010	Complete preclinical tests of one chemical agent therapy *(Baseline):* Several therapeutic approaches show promising activity in initial tests	N/A
	2009	Develop a prototype technology to diagnose chemical exposure in an emergency setting *(Baseline):* (FY07) Current diagnosis of chemical exposure in an emergency setting is limited to assessment of visible clinical symptoms	Prototypes developed for two hand-held EEG and two biosensor devices for detecting nerve agents in blood. (Target Met)
	2008	Determine whether three molecules associated with chemical injury show promise as new therapeutic targets *(Baseline):* (FY07) Several new potential therapeutic targets have been identified through basic research on the biological effects of chemical exposure	Modifying the activity of TRPA1, GluR5K5, and EP had protective effects in models of chemical injury (Target Met)

Data Source and Validation
U01NS058161 (Lin): Innovative biomonitoring device for rapid diagnosis of exposure to nerve agents. Progress report. U44NS058229 (Nagy): Development of a selective biosensor for detecting OP exposure. Progress report. U44NS057969 (Modarres): Field deployable, automatic, EEG seizure detector and brain dysfunction monitor. Progress report. U44NS057951 (Wilson): A first-responder EEG device for seizure management in a nerve gas attack. Progress report. (Contact: NINDS Office of Science Policy and Planning)

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met with the development of two EEG prototype devices and two hand-held prototype devices for detecting nerve agents in blood. The ground work research for this successful development was supported by the NIH CounterACT program through several small business (SBIR) and Cooperative

Agreement (U01) projects to develop portable electroencephalogram (EEG) devices for diagnosing seizures due to nerve agent exposure, in an emergency setting. In addition, CounterACT supported three projects to develop biosensor devices for detecting signs of nerve agent exposure in biological samples, such as blood. In 2009, two EEG prototype devices and two hand-held prototype devices for detecting nerve agents in blood were completed. The researchers provided a technical demonstration of the prototype EEG and biosensor devices at the April 2009 CounterACT Symposium.

Advances or Other Highlights

The FDA approved the use of an exception to informed consent procedures that facilitates the midazolam trial's need to enroll patients in emergency settings. The trial began recruiting in June 2009, and at the end of 2009, recruitment was ahead of schedule, with approximately 150 out of a total of 800 planned participants and 13 of 17 trial network sites enrolling nationwide. When 400 participants have been recruited, the Data Safety and Monitoring Board will review the data collected up to that point in order to determine if there is enough evidence to draw a conclusion and end the trial early.

Cobinamide, a new cyanide antidote, is in the final stages of preclinical testing. The definitive preclinical pharmacology and toxicology studies should be completed in 2010. In June 2009, the lead researchers met with the FDA to discuss plans for submitting an Investigational New Drug (IND) application, which will allow clinical trials to be initiated. If the IND application is approved, cobinamide could enter phase I clinical testing in FY 2011.

Galantamine, a drug that has been approved for treatment of Alzheimer's disease, shows promise as both a pre-exposure and post-exposure treatment for a broad spectrum of nerve agents. The patent for using galantamine as a nerve agent treatment has been licensed to a small business, which plans to complete all of the preclinical studies required for an IND. A pre-IND meeting was held with the FDA in FY 2009.

A new antioxidant drug, AEOL 10150, protected rat lungs from sulfur mustard-induced injury and inflammation. CounterACT researchers are now testing AEOL 10150 in a skin injury model and optimizing treatment regimens for skin, nasal, and airway/lung injuries. Because there is already a substantial amount of data on the toxicity and pharmacology of AEOL 10150, this drug could be developed relatively quickly into a new sulfur mustard countermeasure. The NIH radiation and nuclear countermeasures program is also working extensively with this compound, including conducting studies in non-human primates.

BACKGROUND

The World Trade Center and anthrax attacks of 2001 exposed the vulnerability of the U.S. civilian population to terrorist groups armed with unconventional weapons. Chemicals are attractive terrorist weapons in that they are relatively easy to obtain and have the potential to cause mass casualties. Terrorists could also sabotage manufacturing plants, storage sites, or transport vehicles to release any number of toxic industrial chemicals (e.g., cyanide). According to a 2003 report published by the General Accounting Office (GAO), the Environmental Protection Agency (EPA) has identified 123 chemical plants in the U.S. where a terrorist attack or accident could potentially expose more than 1 million people to a cloud of toxic gas.

Rationale

The U.S. military has developed some countermeasures (combats chemical attacks) to protect military personnel from a chemical attack, but many of these are ill-suited for chemical terrorism scenarios. Protective clothing, gas masks, and prophylactic (disease preventing) drugs used by the military can be effective with advanced preparation, but a terrorist chemical attack against civilians is likely to come without warning. In order to respond to a chemical terrorist attack, medical personnel will require rapid and effective diagnostic technologies, as well as safe and effective post-exposure treatments appropriate for a diverse population. Currently, diagnosis is limited to observation of clinical signs and symptoms, which can be similar for chemicals that require very different treatment regimens. Available treatments for chemicals that affect cellular

respiration (e.g., cyanide) or the nervous system (e.g., nerve agents) have dangerous side effects and a short therapeutic window. Post-exposure treatments for chemicals that affect the respiratory system, skin, and eyes are largely limited to supportive therapy and alleviation of symptoms.

At the request of the U. S. Department of Health and Human Services (HHS), in 2007, the NIH developed the "NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats" for the development of improved medical countermeasures that could be used in the case of chemical terrorist attack or accident,. The plan focuses on therapeutics and diagnostics for chemicals that affect the nervous system; respiratory tract; skin, eyes, and mucous membranes; and cellular respiration.

TARGET CONTEXT AND CONDITIONS

The NIH established the Countermeasures Against Chemical Threats (CounterACT) Research Network in 2006 to develop new and improved diagnostic technologies and therapies for conditions caused by chemicals that could be used in a terrorist attack or released by accident. The Network includes research projects, research centers, small business grants, and contracts. All of the research activities are milestone-driven, and progress is reviewed annually.

The CounterACT Network has launched several diagnostic development projects. Research teams are designing portable devices that can be used in an emergency setting to detect chemically induced seizures that may be masked by paralysis. Others are developing "biosensors" that can rapidly detect signs of chemical exposure in blood or saliva samples. Each CounterACT diagnostic development project includes milestones for prototype development and clinical validation.

The majority of CounterACT research is directed toward therapy development. Researchers are dissecting and manipulating the biological pathways affected by various chemicals to identify promising therapeutic targets. Several potential targets have been identified and are undergoing further characterization. These include at least two classes of receptor molecules associated with chemically induced seizures, a signaling molecule involved in inflammation, and a family of sensory proteins that appear to activate nerve endings in response to chlorine and other toxic industrial compounds.

CounterACT researchers are also conducting preclinical safety and efficacy studies on promising new lead therapeutic compounds. These include a new treatment for cyanide exposure, a compound to prevent chemically-induced neurodegeneration, a treatment for chemically induced skin injuries, and a protein-based "bioscavenger" that captures and deactivates nerve agent molecules.

One especially promising chemical countermeasure is being tested in clinical trials under the CounterACT program. Department of Defense (DoD) researchers discovered that midazolam, a Food and Drug Administration (FDA)-approved intravenous sedative and anesthetic, stops seizures in animals exposed to nerve agent. The CounterACT program includes a clinical trial to test intramuscular midazolam as an emergency treatment in patients with a prolonged type of seizure called status epilepticus. This trial will determine whether intramuscular injection of midazolam works as well as giving another medication (lorazapam) intravenously. If a shot in the muscle works as well or better, it may be an easier method for stopping prolonged seizures in emergency settings. Clinical efficacy data from this trial will support a NIH/DoD joint effort to obtain FDA approval for use of midazolam against nerve agent-induced seizures. The NIH is also collaborating with the DoD to complete the animal studies necessary for FDA approval of midazolam as a nerve agent treatment.

Long Term Objective: (SRO-2.8) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.8 By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials. (Outcome)	*2011*	Complete preclinical testing of an appropriate delivery protocol and an immune-suppression regimen for a gene therapy approach in MD patients. *(Baseline):* Systemic delivery of therapeutic genes currently can only be achieved in mouse models.	N/A
	2010	Assess the activity of two promising small molecule drugs in cell and animal models *(Baseline):* 27 drug scaffolds identified in a screen	N/A
	2009	Test a new strategy for systemic delivery of a therapeutic gene in a large animal model *(Baseline):* (FY07) Systemic delivery of therapeutic genes currently can only be achieved in mouse models	Single injections of an AAV vector in dogs demonstrated effective systemic delivery to the skeletal muscles throughout the body. (Target Met)
	2008	Test a new strategy to improve the efficacy of an oligonucleotide-based therapy in animal or cell models *(Baseline):* (FY07) Oligonucleotides show promise in enabling cells to repair or bypass MD-causing mutations	Three oligonucleotide strategies were found to restore gene expression in cell or animal models of MD (Target Met)

Data Source and Validation
Duan, R21- AR57209: Exploring systemic AAV gene delivery in the dystrophic dog. Yue, Y, Ghosh, A, et a., A single intravenous injection of adeno-associated Virus Serotype-9 leads to whole body skeletal muscle transduction in dogs. Mol Ther. 2008 Dec; 16(12):1944-1952. http://www.ncbi.nlm nih.gov/pubmed/18827804?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel. Duan, R01-AR49419: Dual AAV vectors for Duchenne muscular dystrophy therapy. Progress Report (for period 06/15/2008 - 05/31/2009) available from the NINDS Office of Science Policy and Planning. Stedman, R01-NS 042874: Systemic molecular therapy for muscular dystrophy. 2009 Type-2 Application. Mendell U54- NS055958: Diverse strategies to correct the dystrophin gene using vascular delivery. Progress Report (for period 09/10/2008 – 08/31/2009) available from the NINDS Office of Science Policy and Planning.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH-funded researchers demonstrated whole-body systemic delivery of a reporter gene using an AAV vector in dogs. The research showed that single intravenous injections of the vector led to robust transduction of skeletal muscles throughout the body. Gene delivery was only successful in young pups and did not require immune suppression or additional pharmacological intervention. However, cardiac and smooth muscle was not efficiently transduced. The results suggest that gene therapy might be more feasible in infants that have yet to develop a robust immune system and which do not yet exhibit the symptoms of DMD. The researchers have also developed gene vectors with small regions of the dystrophin gene and tested them for delivery and functional improvement in a mouse model of muscular dystrophy. Following systemic delivery of these vectors, improved muscle function, including improvement in certain cardiac measures in these mice was demonstrated. Successfully engineered canine versions of the microgene will be tested in a DMD dog model via local and systemic delivery.

Researchers have also tested a technique known as "afferent transvenular retrograde extravasation" (ATVRX) for gene delivery in dogs. This technique involves the use of a high pressure injection of saline in conjunction with typical gene-delivery techniques to improve gene uptake by skeletal muscles. The force from the high pressure injection seems to push the vectors from the blood vessels into the muscles, increasing the efficiency of the therapy. The technique was found to be effective for transduction of the majority of skeletal muscles in healthy dogs in their first year of life and is now being tested in dog models of DMD.

Another group of NIH-funded researchers also demonstrated effective transduction of hindlimb muscles in non-human primates (rhesus macaques) with an AAV vector containing a reporter gene delivered via vascular injection. The researchers also completed production of an AAV vector containing a micro-dystrophin gene and carried out preliminary studies demonstrating the efficient transduction of hindlimb muscles with the dystrophin-containing vector via targeted vascular delivery in the non-human primates.

Advances or Other Highlights

A public-private partnership funded by NIH, Parent Project Muscular Dystrophy, and PTC Therapeutics is underway to chemically optimize small molecules that alter the levels of four proteins (utrophin, myostatin, IGF-1a, and α7 integrin) that have been shown to affect the muscular dystrophy disease process. Based on initial studies, the researchers have chosen to move forward with the utrophin and myostatin scaffolds and have identified promising compounds that increase the levels of these proteins in the muscles of the mdx mouse model. Further testing of these compounds is underway.

BACKGROUND

The muscular dystrophies are a group of diseases that cause weakness and progressive degeneration of skeletal muscles. There are many different forms of muscular dystrophy, which differ in their mode of inheritance, age of onset, severity, and pattern of muscles affected. Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy, which is caused by mutations in the dystrophin gene, resulting in an absence or deficiency of this protein. DMD usually becomes clinically evident when a child begins walking, and patients die in their late teens or early 20s. Becker muscular dystrophy is also caused by mutations in the dystrophin gene, but results in production of a truncated form of the protein and a less severe course of disease progression. An animal model, the mdx mouse, is extensively used to study these disorders, and large animal models (e.g., dog) also exist. The most common adult form of muscular dystrophy is myotonic dystrophy. It is marked by myotonia (an inability to relax muscles following contraction) as well as muscle wasting and weakness. Myotonic dystrophy type 1 and type 2 are caused by nucleotide repeat expansions (repeated sequences of DNA components) in different genes. Recent studies have uncovered important underlying genetic and molecular mechanisms and developed animal models appropriate for testing new therapeutics. Other forms of muscular dystrophy include facioscapulohumeral muscular dystrophy (FSHD), the limb-girdle

muscular dystrophies (LGMDs), and the congenital muscular dystrophies. There are varying levels of knowledge about the mechanisms underlying these different forms; this allows disease mechanism-targeted therapeutic development to proceed for some types of muscular dystrophy while further basic studies are required before targeted therapies can be developed for other types.

Prevalence/Incidence

Research data compiled in 2006 from the CDC National Center on Birth Defects and Development Disabilities shows that Duchenne and Becker muscular dystrophies together affect 1 in 3,500 to 5,000 male births. Between 400 and 600 boys in the United States are born with these conditions each year. Females are typically carriers of the genetic mutations and are rarely affected by these forms of muscular dystrophy. Myotonic dystrophy affects about 1 in 8,000 people worldwide. Type 1 is the most common form of the condition, accounting for about 98 percent of all cases. The remaining 2 percent of cases are myotonic dystrophy, type 2. NIH data compiled in 2009 indicates the prevalence of the two types of myotonic dystrophy varies among different ethnic populations. For other forms of muscular dystrophy, it is difficult to estimate incidence, due to variability among different forms of the disease and/or lack of precise diagnostic methods.

Rationale

There is currently no treatment that can stop or reverse the progression of any form of muscular dystrophy. However, advances in the understanding of disease mechanisms (particularly for DMD), diagnostics, and research technologies make this an opportune time to emphasize therapeutic development. In addition, the MD-CARE Act (signed into law in 2001), which promotes coordination of federal research on muscular dystrophy, required the Muscular Dystrophy Coordinating Committee (which includes NIH and other federal agencies) to develop a plan for conducting and supporting research and education on muscular dystrophy. The resulting Action Plan for the Muscular Dystrophies identified a series of promising therapy development goals. A recent workshop convened by NIH reviewed the status of therapy development for the muscular dystrophies and also concluded that a number of therapeutic strategies are showing promise and have a strong likelihood of leading to clinical trials in the next few years.

TARGET CONTEXT AND CONDITIONS

Based on a better understanding of the disease mechanisms at play in the muscular dystrophies, there are now multiple potential pathways to therapeutic development, including: drug-based therapies to maintain muscle mass; strategies to enhance the normal regenerative process of muscle; cell-based muscle therapeutic strategies; strategies for gene replacement; and genetic modification therapies to bypass inherited mutations.

Many NIH activities have enhanced research utilizing a number of these approaches. NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, which have been designed to accelerate the translation of fundamental scientific advances to the clinic through close interaction between basic researchers and clinicians. Translational research projects at the Wellstone Centers are focused on optimizing gene therapy and stem-cell-based therapeutic approaches as well as identifying therapeutic strategies to enhance muscle regeneration. NIH has also funded research through the program announcement, "Muscular Dystrophy: Pathogenesis and Therapies," and broader solicitations for preclinical therapy development projects for neurological conditions. The NIH specialized program announcement, "Translational Research in Muscular Dystrophy," released in late 2005, has already resulted in a dramatic increase in the number of applications received and funded by NIH for development of novel therapies for muscular dystrophy. Successful applications have focused on both DMD and myotonic dystrophy, and use a range of strategies. While NIH is rigorously pursuing all pathways to therapeutic development, a few approaches are showing significant promise.

Genetic modification strategies using synthetic oligonucleotides (short sequences of DNA or RNA) to either bypass or correct the genetic mutations responsible for muscular dystrophy are showing promise in animal models. This strategy is particularly relevant to DMD, where mutations in the dystrophin gene prevent the dystrophin protein from being produced. NIH currently funds studies employing synthetic oligonucleotides to

correct the mutations in the dystrophin gene or to alter the translation of the mutated dystrophin gene into protein such that the mutations are bypassed ("read-through") resulting in the restored production of dystrophin protein. Although clinical trials using synthetic oligonucleotides have been initiated in Europe, these are early-stage, single muscle tests, and the development of a therapeutically significant treatment requires more research on oligonucleotide chemistry and systemic delivery.

Gene replacement therapy (replacing the defective gene or increasing the expression of functionally equivalent genes) is also showing promise in the mdx mouse and other animal models. However, one of the major hurdles of this approach is determining ways to deliver the gene systemically, allowing delivery of the gene to all muscles of the body. Research currently funded by NIH is developing ways to address this problem. One project is utilizing pharmacological agents to permeabilize the blood vessel walls to allow for better access of the vector (delivery vehicle) to muscle and testing this approach in a canine model of DMD. Another NIH-funded investigator is pursuing the use of stem cell technologies for DMD gene therapy by developing vectors that can be used to integrate the corrected genes into muscle stem cells, which can then be transplanted into diseased animals. Plus, investigators who recently received an NIH grant are working to develop the optimal vector for vascular delivery of genes. The optimal vector would be one that does not elicit a strong immune response and would enable the human body to accept the therapy.

Small molecule drugs represent another promising therapeutic approach. NIH recently funded a large-scale project to develop new small molecule drugs for the treatment of DMD and potentially other forms of muscular dystrophy as well. The project will pursue a number of strategies for therapy development, including stimulating muscle growth by modulating growth factor pathways, and upregulating proteins that may structurally and functionally substitute for dystrophin or contribute to the dystrophin protein complex in normal muscle cells. The researchers have completed a high-throughput screening process on each of these strategies in order to identify small molecules that are candidate therapies. The project will focus on improving the properties of these small molecules as drug candidates and carry out research that will help support further clinical studies using these compounds. An exciting aspect of this project is the collaboration between patient voluntary organization as well as a biopharmaceutical company to support this project, thereby creating a public-private partnership to leverage funding for this project.

Long Term Objective: (SRO-2.9) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.9 By 2015, advance understanding of social determinants of health and health disparities using multilevel, transdisciplinary team science approaches by developing intervention models of how various factors affect individual health outcomes and their distribution in populations. (Outcome)	*2011*	Develop new comprehensive training strategies and programs for junior scientists that emphasize collaborative transdisciplinary team science approaches for addressing health disparities. *(Baseline):* Based on results of FY 2010 activities.	N/A
	2010	Fund up to ten new Centers for Population Health and Health Disparities, with each center including teams of scientists from the following disciplines: basic, clinical, and social sciences. *(Baseline):* Currently funding five total centers that address health disparities through interdisciplinary research.	N/A

BACKGROUND

Health inequities remain a significant public health problem, marked by disparities in health promotion (such as better neighborhoods, housing, insurance) and in access to care (including, screening, incidence, treatment, and prognosis of many common diseases). These are avoidable inequalities in health which arise largely from inequalities in social and economic conditions and their effects on people's lives that determine their risk of illness. The most striking disparities in health outcomes include: shorter life expectancy, higher rates of cardiovascular disease, cancer, infant mortality, birth defects, asthma, diabetes, stroke, sexually transmitted diseases, and mental illness.

Traditionally, research in understanding and eliminating health disparities has been carried out on a single level and factor, with limited success. It is likely that a multitude of factors, such as those related to biology, behavior, social circumstances, and access to care, influence health outcomes and thus have a role in affecting individual and population health. Therfore, interventions that are comprehensive need to be developed and implemented to prevent people from becoming ill or treat illness when it occurs. In order to reduce and eliminate inequities in health outcomes, a transdisciplinary approach that includes the biological, genetic, social, behavioral, and environmental sciences is needed to account for these many complex, interrelated factors that affect the development and progression of disease. The adoption of this transdisciplinary approach is necessary to develop comprehensive interventions to reduce and eliminate health disparities.

Prevalence/Incidence

Health disparities represent a significant public health problem in the United States. Disparities exist across groups defined by race, ethnicity, gender, age, socioeconomic status, and geography. For example, the life expectancy gap between urban black males and Asian females was 20.7 years in 2001. In 2006, published research data on investigating mortality disparities across races and counties in the US show the gap between highest and lowest life-expectancy counties in the United States was more than 35 years. Minority and underserved groups suffer disproportionately from cancer, in both incidence and mortality. For example, African American men have the highest rates of prostate, lung, colon/rectum, and oropharyngeal cancers as

reported in statistical data from 1975-2004 from the Surveillance Epidemiology and End Results (SEER) review at the NIH. The National Center for Health Statistics reported that for 1976-80 through 2005-2006 the prevalence of being overweight is greater among black and Mexican-American females than among white females. In 2004, a Centers for Disease Control and Prevention (CDC) report on the prevalence of cigarette use among racial/ethnic populations in the US indicated that smoking is also more prevalent among black males than among their white counterparts. In 2004, age-adjusted death rates for coronary heart disease in the US was higher for blacks than for whites, and overall, was considerably higher for males than for females as detailed in an NIH 2007 report on morbidity and mortality of cardiovascular, lung and blood diseases. Frequently, the disparity in mortality is greater than that in incidence, suggesting that factors related to biology, behavior, social circumstances, access to care, and other prevention and post-diagnostic factors influence clinical outcomes.

Disease Burden

Cancer is the second leading cause of death in the United States and the economic cost of cancer in 2005 has been estimated at over $200 billion. Although significant progress has been made toward reducing the burden of cancer in America, one of every four deaths is due to cancer. It is estimated that in 2008 there will be about 1,437,180 new diagnoses of invasive cancer and 565,650 Americans will die of cancer.

Scientific research on the future of cancer incidence in the US from April 2009 estimates that between 2010 and 2030, the total projected cancer incidence will increase approximately 45%. A 99% increase is anticipated for minorities, compared with a 31% increase for whites. Rates of cancer in blacks, American Indian-Alaska Native, multi-racial, Asian-Pacific Islanders, and Hispanics are expected to increase by 64 percent, 76 percent, 101 percent, 132 percent and 142 percent, respectively.

Trends observed in cancer incidence are similar to those seen with other diseases. A recent study estimated that by 2035, the prevalence of coronary heart disease will increase by a range of 5 to 16%, with more than 100,000 cases attributable to increased prevalence of obesity. In 2003, research on 30-year projections for deaths from ischemic stroke in the US indicated that for stroke, the total predicted number of deaths is projected to increase by 98% from 139,000 in 2002 to 275,000 in 2032, whereas the total US population is projected to increase by only 27% in the same period. The largest percentage increases in stroke deaths are predicted to occur in blacks (134%) and nonwhite, nonblack races (221%).

Rationale

While advances have been made in human biology that may lead to new preventive, diagnostic, or therapeutic approaches to disease, the impact of these discoveries may be limited without an effective long-term strategy for linking knowledge of disease biology with knowledge of factors that affect prevention, diagnosis, and treatment of disease at the population level. This can be achieved by a transdisciplinary approach that integrates research in biological, behavioral, and social sciences to create a more comprehensive understanding of disease pathways from a molecular to a societal level. This approach is critical for addressing health disparities, as it facilitates the investigation of the interrelationships and interactions within and between the various biological and sociological factors that account for differences in disease incidence, morbidity, and mortality. Increased knowledge on the social, behavioral, and biological factors that influence health disparities and the nature of their interactions will be disseminated through various channels to a wide audience, including members of vulnerable populations, community-based organizations and agencies, and scientific investigators. Knowledge advances could be used by stakeholders to inform public health policy, advocacy, and further research on health disparities.

This transdisciplinary, integrated approach to research is best supported through research centers, in order to integrate teams of scientists with the diverse disciplinary expertise needed to collaboratively advance research on the social determinants of health and health disparities.

TARGET CONTEXT AND CONDITIONS

In order to address the wide variety of factors that play a role in health inequalities, the NIH Centers for Population Health and Health Disparities (CPHHD) program focuses on bringing together transdisciplinary teams to address health disparities using multilevel and multi-factorial approaches and by combining approaches from a variety of disciplines, such as physical, biological, and social sciences. The variety of expertise among teams of scientists at CPHHD program centers facilitates an enhanced understanding of the interrelated factors that influence disease initiation and progression, such as the interaction among social, behavioral, environmental, biological, genetic, public health, and economic factors.

The centers funded under the original RFA increased understanding of the persistence of health disparities, and began to identify approaches to address these inequities. The centers also began to identify challenges and successes in developing transdisciplinary teams and comprehensive intervention models for addressing health disparities. The lessons learned through the original centers inform the targets that will demonstrate progress in using multilevel, transdisciplinary team science and comprehensive intervention models to advance understanding of social determinants of health and health disparities.

The NIH plans to establish up to 10 new Centers at which transdisciplinary teams of scientists from basic, clinical, and the social sciences will collaborate to advance understanding of health disparities. Bringing together scientists across multiple disciplines utilizes the best expertise, tools, and theoretical models from a variety of research traditions and will facilitate the development of comprehensive models of how various social, economic, cultural, environmental, biological, behavioral, physiological, and genetic factors affect health outcomes and their distribution in populations.

Following the creation of Center-based, transdisciplinary teams, a series of programs will be developed to train junior scientists in collaborative, team science approaches to addressing health disparities. Development of a work force skilled in transdisciplinary science is critical to advancing research in health disparities and to bringing new expertise into the field.

Transdisciplinary team science is not only essential within a center, but between the centers as well. After transdisciplinary teams of scientists have been assembled, common metrics and processes for sharing measures, and for combining, and reporting data will be developed. Common metrics will benefit collaborative efforts in the evaluation of the research and intervention models that address health disparities at both the individual and community levels.

The transdisciplinary interactions and collaborations form the basis of a truly multilevel and multi-factorial approach to understanding and resolving health disparities. Therefore, it is important to assess whether the scientists involved in the centers are working in a transdisciplinary manner. Social network analysis and other methods will be used to determine the number of new disciplines that have been added to the research portfolios of principal investigators, as measured through new publications, participation at professional conferences, and/or involvement with new transdisciplinary projects.

The strategies that have been successfully used by these transdisciplinary teams of scientists will be identified and adapted into intervention models that can be implemented by institutions that are interested in using a broad array of scientists to understand how various social, economic, cultural, environmental, biological, behavioral, physiological, and genetic factors affect health outcomes.

Long Term Objective: (SRO-2.10) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.10 By 2014, identify three clinical candidate compounds for rare or neglected diseases. (Outcome)	*2011*	Select rare disease lead compounds that will be further studied to assess for potential therapeutics. *(Baseline):* Project selection criteria are needed to establish research priorities	N/A

BACKGROUND

NIH conducts research on rare and neglected diseases as part of its mission. A rare disease affects fewer than 200,000 Americans. NIH estimates that more than 6,000 rare diseases afflict more than 25 million Americans. Treatments exist for only about 200 of these illnesses. A neglected disease is one that is often overlooked by drug developers or by others instrumental in drug access. Many neglected diseases also lack treatments or have a therapy under development. Unlike rare diseases, neglected diseases may be quite common in some parts of the world, especially developing countries where sufferers cannot afford existing treatments.

Numerous obstacles impede the development of new drugs for rare and neglected diseases. In addition to the reluctance of private companies to risk their capital on a potentially low return, relatively few basic researchers study rare diseases, so the underlying cause of the illness frequently remains unknown. Research is also complicated by difficulties in recruiting sufficient patients with these types of disorders to participate in clinical trials, and by a lack of relevant clinical measures that can demonstrate whether a treatment is effective.

The drug development process is complicated and expensive. Typically, drug development begins when academic researchers studying the underlying cause of a disease discover a new molecular target or a chemical that may have a therapeutic effect. Too often, the process gets stuck at the point of discovery because few academic researchers can conduct all the types of studies needed to develop a new drug. If a pharmaceutical company with the resources to further the research does get involved, substantial preclinical work begins with efforts to optimize the chemistry of the potential drug. This involves an iterative series of chemical modifications and tests in progressively more complex systems — from cell cultures to animal tests — to refine the potential medicine for use in people. Only if these stages are successful can a potential treatment move to clinical trials in patients.

Rationale

Unfortunately, the success rate in this preclinical process is low, with 80 to 90 percent of projects failing in the preclinical phase and never making it to clinical trials. Non-government entities seldom pursue new therapies for rare or neglected diseases because of high costs and failure rates and the low likelihood of recovering investments or making a profit.

NIH will support research efforts that focus on the development of promising treatments for rare and neglected diseases. These activities are part of an overall process to sufficiently "de-risk" drug development for rare and neglected diseases so that pharmaceutical companies, disease-oriented foundations, or others, can undertake the necessary clinical trials.

TARGET CONTEXT AND CONDITIONS

NIH already has components of the drug development process within its research programs. One of these components is a robotic, high-throughput screening system and a library of more than 350,000 compounds that can be used to make basic discoveries and probe cellular pathways. Researchers will develop assays

representing disease processes that can be tested in its screening system to support the identification of candidate clinical compounds. Molecules with potential therapeutic properties that emerge from this screening process could be fed into the drug development pipeline.

NIH also will seek a wide range of collaborations with academic researchers, as well as partnerships with patient advocacy organizations, disease-oriented foundations and others interested in treatments for particular illnesses. NIH will support teams of investigators to facilitate progress through the drug development process. These efforts may support long term research activities and potential clinical trials.

Long Term Objective: (SRO-2.11) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-2.11 By 2014, conduct studies of young children to determine whether the plant estrogens in soy formula produce hormone-like effects. (Outcome)	*2011*	Enroll 224 mothers and complete 199 birth and 2 week examinations and specimen collections from the children. Enroll 480 toddlers and do 1 year evaluations *(Baseline):* Detection of hormonal influences on infants possible	N/A

BACKGROUND

Soy fed infants have much higher exposure to hormone-like compounds in their diets than do cow milk or breast milk fed infants. It is not known, though, whether these exposures are high enough to act as hormones in children. Pilot studies have been conducted to develop physical examination, ultrasound, and laboratory measures that are designed to detect hormonal influences on infants, and this study will apply those methods. In addition, a series of workshops were held to identify the most promising methods to evaluate toddlers – 1 to 2 year old children – for the effects of early life exposure to hormones using various assessments, such as: language development, toy preference, and bone density. Results from the analysis of pilot studies are being published.

Rationale

The endocrine disrupter hypothesis states that hormone like chemicals in the environment are causing changes in hormone function in human beings. Although there is substantial laboratory evidence, there is very little direct support from studies in human beings and even less in infants and children, who may be the most susceptible. This study examines in detail the hypothesis that moderately high doses of plant estrogen produce hormone like effects in infants. Soy formula use is common and there is a public health concern about its effects on infants and young children. Soy fed infants may be the group with the highest exposure to any environmental estrogen, and thus the findings in them are relevant to the whole field.

TARGET CONTEXT AND CONDITIONS

Initially, the project must enroll participants (mothers and children) to establish the study cohort. There will be 2 components of the study. One component will be comprised of mothers and at least 90 infant girls who are their children. The other component will be composed of several hundred toddlers. In following years, the project's success is contingent upon further enrollment of children and follow-up exams.

The reason for two components is to more fully evaluate the effects of how environmental estrogens affect maternal- infant development as well as the development in early life stages, i.e., toddlers. Through the evaluation of these two groups it is likely that the affects of environmental estrogens on hormone function in infants and young children will be better understood.

The overarching aim of the study is to test through direct evidence whether or not hormone-like chemicals in the environment are causing changes in hormone function and whether or not children are most susceptible to these environmental estrogens. The outcome of this study will shed light on health effects of environmental estrogens at young ages and further clarify the levels of environmental estrogens that lead to any adverse human health effects.

Long Term Objective: (SRO-3.1) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.1 By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD). (Outcome)	*2011*	Start a phase III clinical trial based on existing Phase II clinical trials. *(Baseline):* Preclinical and clinical studies suggest a number of potentially effective interventions.	N/A
	2010	Identify at least one imaging or biological marker and/or clinical or neuropsychological evaluation method that will help researchers perform less expensive, shorter, and more efficient drug trials for AD. *(Baseline):* (FY08) No neuroimaging or other biological markers have yet been validated as measures of Alzheimer's disease progression.	N/A
	2009	Start at least one additional pilot clinical trial on promising interventions based on results of previous trials and new leads for drug discovery. *(Baseline):* (FY07) Studies are suggesting a number of interventions that may be appropriate for testing in clinical trials.	NIH initiated pilot clinical trials of simvastatin and prazosin to treat, forestall, or prevent cognitive decline and AD. (Target Met)
	2008	For at least one promising drug candidate for the treatment of AD, complete at least one of the four preclinical steps necessary for regulatory approval: chemical optimization; proof of efficacy in an animal model relevant to the disease; pharmacokinetic profiling; and/or early toxicology screening. *(Baseline):* (FY06) It is anticipated that 1-3 promising drug candidates will emerge from NIH's research programs by FY 2008; these have not completed the preclinical steps necessary for regulatory approval.	NIH-supported investigators identified the compound MW01-2-069A, which reduced brain inflammation and behavioral deficits in a mouse model of AD. (Target Met)

Measure	FY	Target	Result
	2007	Identify and characterize molecular events that may prove to be targets for treating or preventing Alzheimer's disease through initiatives and projects focused on mechanistic and basic studies. *(Baseline):* (FY05) New targets need to be identified and known ones characterized to develop therapeutic or preventative interventions.	NIH-supported research has helped to identify and characterize two particularly promising target molecules for AD treatment and development: beta-amyloid production and p38 alpha MAPK. (Target Met)
	2006	Identify around 1,000 new late onset AD families to allow geneticists to locate additional late onset risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials. *(Baseline):* (FY04) The genetics initiative has identified 259 families, too few for researchers to identify the remaining risk factor genes.	Nearly 1000 new late-onset AD families have been identified and recruited to the AD Genetics Initiative. (Target Met)

Data Source and Validation
Metformin in Amnestic Mild Cognitive Impairment: http://clinicaltrials.gov/ct2/show/NCT00620191?cond=mild+cognitive+impairment&intr=metformin&rank=1 Pioglitazone or Exercise to Treat Mild Cognitive Impairment: http://clinicaltrials.gov/ct2/show/NCT00736996?cond=mild+cognitive+impairment&intr=pioglitazone Because the simvastatin and prazosin trials are newly funded, information about them is not yet available in clinicaltrials.gov. For more information, contact Laurie M. Ryan, Ph.D., ryanl@mail nih.gov.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH initiated two new pilot clinical trials of interventions that may be effective in preventing, slowing the progression of, or treating Alzheimer's disease (AD):

- A clinical trial to determine the effects of the cholesterol-lowering drug simvastatin on AD biomarkers and cerebral blood flow in middle-aged adults at risk for AD. Previous observational studies have shown that use of statin drugs is associated with a reduced risk of AD. This new clinical trial is based on prior NIH-funded studies, including an earlier small pilot trial of simvastatin in asymptomatic middle-aged children of persons with AD. This new trial is of significantly longer duration (18 months vs. 9 months) and will evaluate additional biomarkers as well as neuroimaging results.
- A clinical trial of the drug prazosin to treat disruptive agitation, a common symptom of AD. Prazosin blocks the excessive brain adrenaline arousal that contributes to agitation in AD, and both therapeutic and tolerability results of a recent small prazosin feasibility trial were very promising.

Advances or Other Highlights

NIH maintains an active pilot trials program for Alzheimer's disease, and additional pilot trials are both ongoing and planned. Two additional pilot trials, started in FY 2008, began active recruitment during FY 2009:

- A clinical trial of the diabetes drug metformin to slow or halt cognitive decline in patients with amnestic mild cognitive impairment, a precursor condition to AD. Epidemiological, clinical, and laboratory studies have identified elevated insulin levels as a potential risk factor for AD. A previous clinical trial of diabetic patients who were treated with metformin showed improved cognition. Other ongoing clinical trials are also exploring the use of diabetes drugs to treat or forestall cognitive impairment and/or AD.
- A clinical trial to investigate whether two interventions (endurance exercise training or treatment with the drug pioglitazone) to treat metabolic syndrome in older adults with co-existing mild cognitive impairment can improve, stabilize or lessen the decline in cognitive function compared to a control group. Metabolic syndrome is a collection of inter-related metabolic abnormalities with the cardinal feature being insulin resistance. This study is based on promising results of previous NIH-supported small trials of both exercise and pioglitazone.

NIH has made additional advances that support the overall achievement of this measure. NIH investigators at the Alzheimer's Disease Neuroimaging Initiative have made a significant step forward in developing a test to help diagnose the early stages of AD sooner and more accurately by measuring two biomarkers—tau and beta-amyloid proteins—in cerebrospinal fluid. The investigators confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's. The investigators also established a method and standard of testing for these biomarkers. This effort may support the discovery of an entire panel of cerebrospinal fluid biomarkers that could predict those at risk of developing Alzheimer's disease, and reveal how the disease is responding to therapies. These advances could have the potential to improve the efficiency of clinical trials.

NIH investigators have also used positron emission tomography (PET) in conjunction with a new tracer compound, Pittsburgh Compound B (PiB), to identify AD-like pathology in the brains of living, cognitively normal individuals. These findings suggest two scenarios that may speed our progress in understanding brain aging and AD. First, if beta-amyloid deposition occurs before signs of cognitive impairment surface, PiB imaging earlier in life could help identify those at risk for AD. Such an early determination of AD risk may also prove important in the development of new prevention strategies and therapeutic approaches. On the other hand, if beta-amyloid deposition alone proves to be insufficient to disrupt cognitive function, this finding presents researchers with additional insights about the mechanisms of brain aging and AD and will help focus therapeutic targets in different directions.

In addition, NIH has established a new study, the Dominantly Inherited Alzheimer's Disease Network (DIAN), to study adult children of biological parents with a known genetic mutation causing rare and typically early-onset forms of the disorder. Network scientists hope to identify the sequence of brain changes in early-onset Alzheimer's, even before symptoms appear, and by understanding this process, to also gain insight into the more common late-onset form of the disease.

BACKGROUND

Prevalence/Incidence

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

- Prevalence estimates based on the 2000 Census suggest that as many as 5.1 million Americans may have Alzheimer's disease.
- Prevalence of the disease doubles with each 5-year increment in age in persons older than 65.
- Studies suggest that if current trends hold, the annual number of incident cases of AD will begin to sharply increase around the year 2030, when all the baby boomers (born between 1946 and 1964) will

be over age 65.

Disease Burden
The cost of AD care varies by stage of the disease. The national direct and indirect costs of caring for people with AD are estimated to be more than $100 billion a year. A 2004 study by the Alzheimer's Association estimated that if current AD trends continue, total Federal Medicare spending to treat beneficiaries with the disease will increase from $62 billion in 2000 to $189 billion in 2015.

Also significant is the physical and emotional toll AD exacts on family, caregivers, and friends including:

- the changes in a loved one's personality and mental abilities
- the need to provide constant attention for years on end
- the demands of bathing, dressing, and other caregiving duties can cause tremendous stress to the caregiver, often impacting his or her health and well-being.

Not surprisingly, caregivers of people with dementia spend significantly more time on caregiving tasks than do caregivers of people with other types of illnesses.

Rationale
The few agents that are currently approved by the Food and Drug Administration for treatment of Alzheimer's disease have demonstrated only modest effects in modifying the clinical symptoms for relatively short periods. Likewise, the first, and to date the only, agent shown to delay clinical diagnosis of AD in people with mild cognitive impairment (donepezil [Aricept®]) appears to forestall the transition from MCI to full-blown AD for only a brief period of time. However, a number of promising findings are now emerging to provide directions for potential interventions.

TARGET CONTEXT AND CONDITIONS

The NIH has a comprehensive plan to discover and validate an intervention that delays or prevent the onset of Alzheimer's disease. Researchers have made important progress toward this goal, and are continuing to build on previous research accomplishments to refine our understanding of AD's underlying pathology, identify risk factors for the disease, and develop and refine interventions that may prove effective. However, full achievement of this measure will require continued progress on a number of fronts. NIH is working to facilitate discovery in each of the following areas:

Neuroimaging and other Biological Markers
Neuroimaging research has suggested that positron emission tomography (PET) or magnetic resonance imaging (MRI) may serve as a more sensitive and consistent measure of Alzheimer's disease progression than the neuropsychological and cognitive assessments now typically used in research. Furthermore, identification of valid biomarkers – biochemical indicators that can be used to measure progress of a disease or physical response to treatment -- could help scientists accurately monitor disease progression and detect the effects of treatments intended to slow that progression. In late 2004, the NIH, in conjunction with several other Federal agencies, private companies, and organizations, launched the Alzheimer's Disease Neuroimaging Initiative (ADNI). This initiative is testing whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease. The project is the most comprehensive effort to date to find neuroimaging and other biomarkers for the progressive changes associated with MCI and AD.

Having reached its target enrollment of 800 participants, the study has supported development of a number of tools and methods now in use in the United States and worldwide. The development of these tools and methods has laid the groundwork for the identification of imaging and/or fluid biomarkers with the potential to enable earlier detection and less expensive, shorter, and more efficient drug trials for AD. For example, a recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild

Alzheimer's. The study also established a method and standard of testing for these biomarkers. Although more research is needed to validate these findings, these results represent an important step forward in efforts to detect and understand the very earliest stages of the disease. This will be particularly important as researchers continue working to develop new interventions aimed at forestalling the disease before clinical symptoms appear or become disabling. [FY 05 and FY 10 performance targets]

Genetics
To date, only one risk factor gene for late-onset AD has been validated, although several other candidate genes have been identified. The AD Genetics Initiative was started to develop much-needed resources for geneticists to find the additional key late onset genes; NIH-supported investigators have recruited approximately 1000 families as part of this effort, which included the establishment of a data base for studies of familial inheritance of AD. [FY06 performance target]

Basic Research
NIH is working to identify promising targets for treating and preventing disease through basic research. This includes conducting research to accelerate the discovery of new AD risk and protective factors and to identify how these factors interact with different genetic factors such as apolipoprotein E-4. Basic research studies have identified new pathways involved in the brain mechanisms that lead to AD. The identification of these pathways, in turn, indicates new targets for the development of therapeutic agents for AD, MCI, and age-related cognitive decline. [FY07 performance target]

Pre-Clinical and Translational Research
Through years of research, much of it supported by NIH, scientists have gained tremendous insight into AD's underlying pathology, and are using this information to inform development of drugs that may prevent or modify the course of the disease. For example, studies of AD's characteristic amyloid plaques in the brain have moved forward to the point that scientists are now carrying out preliminary tests in humans of potential therapies aimed at removing beta-amyloid, halting its formation, or breaking down early forms before they can become harmful. The development, within the past decade, of reliable transgenic animal models that closely replicate AD's pathology, symptoms, and disease course has also accelerated the pace of progress in this area.

NIH is supporting research to speed drug discovery and the movement of promising new treatments and prevention strategies into clinical trials. This includes launching a major new translational research effort to expand the range of novel compounds to be tested for cognitive decline, mild cognitive impairment, and AD, and to more quickly move research from the laboratory to clinical trials in humans. Four key steps are needed in the preclinical development of new agents prior to clinical testing: Chemical optimization; proof of efficacy in an animal model relevant to the disease; pharmacokinetic profiling; and/or early toxicology screening. Promising new agents will enter preclinical development. [FY08 performance target]

Clinical Trials
As new agents are developed that are aimed at treatment targets identified through basic research, NIH initiates pilot clinical trials to establish safety, efficacy, and optimal dosage. These are followed by full-scale clinical trials, as appropriate. Potential interventions may also be identified through studies that point to a link between a particular disease or condition and AD. For example, type 2 diabetes appears to be associated with cognitive decline, including AD, suggesting that effective diabetes treatments may also be effective against cognitive decline and AD. NIH is currently supporting AD treatment studies of diabetes drugs such as metformin and insulin. Finally, investigators on epidemiological and longitudinal studies sometimes observe that interventions for other conditions appear to be associated with a reduction of risk of AD. For example, some studies have shown that people who use statin drugs to lower their cholesterol appear to be less likely to develop AD. The NIH-supported CLASP trial of the drug simvastatin was initiated in response to these studies.

NIH currently supports over 30 clinical trials of a wide range of interventions to prevent, slow, or treat AD. Interventions under study include:

- treatments to stimulate the immune system to fight AD
- hormonal treatments, including testosterone and raloxifene
- antioxidants; physical and mental exercise
- commonly used psychiatric drugs and many others

NIH also plans to use the knowledge gained through the basic and mechanistic studies described above to select the most promising imaging and biological markers, as well as improved clinical and neuropsychological evaluation methods, to perform less expensive, shorter, and more efficient drug trials. [FY03, FY09, and FY11 performance targets]

Long Term Objective: (SRO-3.2) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.2 By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. (Outcome)	*2010*	Clinically evaluate a compound with demonstrated broad spectrum activity in a Phase I (safety) trial. *(Baseline):* (FY08) NIH has a small number of candidate broad spectrum products that are approaching readiness for clinical testing.	N/A
	2009	Conduct IND enabling toxicology and preclinical animal studies on at least 1 candidate compound that has shown broad spectrum activity in vitro. *(Baseline):* (FY07) NIH has not yet begun toxicology and preclinical studies for candidate compounds that have demonstrated broad spectrum activity in vitro.	Developed safety and pharmacology profiles of one candidate compound, K777 that has potential broad spectrum indications. (Target Met)
	2008	Begin determining safety and pharmacology profiles (e.g. bioavailability) of at least 1 candidate compound that has shown broad spectrum activity in vitro. *(Baseline):* (FY07) NIH has not yet begun safety and pharmacology profile determinations for candidate compounds that have demonstrated broad spectrum activity in vitro.	NIH began determining safety and pharmacology profiles (e.g. bioavailability) of two candidate compounds. (Target Exceeded)
	2007	Through medicinal and/or combinatorial chemistry, optimize several compounds for antimicrobial activity. *(Baseline):* (FY05) Resources provided to the scientific community for development of medicinal and combinatorial chemistry capacity and assay optimization.	NIH optimized several compounds for antimicrobial activity through medicinal and combinatorial chemistry approaches. (Target Met)

Measure	FY	Target	Result
	2006	Use screening tools to evaluate potential compounds or classes of compounds for activity against multiple classes of infectious diseases. *(Baseline):* (FY04) Screening tools for evaluation of potential compounds/classes of compounds for activity against multiple bacterial and viral infections developed.	Screening tools were used to evaluate compounds for potential activity against multiple classes of organisms of infectious disease. (Target Met)

Data Source and Validation
Submitted Meeting Abstract: Simmons, G. et al. High Throughput Screening of Protease Inhibitor Libraries Using a Novel Dual Pseudotype-Based Assay for SARS Co-V Entry. 22nd International Conference on Antiviral Research, Miami, FL, May 2009.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The 2009 target was Met. NIH supported research developed safety and pharmacology profiles (e.g. bioavailability) of one candidate compound that has shown broad spectrum activity in vitro.

In 2009, researchers performed bioavailability and pharmacokinetic studies on K777 (N-methyl-piperazine-Phe-homoPhe-vinylsulfone-phenyl) analogs that are active against multiple viruses: SARS Co-V, Ebola, Marburg, Nipah, Hendra, and coronavirus.

K777 is a novel cysteine protease inhibitor under investigation as a therapeutic candidate for several parasitic diseases. Cysteine proteases play a number of essential roles in the biology of parasitic organisms, including general catabolic functions and protein processing, as well as more recently characterized roles in immunoevasion, excystment/encystment, exsheathing and cell and tissue invasion. The presence of cysteine proteases in many parasitic organisms makes these proteases an ideal target for anti-infectives. K777 has shown activity against the parasites that cause Chagas' Disease, African Sleeping Sickness, schistosomiasis and cryptosporidiosis. K777-related compounds that target other cathepsin-L like proteases also potentially expand the antimicrobial spectrum of this class of drugs to cover parasites such as Giardia and Entamoeba. In addition, K777 appears to be able to disrupt cysteine protease-mediated entry of viruses into host cells. Recent studies have shown that second generation K777-related compounds are active against viral diseases such as SARS and Ebola. Thus, K777 and related compounds represent a new class of anti-infective/antimicrobial with potential broad spectrum indications.

Through the preclinical services program, NIH has supported metabolic, pharmacokinetic and New Drug Application (NDA)-enabling toxicology studies for K777 as a candidate therapeutic for Chagas' Disease. In a study that evaluated metabolism and pharmacokinetic profiles of K777, rat and human microsomes were incubated with K777 in vitro to identify major metabolites of K777. In addition, the bioavailability and pharmacokinetics of both oral and intravenous K777 were determined in a rat model system. NIH-supported researchers found that oral bioavailability was higher in females than in males, and that the drug appeared to cycle between the liver and intestines. K777 toxicity was also studied, and they found that all rats tested with a single dose, 7 day or 14 day regimens survived. Chronic administration seemed to result in increased clearance of K777 from the system. At the highest dose (300 milligrams per kilogram), liver damage was observed. Results of the study suggest that low doses had no observed adverse effects and would be preferable for use in future clinical studies.

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. Because the existing repertoire of antimicrobial therapeutics may not in the future provide an effective defense against newly emerging and resistant organisms and bioterrorism agents, there is a need to develop new treatments that may be effective against a range of pathogens. Development of a "universal antibiotic," a drug effective against a wide spectrum of infectious diseases, would help address these challenges.

A "universal antibiotic" is defined as any broad-spectrum antibiotic/antimicrobial/anti-infective that is effective against multiple biological pathogens. This may include: antibiotics with demonstrated efficacy against multiple gram negative and/or gram positive bacterial species, possibly including drug-resistant strains or biodefense priority pathogens for which there are few or no available drugs; broad-spectrum antivirals that demonstrate activity against multiple viruses, possibly including viruses belonging to different viral families; broad spectrum anti-infectives that may have efficacy against more than one species of parasite; antimicrobials that may have activity across two or more of the groups mentioned above (bacteria, viruses and parasites); and immunomodulators that generally strengthen the body's ability to fight a variety of different infectious diseases. While some broad-spectrum antibacterial drugs are currently available, many of those are ineffective against drug-resistant bacteria or unproven against biodefense priority pathogens. No major broad-spectrum antivirals, anti-infectives or immunomodulatory drugs have been developed to date. A "universal antibiotic" with broad-spectrum activity against multiple pathogens, such as those described above, would add a significant new capability to treat infectious diseases for which few or no therapeutics currently exist.

Rationale

From a strategic perspective, a broad-spectrum antimicrobial therapeutic could be used either alone, or in combination with currently available antimicrobials, to protect individuals exposed or potentially exposed to pathogens of unknown identity. This would provide a valuable countermeasure in the case of an outbreak or bioterrorism attack. In addition, there is increasing concern about both naturally evolving drug resistant pathogens and the potential to engineer drug resistance into microbes to create bioterrorism agents. A new broad-spectrum antimicrobial could be used to treat or to increase the effectiveness of current drugs against drug-resistant infections. Better understanding of intracellular pathogens, and the components of the immune response they may commonly activate during infection, could identify new pathways to target for the development of universal/broad-spectrum antimicrobials with efficacy across multiple classes of pathogens. In addition, genomics, the science of deciphering and drawing information from the genetic code of an organism, is a powerful tool that the NIH is using to understand the microbes that cause disease and to devise strategies to overcome infection.

TARGET CONTEXT AND CONDITIONS

NIH's standard role in product development is to support basic research (fundamental discovery and identification of product concepts), applied research (subsequent efforts to refine concepts and develop candidate products) and advanced R&D (preclinical and clinical development). Once a candidate product has been developed through Phase I/II clinical testing, the developed candidate product may move from NIH to a partner, which can be a drug company, another government agency or a public-private partnership, for commercial scale development and activities leading toward licensure, marketing, government acquisition and/or utilization (including emergency use). In the case of products of high priority to the US government for biodefense and emerging infectious diseases, Congress has created the DHHS Biomedical Advanced Research and Development Authority (BARDA) to support advanced product development activities, and Project Bioshield to facilitate acquisition of those products for the US Strategic National Stockpile.

To accomplish the goal of developing one universal or broad-spectrum antibiotic/antimicrobial/anti-infective, NIH is stimulating basic and applied research toward the development of broad-spectrum antimicrobials through targeted solicitations and is continuing to expand the availability of critical research resources to the community. Examples of research resources that are being expanded include development of screening assays and screening capacity to support discovery of novel antimicrobials and broad-spectrum activity, increased capacity for medicinal and combinatorial chemistry, and enhanced library and database resources. New methodologies, chemical libraries, and software tools are expanding the pool of compounds that can be screened for antimicrobial properties. Expansion of NIH genomic, proteomic, and bioinformatic resources will accelerate basic and applied research on microorganisms responsible for emerging and re-emerging infectious diseases, including those considered potential agents of bioterrorism, as well as identification of gene products critical to bacterial growth and pathogenicity that may serve as targets for broad-spectrum antimicrobials. In addition, NIH is supporting research under several initiatives of the NIH Common Fund to develop a small molecule repository and PubChem database, a Molecular Screening Centers Network, and to support the development of screening tools and new assays for high-throughput screening. NIH also supports preclinical and clinical development services to facilitate the advanced R&D phases of product development leading toward a candidate product.

Long Term Objective: (SRO-3.3) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.3 By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease. (Outcome)	*2011*	Complete the data collection phase of clinical trials addressing salivary proteomics in Sjögren's syndrome and head and neck cancers so that diagnostic and therapeutic applications can be evaluated. *(Baseline):* There is currently no clinical trials data available to study salivary proteomics in patients with Sjögren's syndrome or head and neck cancers.	N/A
	2010	Initiate pre-clinical trials to test the compact device that will perform diagnostic evaluation of saliva specimens *(Baseline):* No-preclinical trial protocols have been established.	N/A
	2009	Complete integration of the individual components of the compact device and establish the limit of detection, accuracy, precision and specificity for the device in detecting analytes associated with both oral and systemic diseases. *(Baseline):* (FY07) Individual components of the device have been developed but further refinement is necessary for the integration of these individual components to a handheld device.	The compact sensor and analytical components of the device have been integrated and tested. Probe and reagent development enabled acceptable sensitivity and specificity in detecting oral cancer. (Target Met)
	2008	Complete the design of bioinformatics management systems for storing, searching, and disseminating salivary proteomics data. *(Baseline):* (FY06) Scientists have begun efforts to design bioinformatics systems to store salivary proteomics data.	A bioinformation management system has been designed and developed. The SPKB system currently stores searchable information on 1166 proteins. (Target Met)

Measure	FY	Target	Result
	2007	Establish a common proteome database that will include data from 2 subject groups that cover over 80 percent of the salivary proteome. *(Baseline):* (FY05) Three groups of researchers are currently working to catalog the salivary proteome.	A common proteome database has been established that includes data from 3 subject groups. 1166 proteins have been identified, comprising 84 percent of the human salivary proteome. (Target Exceeded)
	2006	Finalize the fabrication of a portable handheld diagnostic device that can detect C-reactive protein and other analytes associated with oral and/or systemic diseases, and develop methods for its quality assurance and standardization. *(Baseline):* (FY04) Currently the individual components needed for a portable handheld diagnostic device are under fabrication and validation	A portable handheld diagnostic device has been fabricated. (Target Met)

Data Source and Validation

Wei F, Patel P, Liao W, et al. Electrochemical sensor for multiplex biomarkers detection. Clin Cancer Res 2009; 15(13) July 1, 2009.
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Tan W, Sabet L, Li Y, et al. Optical protein sensor for detecting cancer markers in saliva. Biosensors and Bioelectronics 24 (2008) 266-271.
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Salivaomics Knowledge Base
http://hspp.dent.ucla.edu

Wei, Liao W. Probe immobilization and signal amplification for polymer-based biosensor. Patent Cooperative Treaty (PCT). UCLA Case # 2008-306. Filed November 9, 2008.

Wei F, Zimmerman BG, Wong DT. High specificity and high sensitivity detection based on steric hindrance and enzyme-related signal amplification. Patent Cooperation Treaty (PCT). Application No. PCT/US2008/065286. Filed May 30, 2008.

Wong DT. A Universal pre-analytic solution for concurrent stabilization of salivary proteins, RNA and DNA at ambient temperature. USA. US Patent Application # 61/105,323. Filed October 14, 2008.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. The compact sensor and analytical components of the device have been integrated and tested. Probe and reagent development enabled acceptable sensitivity and specificity in detecting oral cancer. Major advances occurred to make a hands-free salivary diagnostics system that would be available at the point of oral health care and that would return information in a short period of time. The integration of multiple components was required. The initial instrumentation included a desktop full of bulky instruments. In contrast, the dimensions of the current prototype are 8” x 7” x 4”. The desk system required about 3.5 hours for the total assay time. The current prototype returns information on three oral cancer markers (from two protein assays and one RNA assay) within 15 to 30 minutes. Improvements in the instrumentation came from the use of

an electrochemical sensor, which improved the accuracy of detection by permitting the testing of multiple biomarkers (proteins and RNA) and which was simpler in instrumentation than earlier versions. Also, replacing the manual pipetting and manual preparation time with a microfluidic cartridge reduced the total assay time. These advances allow the operator insert a cartridge with a saliva sample, push a button, and wait for the readout on the display panel. Continued improvements are expected in system optimization and automation, improved robustness, standardization, and improved sample collection, preparation, and quantification.

Investigators tested the device's limits of detection, accuracy, precision, and specificity and demonstrated that:

- the sensor can robustly and reproducibly detect salivary RNA markers,
- that salivary RNA and protein can be multiplex-detected on the same electrochemical chip,
- that two specific salivary proteins are highly discriminatory for oral cancer,
- that the combination of two design features (optimal hairpin probe with optimal electrical field control) permits detection of salivary RNA biomarkers over a wide dynamic range of target concentration,
- and that the success of the sensor in discriminating oral cancer is comparable to existing methods using a conventional salivary analysis.

Advances or Other Highlights

NIH researchers have made advancements in the translational utility of the device by identifying two specific disease areas for investigation. One group of researchers will explore the testing and validation of the microchip sensor system in patients with a suspected or verified squamous cell cancer in the mouth. A second group of researchers will explore the relationship between salivary fluid and cardiovascular disease. Persons who are admitted to participating hospitals with heart attacks will provide samples of salivary fluid for testing with the diagnostic device. These new studies, together with existing NIH research may accelerate the progress of the salivary diagnostics research and hypothesis testing and aid in the rapid identification and more effective intervention and management of oral cancer and heart disease patients.

BACKGROUND

Saliva assists with intake and digestion of food as we chew and swallow. It also contains information about many physiological aspects of health and bodily function. Properties of saliva, including quantity, thickness, smell, and taste, have been associated with diseases for many years. However, in spite of ongoing saliva research, blood has been much more often used than saliva to detect disease and other biological conditions because most molecular compounds that are found in saliva are also found in blood but in larger concentrations.

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, often after the condition has substantially progressed. 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

Over the last several decades, scientists have begun to talk more actively about using a person's saliva to detect a range of oral and systemic diseases. Saliva is easy to collect and poses none of the risks, fears, or invasiveness concerns occasioned by blood tests. Unlike blood, which involves a painful needle stick, must be carefully processed, and often sent elsewhere for analysis, saliva can be collected quickly and painlessly and possibly analyzed right there in a dentist or doctor's office. The possibility exists for test results to be delivered within minutes, allowing patient and health professional to consult immediately and develop a plan of follow up care.

In 2008, oral health monitoring research advanced in two major areas: the identification of disease biomarkers and the development of biosensor micro-technology, have supported the field of salivary diagnostics and are making new diagnostic tools a reality. Miniaturization of the "lab on a chip" may allow placement of the detection device directly in the mouth, facilitating sample collection. As oral levels of most molecules and proteins of interest are lower than blood levels, sensitive analytical techniques are required. 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 substances 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 as part of research to determine the efficacy of salivary diagnostics. 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.

TARGET CONTEXT AND CONDITIONS

Salivary diagnostics projects are breaking new ground in making new diagnostic tools a reality. Compared with existing diagnostic systems, the ability to screen and discover multiple biomarkers simultaneously may provide a more valid clinical diagnosis and may be more useful to recognize molecular patterns predictive for disease development. In the next five years of the project, known as Phase II, development will proceed on an easy-to-use diagnostic prototype with wireless communication systems that has the potential to attract commercial development. Specifically, the fabricated platforms will be integrated with existing front-end technologies to create a fully functional compact salivary diagnostic test that can be used in different settings, from the hospital to the home.

The Human Salivary Proteome program, which complements the Salivary-Based Diagnostic Technologies program, continues to make substantial progress towards deciphering the entire spectrum of salivary proteins. Intense efforts are now ongoing towards the comprehensive identification of all proteins in saliva. The human salivary proteome will present, for the first time, a complete alphabet for the translational and clinical utility of saliva as a diagnostic fluid. This toolbox will contain the information necessary for scientists to harness, from saliva, the proteomic elements that will mark clinical diseases such as caries, Sjögren's syndrome, and oral cancer.

The sequence of activities leading to knowledge of the efficacy of a compact biosensor for salivary diagnostics is complex. Advances have to be made in biomarker identification (the Human Salivary Proteome program) and in micro-technology (the Salivary-based Diagnostic Technologies program). NIH-funded research has pointed to the potential of salivary markers in cancer, auto-immune disease, and diabetes. The NIH will continue to study salivary biomarkers for these and other diseases through the proteome database. Funded research has also led to the development of hand-held prototypes of biosensors for salivary diagnostics, which will continue to be supported.

Pre-clinical research activities leading to the routine use of a compact biosensor for salivary diagnostics include the selection of a specific disease for research, identification of biomarkers in saliva that are sensitive and specific to that disease, the tailoring of those disease biomarkers to the biosensor, and preliminary engineering of the biosensor. Once basic technological needs were achieved in prototypical devices, limited refined production of the biosensor was undertaken so that pre-clinical tests can be conducted. These pre-clinical tests addressed such questions as the method of sample collection (suction, spit, or swab, for example), sample volume, sample storage, and display and recording of sample information on the biosensor. Following these pre-clinical tests, clinical trials can be developed. The clinical trials of the device will address accuracy, reliability, and utility of the device in human samples.

Long Term Objective: (SRO-3.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.4 By 2015, evaluate an HIV vaccine candidate in a test of concept (phase IIB) efficacy trial in order to move towards an HIV/AIDS vaccine. (Outcome)	*2011*	Develop two additional methodologies to evaluate the immune responses induced by candidate HIV vaccines, in order to assess whether those responses correlate with the efficacy of HIV/AIDS vaccines in future Phase III clinical trials. *(Baseline):* Studies already have validated two methodologies (elispot assays and intracellular cytokine staining), which measure polyfunctional vaccine responses. Knowledge of which assays will best predict clinical outcome in human trials remains unknown.	N/A
	2010	Initiate studies of the human immune response to three new prototype HIV vaccines to begin to determine their promise as HIV preventive vaccines. *(Baseline):* Non-human primate and human clinical studies of three novel Adenovirus vector vaccines are underway or planned.	N/A
	2009	Begin analyzing final data from a phase III trial of a second generation vaccine. *(Baseline):* (FY07) To date 16,402 participants have been enrolled in a phase III trial in Thailand (RV 144).	Data from the phase III Thai HIV vaccine trial found the vaccine regimen to be safe and 31.2% effective in preventing HIV infection. (Target Met)
	2008	Initiate a Phase IIb trial of a promising vaccine candidate that may protect across viral clades (or subtypes). *(Baseline):* (FY06) NIH is conducting 3 phase I/II trials (HVTN 502, HVTN 050, HVTN 204) of products that might be further tested for protection across viral clades (or subtypes).	NIH did not initiate a Phase IIb trial of a promising vaccine candidate. (Target Not Met)

Measure	FY	Target	Result
	2007	Initiate another Phase II/IIb trial(s) of the most promising third generation vaccine candidate. *(Baseline):* (FY05) NIH is conducting Phase I trials of a second third generation candidate (6 plasmid DNA plus Adv boost).	NIH initiated a Phase II/IIb trial to evaluate the safety and efficacy of Merck's clade B–based Adenovirus HIV-2 gag/pol/nef vaccine in South Africa. (Target Met)
	2006	Initiate 1 new phase IIb trial to determine if a third generation vaccine candidate has efficacy. *(Baseline):* (FY04) NIH is conducting a phase III trial of a second generation vaccine (canarypox) in Thailand	NIH initiated a Phase IIb study (test of concept) to evaluate the safety and efficacy of Merck's Adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in high-risk adults. (Target Met)

Data Source and Validation
http://www hivresearch.org/phase3/index html http://www3 niaid.nih.gov/news/newsreleases/2009/ThaiVaxStudy htm http://www3 niaid.nih.gov/topics/HIVAIDS/Research/vaccines http://www hivvaccineenterprise.org/conference/2009/scientific_program.html http://content nejm.org/cgi/content/full/NEJMoa0908492

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The 2009 target was Met. Data from a phase III clinical trial of an investigational HIV vaccine regimen (RV144), also known as the Thai phase III HIV vaccine trial, were analyzed. The U.S. Department of Defense, the trial sponsor announced the results from the trial in September 2009. Additional data from the study were presented at the AIDS Vaccine 2009 Meeting in Paris in October 2009 and published in the New England Journal of Medicine. The study was an international collaboration, involving the U.S. Army, the Thai Ministry of Public Health, NIH, Sanofi Pasteur, and Global Solutions for Infectious Diseases (GSID).

RV144 is the largest HIV vaccine clinical trial conducted to date involving more than 16,000 Thai men and women at various levels of risk. The trial tested the "prime-boost" combination of two vaccines: ALVAC-HIV® vaccine (the prime), and AIDSVAX® B/E vaccine (the boost). The combination of vaccines was based on HIV strains that commonly circulate in Thailand. The trial was designed to test the vaccine's ability to prevent HIV infection, as well as its ability to reduce the amount of HIV in the blood (viral load) of those who became infected after they enrolled in the study.

In the final analysis of the trial data, the vaccine regimen was found to be safe and 31.2 percent effective in preventing HIV infection. Seventy four of 8,198 placebo recipients became infected with HIV compared with 51 of 8,197 participants who received the vaccine regimen. The vaccine regimen had no effect on the viral load of volunteers who acquired HIV infection during the study. While this is a modest level of efficacy, it represents a major step forward for HIV vaccines, providing the first evidence that development of a safe and effective preventive HIV vaccine may be possible. HIV-infected volunteers continue to be followed in a separate study (RV152) to assess the long term effects of vaccination on viral load, as well as to provide the study participants with access to HIV care and treatment.

Advances or Other Highlights

NIH and the collaborating partners are working with other scientific experts to determine the next steps, both in terms of future development of vaccine candidates, as well as more fundamental HIV vaccine research. The impact of these findings on the development and testing of other HIV vaccine candidates as well as NIH's current vaccine pipeline and research direction will also be reviewed.

In addition, the trial sponsors are encouraging the evaluation of the limited specimens from the RV144 trial by the broader scientific community. Scientific concept proposals are being solicited from investigators who would like access to these specimens for their research studies. The concept proposals will be initially reviewed by the RV 144 Scientific Steering Committee and its Working Groups and feedback will be provided to the investigators for further development.

BACKGROUND

The development of a universal HIV/AIDS vaccine continues to be a priority to control the pandemic. Progress has led to the development of current alternative medical treatments. Highly active antiretroviral therapy (HAART) has been beneficial to many HIV-infected individuals, but does not cure HIV or the onset of AIDS. Most importantly, antiretroviral therapy does not prevent the spread of HIV through people with undiagnosed HIV infections. Safer sex measures have also proven insufficient to halt the spread of AIDS, despite some success in reducing infection rates. Therefore, an HIV vaccine may be the most feasible way by which the HIV/AIDS pandemic can be halted.

Prevalence/Incidence

In 2007, there were an estimated 2 million deaths worldwide due to HIV/AIDS. While there has been a decline in HIV/AIDS mortality as a result of increased antiretroviral treatment, HIV/AIDS remains a leading cause of death worldwide and the primary cause of death in sub-Saharan Africa. In 2007, there were an estimated 2.7 million new HIV infections and a total of 33 million people living with HIV/AIDS globally. The number of children living with HIV/AIDS increased from 1.5 million in 2001 to 2 million in 2007, although the number of new infections per year decreased among children from 460,000 in 2001 to 370,000 in 2007. Sub-Saharan Africa continues to be the most affected region: More than 2 out of 3 adults (68%) and 90% of all children with HIV/AIDS live in this part of the world.

In the United States, the most recent statistics from the Centers for Disease Control and Prevention revealed that 56,000 people became newly infected with HIV in 2006, with African-Americans continuing to face the greatest burden of HIV/AIDS. The rate of new HIV infections among African Americans in the United States is seven times the rate among whites. There is also evidence of resurging HIV/AIDS epidemics among men who have sex with men in the United States; 53% of new HIV infections in 2006 were in men who have sex with men.

Disease Burden

The impact of the HIV/AIDS pandemic is profound. Although global availability of resources to combat HIV/AIDS has increased since 2001, the populations most affected by HIV/AIDS are still at greater risk of poverty, hunger and childhood mortality than those less affected by the pandemic. The HIV/AIDS pandemic continues to destroy families and communities and thereby to weaken the social stability and threaten the national security of developing nations. According to a 2009 report by the Joint United Nations Program on HIV/AIDS (UNAIDS), Sub-Saharan Africa remains the most severely affected region of the world. The Sub-Saharan region alone accounted for 67% of all HIV infections globally in 2008, with 68% of new HIV infections in adults and 91% of new infections in children. In 2008 more than 14.1 million children in Sub-Saharan African were estimated to have lost one or both parents to HIV/AIDS.

Rationale

Safe and effective vaccines to prevent HIV infection, disease and/or transmission are essential for global

control of the HIV/AIDS pandemic. The research presented is an integral part of the NIH's efforts to develop such a vaccine with potential for licensure by the FDA.

The development of an HIV/AIDS vaccine is one of the most complex and daunting scientific challenges because of HIV's unique ability to destroy the immune system and integrate into human cells, thereby evading clearance. A vaccine would need to induce a protective immune response that is more effective than the immune response resulting from natural infection with HIV. Such a vaccine might prevent HIV infection (which would be a "classical" vaccine), or it might prevent the progression of HIV disease in people who are vaccinated and later become infected.

NIH has held extensive consultations with experts in the field and stakeholders including researchers, advocacy groups, patients, and the general public to solicit input on how best to reinvigorate and advance HIV vaccine research. This dialogue revealed a broad scientific consensus that designing a safe and effective vaccine to prevent HIV infection will require enormous advances in fundamental research beyond present-day knowledge. As a result, NIH is shifting emphasis from product evaluation to basic research, non-human primate research and other clinical research that may contribute to vaccine discovery. In addition, NIH will continue to conduct clinical vaccine research and tests of promising candidates, when appropriate. Enhancement of research resources and animal models will continue to play an important role in facilitating basic, applied, and clinical research. This new strategy should lead to the development and evaluation of a new vaccine candidate in a test concept efficacy trial by 2015. Such a trial would be an important milestone toward the identification of a preventive HIV vaccine. It would help confirm the vaccine's safety and determine if it has potential efficacy. If the vaccine does hold promise, expanded trials of the same or related products could then proceed to further testing and eventually lead to an HIV vaccine.

TARGET CONTEXT AND CONDITIONS

NIH recently redesigned its strategy for HIV/AIDS vaccine research, in response to several factors. In late 2007, two Phase II trials (STEP and the related Phambili trial) of a Merck-designed HIV/AIDS vaccine were stopped before reaching the planned conclusions because the mid-trial data from the STEP study demonstrated that the vaccine failed to prevent HIV infection and also did not affect the level of HIV in those who were vaccinated but still became infected with HIV. Scientists continue to analyze data and samples from the volunteers to clarify why this vaccine might have even increased the risk of infection in a subset of study volunteers who were uncircumcised and who, at the time they enrolled in the trial, had naturally occurring neutralizing antibodies to adenovirus 5, the virus used to make the vaccine vector that delivered the HIV vaccine. In addition, recent basic and preclinical research studies in non-human primate models of AIDS suggest that the window of opportunity during which a vaccine can trigger immune responses to stop the virus from gaining a foothold is shorter than originally thought (days to a week, not several weeks). These scientific factors and significant resource constraints have driven NIH to redesign its vaccine research strategy to ensure the most efficient use of resources.

When the STEP trial was suspended, numerous consultations were held to discuss the future directions of vaccine research efforts. In March 2008, the NIH convened a summit on HIV vaccine research and development to garner input from experts in the field regarding the most appropriate balance between vaccine discovery and development. During the summit, panels of experts facilitated discussion within three broad areas: vaccine-related basic research, vaccine discovery and vaccine development; animal model development and utilization and clinical research and trials. Consensus emerged from the summit that traditional approaches to vaccination are likely not to be effective for HIV prevention. A shift in the balance between product development and discovery of innovative vaccine concepts was recommended to ensure flexibility and streamlining of discovery research. There was also consensus that NIH should be more selective in moving candidate vaccines into clinical trials and that non-human primate studies should be performed in parallel with human studies to determine whether a vaccine candidate should be developed.

To begin shifting the balance between basic and clinical HIV vaccine research, two new Requests for Applications (RFAs) were released in 2008. The Basic Vaccine Discovery RFA aims to accelerate vaccine discovery efforts by generating new knowledge to inform new conceptual approaches to vaccine design through 20 awards made in 2009. With 16 awards made in 2009, the Highly Innovative Technologies to Interrupt Transmission of HIV (HIT-IT) RFA aims to stimulate the development of novel, unconventional, high-risk, high-impact approaches. As a result of this shift, new awards for two long-standing programs will be paused for at least a 2-year period, the Integrated Preclinical/Clinical AIDS Vaccine Development Program and the HIV Vaccine Design and Development Team. This will slow the opportunity to advance vaccine candidates into phase I trials.

Long Term Objective: (SRO-3.5) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.5 By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies. (Outcome)	*2011*	Replicate previously identified functional differences in various ethnic populations. *(Baseline):* (FY10) Functional differences identified from fine mapping studies have been characterized and validated.	N/A
	2010	Characterize and continue to validate the functional differences identified from previous fine mapping studies. *(Baseline):* (FY09) The validation of functional differences of specific haplotypes is underway.	N/A
	2009	Validate the functional differences identified from previous fine mapping studies. *(Baseline):* (FY08) Functional differences have been identified from fine mapping studies of haplotypes.	Functional differences related to alcohol dependence and treatment were validated for the A118G SNP of the OPRM1 gene. (Target Met)
	2008	Identify potential functional differences from fine mapping studies of specific haplotypes. *(Baseline):* (FY06) Susceptibility genes located on identified chromosomal regions have been mapped.	Functional differences were identified for the A118 allele of the OPRM1 gene. Research was conducted on functional differences of haplotypes in the GABRA2 gene. (Target Met)
	2007	Perform fine mapping studies to identify specific haplotypes for the most promising genes, and seek potential functional differences coming from these haplotypes. *(Baseline):* (FY06) Susceptibility genes located on identified chromosomal regions have been mapped.	Fine mapping studies were conducted to identify specific haplotypes of genes that influence risk for alcohol dependence. Functional differences of various haplotypes were identified. (Target Met)

Measure	FY	Target	Result
	2006	Validate or replicate previously identified chromosome regions in different sample sources by one or more groups to identify genes. *(Baseline):* (FY04) Regions have been previously mapped on chromosomes 1,4,7, and 15 by one or more independent groups.	Replicated the genetic associations of GABRA2, ADH4, and CHRM2 to alcohol dependence in different sample sources in multiple groups. (Target Met)

Data Source and Validation
Barr CS, Chen SA, Schwandt ML, Lindell SG, Sun H, Suomi SJ, Heilig M. Suppression of Alcohol Preference by Naltrexone in the Rhesus Macaque: A Critical Role of Genetic Variation at the mu-Opioid Receptor Gene Locus. Biol Psychiatry. 2009 Sep 11. [Epub ahead of print] doi:10.1016/j.biopsych.2009.07.026 Oroszi G, Anton RF, O"Malley S, Swift R, Pettinati H, Couper D, Yuan Q, Goldman D. OPRM1 Asn40Asp predicts response to naltrexone treatment: a haplotype-based approach. Alcohol Clin Exp Res. 2009 Mar;33(3):383-93. Epub 2008 Nov 25. http://www3.interscience.wiley.com/cgi-bin/fulltext/121543293/PDFSTART Wang JC, Grucza R, Cruchaga C, Hinrichs AL, Bertelsen S, Budde JP, Fox L, Goldstein E, Reyes O, Saccone N, Saccone S, Xuei X, Bucholz K, Kuperman S, Nurnberger J Jr, Rice JP, Schuckit M, Tischfield J, Hesselbrock V, Porjesz B, Edenberg HJ, Bierut LJ, Goate AM. Genetic variation in the CHRNA5 gene affects mRNA levels and is associated with risk for alcohol dependence. Mol Psychiatry. 2009 May;14(5):501-10. Epub 2008 Apr 15. http://www nature.com/mp/journal/v14/n5/abs/mp200842a.html

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH researchers validated functional differences related to alcohol dependence and treatment for the A118G single nucleotide polymorphism (SNP). Previous studies indicated the A118G SNP, a functional sequence variant in the OPMR1 gene involved in the brain reward system, was associated with reduced alcohol consumption in response to the medication naltrexone. In a recent study, response to naltrexone was tested in nonhuman primates carrying the OPRM1 allele (C77G) that is functionally equivalent to A118G. The results showed reduced alcohol preference, as measured by the amount of alcohol consumed, in primates carrying the G allele in contrast to higher alcohol consumption in primates carrying the C allele. These results reproduced the human finding. In another study, haplotypes of OPRM1 were evaluated for treatment response to naltrexone in Caucasian individuals who participated in the COMBINE study. Of the haplotypes examined, the haplotype that was significantly associated with positive response to naltrexone (defined as abstinence or moderate drinking without problems) was a short DNA sequence that contained the A118G allele.

The results suggest these genetic variants are likely to be associated with increased vulnerability for alcohol dependence in individuals possessing them. The sequence variants may be useful in the future as markers to predict risk of developing alcohol dependence and related disorders, or to predict treatment response to medications and personalize treatment regimens for affected individuals.

Advances or Other Highlights

Investigators also demonstrated and replicated the association between SNPs in the CHRNA5-CHRNA2-CHRNB4 gene cluster and alcohol dependence through population studies. A recent examination of families participating in the Collaborative Study on the Genetics of Alcoholism (COGA) demonstrated an association between alcohol dependence and SNPs in the CHRNA5-CHRNA3-CHRNB4 gene cluster in European Americans. These genes encode nicotinic acetylcholine receptor subunits involved in nicotine dependence. The

association of the SNPs with alcohol dependence was independent of smoking status and replicated in an independent data set also comprised of European Americans. Functional studies using brain mRNA indicated an association between two of the SNPs and increased levels of CHRNA5 mRNA, suggesting alteration of mRNA abundance may be the mechanism of action that influences risk conferred by CHRNA5.

BACKGROUND

Many studies have indicated that genetic components contribute to the risk of substance use disorders and comorbid psychiatric disorders. Identifying susceptibility genes and understanding how they might contribute to these disorders have been a major research focus. These efforts have been limited by the difficulties inherent to the genetic study of complex disorders. However, advances in the development of new technologies such as single nucleotide polymorphism (SNP) and haplotype genotyping have led to the identification of genes such as GABRA2 (chromosome 4) associated with alcohol and drug dependence and CHRM2 (chromosome 7) associated with alcohol dependence and major depressive disorder. In addition, a polymorphism of the catechol-O-methyltransferase (COMT) gene has also been linked to several psychiatric disorders such as alcoholism, schizophrenia, and anxiety.

Recently, the development of high density SNP technologies have been applied to Genome-wide Association Studies (GWAS) to identify novel genes in individual human patient samples to complement classical family-based studies. Identifying additional genes that influence risk for substance abuse and co-occurring psychiatric disorders and understanding their functional implications can support the development of more effective therapies in these complex diseases.

Prevalence/Incidence

The World Health Organization 2009 report on mortality and burden of disease cites alcohol as the third leading risk factor for preventable, premature death in developed countries, after tobacco and hypertension. 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 according to 2000 data from a CDC study published in 2004. Nearly 18 million American adults (8.5% of the population age 18 and older) suffer from a 12-month alcohol use disorder, i.e., alcohol abuse and alcohol dependence (alcoholism) based on a 2004 study on trends in DSM-IV alcohol abuse and dependence for the years 1991-1992 and 2001-2002. Children also are at risk for alcohol related problems. Twenty six percent of 9th to 12th graders report having five or more drinks, in a row, at least one day of the previous month reported in a CDC 2007 Youth Risk Behavior Surveillance summary.

According to the 2008 National Survey on Drug Use and Health, an estimated 22.2 million persons aged 12 or older were classified with substance dependence or abuse in the past year (8.9 percent of the population aged 12 or older). Of these, 3.1 million were classified with dependence on or abuse of both alcohol and illicit drugs, 3.9 million were dependent on or abused illicit drugs but not alcohol, and 15.2 million were dependent on or abused alcohol but not illicit drugs according to results from the 2008 NSDUH.

Co-occurring diagnoses of substance abuse and mental illness are highly prevalent, with some estimates of as many as 7 to 10 million Americans suffering from both. Analyses of data from the National Comorbidity Survey found that 51% of those with a lifetime addictive disorder also had a lifetime mental disorder. For example, individuals diagnosed with major depression are 3 times more likely than those without major depression to also have a diagnosis of alcohol and/or other drug abuse and/or dependence compared according to a study on co-occurring addictive and mental disorders published in 1996. Women with bipolar disorder are seven times more likely to be alcoholics than women without psychiatric diagnoses as reported in research published in 2003 on gender differences in alcoholism comorbidity in bipolar disorder.

Disease Burden

Alcohol use disorders cost U.S. society almost $235 billion each year through injury, lost wages, property damage, death, and other factors according to research published in 2009 on the global burden of alcohol use

and alcohol use disorders. Unlike other drugs of abuse, alcohol can have toxic effects on any organ or system in the body such as the brain, cardiovascular system, liver and pancreas. Alcohol use also is linked to some kinds of cancer. Co-occurring psychiatric and other substance use disorders are associated with severity of alcohol dependence. Individuals who suffer the most severe subtype of alcohol dependence experience the highest rates of Antisocial Personality Disorder and psychiatric disorders such as depression, bipolar disorder and anxiety disorder. These individuals (9% of U.S. alcohol dependent individuals) comprise the largest proportion of alcohol dependent individuals who undergo treatment based on research published in 2007 on subtypes of alcohol dependence.

Rationale

Clinical assessments show that many individuals diagnosed with substance use disorders are also affected by other psychiatric disorders, suggesting the possibility that common pathways may underlie both types of disorders. Recent evidence suggests there are common genetic influences on the risk for substance abuse and psychiatric disorders. To date we do not know the specific genes associated with this shared genetic risk. Genome-wide linkage/association studies have identified many chromosomal regions containing candidate genes that contribute to the susceptibility of alcohol dependence and other comorbid psychiatric disorders. Use of rapid genomic technologies, such as SNP genotyping and haplotype map analysis, have advanced the discovery of genes from previously identified chromosome regions and continue to be useful tools in genomic studies. The identification of gene/allelic variations associated with alcohol and other substance dependence as well as psychiatric disorders will advance understanding of the genetic influences on these disorders, provide important clues to the underlying causes of these disorders, and ultimately, facilitate the development of new prevention strategies and therapeutic interventions.

TARGET CONTEXT AND CONDITIONS

NIH plans to identify genetic variations underlying addiction vulnerability. This will be accomplished through positional cloning using whole genome scanning and a candidate gene association approach in samples that have been previously collected from high-risk family, twin, and special population studies. Studies with high risk family, twin and special populations have been instrumental in identifying the genetic determinants of alcohol dependence and other disorders. Comparisons of genetic materials from individuals with and without alcohol use disorders and comorbid psychiatric disorders from within these groups will help researchers continue to identify genetic variations that confer vulnerability to these disorders. Variations in the identified genes will be examined through the use of knockout and transgenic mice, as well as through human pharmacogenetic studies in the populations indicated above, to understand differences in addiction vulnerability across individuals with different genotypes.

In the first phase of the measure, the association of newly identified genes to alcohol use disorders and comorbid psychiatric disorders were cross-validated by independent studies using different populations and sample sources. In the next phase, more genes and variants of genes validated during the first phase will be identified using rapid genomic technologies. Finally, in the last phase of the goal, the identified genes and variants will be studied and characterized for function. These steps may overlap as new genetic associations to alcohol dependence and co-occurring psychiatric disorders are discovered and genetic variants are identified and characterized for function.

Long Term Objective: (SRO-3.6) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.6 By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues. (Efficiency) (Outcome)	*2011*	Using a rat hindlimb ischemia model, test the hypothesis that encapsulation increases MSC survival in a hypoxic environment. *(Baseline):* It is unknown if encapsulation increases MSC survival in a hypoxic environment	N/A
	2010	(FY10) Test the hypothesis that encapsulated MSCs will provide increased MSC survival in normal animals. *(Baseline):* (FY09) The effect of MSC encapsulation on MSC survival in normal animals is unknown.	N/A
	2009	Demonstrate that encapsulated cells can be tracked non-invasively by X-ray computed tomography. *(Baseline):* (FY08) Biocompatible cell encapsulation agent is available, but its effect on cell tracking is unknown.	Stem cells were enclosed in microcapsules containing an agent that allowed the cells to be tracked non-invasively. The capsules were imaged after injection in animal models of cardiovascular disease. (Target Met)
	2008	Formulate a biocompatible cell encapsulation agent designed to protect and track mesenchymal stem cells for administration to patients to promote cell survival and engraftment. *(Baseline):* (FY07) Current cellular therapies suffer from extremely low cell engraftment due to early destruction of cells.	A biocompatible cell encapsulation agent to facilitate cell tracking and survival has been formulated. (Target Met)
	2007	Initiate validation and toxicity studies. *(Baseline):* (FY06) Verification is needed to determine whether developed probes are selective for and detectable in stem cells.	Due to changes in the scientific field and a new direction for this goal, this step to initiate and validate toxicology studies was not needed at this time. (Target Not Met)
	2006	Complete optical imaging probe development. *(Baseline):* (FY05) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.	Researchers in the NIH intramural program have developed probes that are compatible with optical microscopy techniques developed by intramural scientists. (Target Met)

Data Source and Validation
In Vivo Imaging of Stem Cells and Beta Cells Using Direct Cell Labeling and Reporter Gene Methods Dara L. Kraitchman; Jeff W.M. Bulte, Arteriosclerosis, Thrombosis, and Vascular Biology. 2009;29:1025. http://www ncbi nlm nih.gov/pubmed/19359666?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_Results Multi-Modality Visible Alginate Microcapsules for Mesenchymal Stem Cell Delivery. 2008 World Molecular Imaging Congress. http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={3A27300A-99D2-4F7B-B388-02961A69BED6}&MKey={B47BAE74-CCA9-4C27-80FB-0005AFC9E5C0}&AKey={A4C6DD8F-4BF2-400D-97ED-20C14381CDBB}&SKey={278EAB60-0588-4590-A4FF-6A47832E1D98} Kedziorek, D., Walczak, P., Azene, N., Kraitchman, D. Cell Visibility and Viability Assessment with Novel Bioluminescence Assay of X-Ray-Visible Microencapsulated Mesenchymal Stem Cells. 2008 World Molecular Imaging Congress. http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={B5604733-7132-4162-8BA7-0B39EAD48C72}&MKey={B47BAE74-CCA9-4C27-80FB-0005AFC9E5C0}&AKey={A4C6DD8F-4BF2-400D-97ED-20C14381CDBB}&SKey={278EAB60-0588-4590-A4FF-6A47832E1D98}

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The 2009 target was Met. The target was achieved by encapsulating mesenchymal stem cells in alginate microcapsules containing perfluoro-octyl-bromide, and imaging the capsules after injection in animal models of peripheral arterial disease and reperfused myocardial infarction. These advances will improve cellular therapies that are currently impaired by extremely low cell engraftment due to early destruction of cells. The imaging results demonstrate that the encapsulated cells can be tracked non-invasively in an animal model.

Advances or Other Highlights

Following injection of labeled capsules, persistence of intact capsules could be detected for up to 5 weeks under X-ray fluoroscopy. Viability of cells was also demonstrated in vivo by transfection of cells with a reporter gene producing firefly luciferase and bioluminescence assay.

BACKGROUND

Cardiovascular disease (which includes coronary heart disease (CHD), heart failure, and peripheral arterial disease (PAD)) is the leading cause of death in the United States. CHD occurs when plaque builds up in the arteries that supply blood to the heart muscle. CHD can cause angina (chest pain) or a heart attack and, over time, contributes to serious disability or death. PAD occurs when plaque builds up inside the walls of arteries that carry blood from the heart to the head, internal organs, and limbs. PAD most commonly affects blood flow to the legs, and can cause pain, numbness, infection and, in severe cases, tissue death leading to amputation.

Scientists have begun testing cell based treatments using stem and progenitor cells from a variety of tissues in humans, but imaging modalities are needed to track cells in animals and, ultimately, in humans. The goal of this research is to aid the development of cell-based therapies for cardiovascular disease.

Disease Burden

Although cardiovascular disease (CVD) death rates have declined over the past few decades, CVD (including coronary heart disease (CHD), heart failure, and peripheral arterial disease) remains the leading cause of death and disability in the United States. According to the 2006 National Health and Nutrition Examination Survey, an estimated 16.8 million Americans have CHD and 8 million have experienced a heart attack. CHD accounted for over 1.7 million hospitalizations, at an estimated cost of $106 billion, and 425,000 deaths during that year. The aging of the U.S. population and the growing epidemic of obesity will likely increase the prevalence and cost burden of CVD in the U.S. in coming years. Aggressive approaches to revascularization and advances in medical management have improved the lives of many patients with CVD. Nonetheless, continued disability

for many patients and escalating attendant societal costs, mandate searches for improved treatments.

Rationale

Based on remarkable successes achieved in animal models of ischemia, cell-based treatments using stem and progenitor cells from a variety of tissues have begun to be tested in humans. Results from relatively small numbers of patients have suggested benefit from cell-based approaches, but methods to determine the localization and phenotypic fate of administered cells would provide insight into the mechanism(s) of benefit, enable development of other therapeutic approaches to accomplish similar end-points (e.g., using cells as a 'drug delivery devices'), and facilitate detection of possible toxic effects (e.g., accumulation of cells in nascent neoplasms). Conventional techniques for tracking exogenously administered cells in animal models require fluorescent or genetic marking with identification of cells in histological sections. Imaging modalities are needed to track cells in intact animals and, ultimately, in humans. Ultra-small supermagnetic iron oxide particles have been tested for cell imaging in studies using magnetic resonance imaging (MRI). Because they are incorporated into cells by endocytosis and concentrated in endosomes, resulting in magnification effects on the signals that are used to generate images (Hinds et al. Blood 2003; Arbab et al. Transplantation 2003), they may permit imaging of small numbers of cells over several weeks. Moreover, they appear to be biocompatible and non-toxic, with some preparations already approved by the FDA for non-stem cell applications. Initial work at NIH has used serial MRI of mesenchymal stem cells (MSCs) labeled with iron fluorescent particles in a pig infarct model (Hill et al. Circulation 2003; Dick et al. Circulation 2003) to show that labeled MSCs injected into the myocardium are readily visible up to 21 days post-infarction in the region of the infarct and that injection sites containing as few as 105 MSCs can be detected by MRI.

Scientific understanding of stem cell-based therapy has progressed considerably. Results reported in the literature from several pre-clinical and clinical studies using stem cells to treat cardiovascular disease show promise for reducing the progression of disease but not for reversing damage to the myocardium or generating new blood vessels. Moreover, preclinical data gathered by NIH researchers over the past few years suggest that the differentiation (the process by which an unspecialized cell, such as a stem or progenitor cell, becomes specialized into one of the many cells that make up the body, such as a heart, liver, or muscle cell that performs specific functions) of stem cells is not properly controlled during injection of stem cells into animal or human subjects. For the stem or progenitor cells to be effective at stimulating repair and/or regeneration, the cells need to differentiate into the specific types of cell needed to promote repair and regeneration. Therefore, the inability to control the differentiation of the cells limits their therapeutic potential. NIH-funded researchers have begun to focus on improving understanding of stem cell differentiation in order to develop methods to direct the differentiation or development of stem cells along specific cell lineages to yield replacement cells for clinical use.

Other recent studies suggest that cytokines, proteins produced and secreted by stem cells, may play an important role in the repair of damaged tissues. The unexpected results have shifted thinking in the field. Scientists are now devoting considerable effort to understanding the role of cytokine production by stem cells rather than focusing solely on assessing their differentiation state. Researchers continue efforts to develop noninvasive imaging techniques for monitoring cell-based therapy because cell therapy remains an important potential strategy for delivering secreted factors, such as cytokines, to patients. NIH extramural researchers are currently developing methods to protect and track stem cells using a cell encapsulation strategy designed to be used with X-ray CT imaging. The ultimate goal of the research is to develop a cell-based therapy for peripheral arterial disease (PAD), a form of CVD in which plaque builds up inside the walls of the arteries blocking the flow of blood from the heart to the head, internal organs, and/or limbs.

TARGET CONTEXT AND CONDITIONS

The NIH intramural program has undertaken a multimodality effort to develop imaging tools to track cardiovascular stem cells in vivo, and ultimately in patients. Efforts in the intramural program entail:

- Development and testing of MRI agents for ex-vivo labeling and in vivo tracking of cardiovascular

stem and progenitor cells. Cell labeling for MRI stem cell tracking has been conducted successfully using various iron preparations. The NIH has already demonstrated in vivo cell tracking of mesenchymal stromal cells (Hill et al. Circulation 2003). NIH investigators also have tracked hematopoeietic stem cells accumulating in injured rat hearts using clinical-grade reagents

- Development of a PET/MRI/CT system in which an animal model or patient can be imaged with no motion between the two modalities. Single-modality PET is employed for investigational and clinical applications. Compared with MRI or CT, PET radionuclides may enable detection of cells with higher sensitivity. However, PET suffers from low spatial and temporal resolution. In comparison, MRI or CT can provide superior spatial and temporal resolution, anatomic localization of cells to tissue injury, and generation of functional data. MRI provides local measures of cardiac function that would allow quantification of the recovery of function in areas where labeled cells are administered.

The development of a novel imaging technique to track stem cell mobility through cardiovascular tissues will capitalize on the current aspects of conventional imaging and labeling methodology:

- basic imaging modalities of optics, MRI, and PET
- the promise of studies using particle uptake as a labeling strategy
- the results of using initial genetic modification for fluorescence protein labels

The NIH extramural program is supporting efforts to develop and test a new imaging tool to promote stem cell engraftment and allow stem cell tracking in vivo. Efforts in the extramural program entail:

- Development of a method to prevent rapid destruction of stem cells in vivo. One of the major barriers to the development of allogenic cell-based therapy is the rapid destruction of allogenic cells in vivo. Extramural researchers are developing a cell encapsulation agent to protect and enable tracking of mesenchymal stem cells.
- Because the researchers plan to use allogeneic stem cell therapy, which uses cells from a donor rather than the patient's own cells, the immune system may react to the donor cells causing their rapid destruction. The researchers hypothesize that encapsulation will enhance cellular viability within the capsule and protect the cells from a reaction by the recipients' immune system, leading to enhanced cellular survival and engraftment.
- Evaluation of the use of the cell encapsulation agent to allow stem cell imaging and tracking using X-ray CT imaging.

Researchers have encapsulated stems cells and then tracked them non-invasively in an animal model. These advances will improve cellular therapies that are currently impaired by extremely low cell engraftment due to early destruction of cells. The next steps in research include testing the hypothesis that encapsulation lead to enhanced MSC survival in normal and disease-model environments.

Long Term Objective: (SRO-3.7) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.7 By 2019, develop at least two novel therapies for immune-mediated disease. (Outcome)	*2011*	Complete treatment in the study of rabbit and horse ATG in the treatment of severe aplastic anemia, and begin analysis. *(Baseline):* As rabbit and horse ATG are used interchangeably in hematology, evidence of a difference in efficacy has wide ramifications.	N/A
	2010	Analyze the biological effect of rabbit ATG on patients with aplastic anemia to determine the mechanism of action as an immunosuppressive or immunoregulatory drug and agent. *(Baseline):* No known analysis has been conducted for this purpose	N/A
	2009	Develop a protocol, including ancillary assays of immunologic function, to improve administration of the immunosuppressive biologic anti-thymocyte globulin (from horse and/ or rabbit) in the treatment of an autoimmune disorder. *(Baseline):* The relative efficacy of horse and rabbit ATGs in aplastic anemia needs to be tested with concomitant laboratory studies of lymphocyte phenotype and function.	A protocol has been developed to improve administration of the immunosuppressive biologic anti-thymocyte globulin in the treatment of an autoimmune disorder. The study has enrolled 116 patients to date. (Target Met)

Data Source and Validation
Three Immunosuppressive Treatment Regimens for Severe Aplastic Anemia. Abstract available through Clinicaltrials.gov at http://clinicaltrials.gov/show/NCT00260689

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. A protocol has been developed, including ancillary assays of immunologic functions, to improve administration of the immunosuppressive biologic anti-thymocyte globulin (from horse and/or rabbit) in the treatment of an autoimmune disorder. The study has enrolled 116 patients to date. Cytokine profiles of plasma pre- and post-treatment have been compared. As rabbit and horse ATG are used interchangeably in hematology, evidence of a difference in efficacy has wide ramifications.

BACKGROUND

This goal is one of several new trans-NIH initiatives created within the Office of Intramural Research and focuses on the translation of advances in basic immunology research to the care of patients. The ultimate objective of this goal is to facilitate information sharing among clinicians, between clinical and basic investigators, and to develop new therapies for diseases involving the immune system. As a component of the goal, the NIH may propose to create a new center within the NIH intramural research program to foster collaborations that attempt to rigorously characterize similarities and differences in pathophysiologies, with a major objective being the determination of possible common mechanisms of inflammation or immunologically-based disease that could be treated with common therapies. Other objectives include the development of high-risk projects, less conventional areas; NIH investigator-initiated intra- and extramural clinical collaborations to better utilize the vast resources of the Clinical Research Center; establishment of specific core facilities, as examples, generating valuable reagents and to facilitate the development and execution of clinical protocols and novel drug development, and broader sharing of existing core facilities in tetramer biology, flow cytometry, cytokine measurements and other specific immunologic assays, and nucleotide sequencing; and expansion of current training programs.

Rationale

NIH is in a unique position to foster increased interaction among different clinical specialties and to create trans-disciplinary translational and clinical programs at the research and training levels. This effort would help to achieve horizontal and vertical integration of advances from a wide range of medical sub-specialties and between basic and clinical sciences. The program could be paradigmatic for research at NIH, allowing the more rapid development and testing of novel therapies to directly benefit patients; creating a new perspective for interdisciplinary training; and ultimately providing a model for focused trans-NIH research that is intended to be synergistic in its creation of opportunities without being directive and diminishing the valued role of the individual principal investigator. The NIH intramural research program is in the best position to attempt these types of integrated translational, clinical, or educational approaches because of its concentration of expertise and technical resources.

TARGET CONTEXT AND CONDITIONS

This initiative promotes research that can result in improved translational research for immune-mediated diseases and can directly result in improved therapies important and often unique biologic information from the study of humans. The spectrum of diseases that a trans-NIH initiative in autoimmunity and immunology could include is large and diverse. The broad scope of current disease research in the different Institutes should provide the required resources, communication, and cross-fertilization among the different disciplines that are at the heart of this initiative and justify the uniqueness of NIH in attempting this type of endeavor.

NIH investigators, in collaboration with extramural academic investigators, have launched two clinical projects to address the failure of interferon-based therapy in patients with late-stage chronic hepatitis C and to gain insight into the mechanism of non-response to interferon-based therapy and develop new strategies to improve the treatment response rate. Complementing these areas of investigation will be research to establish the role of early cellular immune responses in the outcome of acute hepatitis C virus.

Antithymocyte globulins (ATG), biological agents with complex immunosuppressive and immunomodulatory effects are widely used and effective in immune-mediated human diseases, including for the treatment of graft-versus-host disease in stem cell transplantation, to prevent and treat graft rejection in solid organ transplantation, and in a variety of autoimmune hematologic diseases. ATGs from horse and rabbit sources are often used interchangeably, but laboratory data suggest that they are not identical, and their mechanisms of action are imperfectly understood. The relative efficacy of horse and rabbit ATGs in aplastic anemia needs to be tested with concomitant laboratory studies of lymphocyte phenotype and function. NIH anticipates developing a protocol, including ancillary assays of immunologic function, to improve administration of the immunosuppressive biologic anti-thymocyte globulin from horse and/ or rabbit in the treatment of an

autoimmune disorder.

With advances in high-throughput technology, researchers engaged in large-scale genome-wide association studies are now able to examine genetic variations in a shorter time frame and at a much lower cost. Sample collection is underway for a genome-wide association study of Behcet's disease, a complex disorder of inflammation affecting skin, eyes, gastrointestinal tract, lungs, vasculature, and joints. NIH researchers have obtained new technology to examine these data in order to identify susceptibility genes that could be used to develop targeted treatment strategies.

Long Term Objective: (SRO-3.8) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.8 By 2017, determine the optimal tailored treatment regimen for patients with early stage breast cancer that maximizes the benefits of chemotherapy while minimizing the side-effects of unnecessary treatment. (Outcome)	*2011*	Perform central testing of hormone receptors per amended protocol. *Previous target:* *Complete scheduled interim evaluation of patient survival and disease recurrence data to decide on trial continuation per protocol criteria.* *(Baseline):* Completed accrual of participants for the trial.	N/A
	2010	Complete accrual of additional patients per the amended protocol. *Previous target:* *Perform central testing of hormone receptors per protocol.* *(Baseline):* Additional participants needed to compensate for higher than anticipated rate of non-compliance	N/A
	2009	Complete accrual for the TAILORx trial. *(Baseline):* (FY08) Two-thirds of trial participants recruited.	Unexpected patient non-compliance with clinical protocol requires that additional patients be recruited. Accrual for the Tailor X trial will be completed in FY2010. (Target Not Met)
	2008	Accrue two-thirds of the TAILORx trial participants. *(Baseline):* (FY07) Approximately one-third of trial participants recruited.	The TAILORx trial accrued 3227 participants (73.5%) to the randomized study. (Target Met)

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Not Met. Patient non-compliance with the clinical protocol has been substantially higher than expected in patient accrual. As a result, additional patients need to be recruited for the trial.

This clinical trial is designed to determine the best treatment cut points for early stage breast cancer patients with an intermediate cancer reoccurrence risk score. Particularly, at what score can a physician say that the patient will not benefit from additional therapy? Patients with a low risk score do not benefit from chemotherapy, in addition to hormonal therapy. Patients with a high risk score do benefit for additional chemotherapy. The intermediate risk patients are randomized to receive hormonal therapy or hormonal plus chemotherapy. However, some patients with a score on the low end of the intermediate group, who are randomized to receive chemotherapy, are opting not to accept it. Conversely, some patients on the high end of

the intermediate group, who are randomized to hormonal therapy alone, are opting to also have chemotherapy. While patients have been fully informed of the purpose of the trial, further clarification of their condition prompts alternative treatment options.

In order to adapt to the increased non-compliance, additional patients are needed in the trial to ensure sufficient statistical power to generate significant results. The change in accrual targets was approved by the statisticians monitoring the trial, in collaboration with the NIH. The new patient target should be adequate to ensure that the trial has sufficient statistical power.Initially, the trial planned to enroll 10,000 patients so that 4,390 could be included in the randomized trial. The new targets are 11,248 enrolled, in order to randomize 6,860. Because more patients are eligible for randomization than originally expected (60% rather than the anticipated 44%), it is not necessary to increase the screened pool of patients proportionally. For this reason, increasing the overall participant pool by 1,500 will easily allow for a total of 6,860 randomized participants.

The revised patient accrual will be completed in FY2010. This will delay testing and data analyses by one year, and the measure will be extended by one year to finish in FY2017.

BACKGROUND

In 2009, the NIH Surveillance Epidemiology and End Results (SEER) program reported that breast cancer is the most frequently diagnosed cancer in women, with an estimated 192,370 new cases of invasive breast cancer expected in the United States in 2009. Over one-half of these women will have estrogen receptor positive, lymph node negative breast cancer. For 80 percent to 85 percent of those women, the current standard treatment practice is surgical excision of the tumor, followed by radiation and hormonal therapy. As summarized in a November 2000 NIH Concensus Statement, chemotherapy is also recommended for most women, but the proportion of women who actually benefit substantially from chemotherapy is fairly small.

Rationale

The majority of women with early-stage breast cancer are advised to receive chemotherapy in addition to radiation and hormonal therapy, yet research has not demonstrated that chemotherapy benefits all of them equally. Because chemotherapy can cause serious side effects such as nausea, hair loss and fatigue, as well as long-term effects such as second cancers, doctors want to find ways to identify patients who will benefit from chemotherapy and those who may be able to avoid it because of little added benefit. For women with node-negative, estrogen receptor-positive breast cancer, the benefit of adding chemotherapy to hormone therapy is small. The use of a molecular profiling test (a technique that examines many genes of the tumor simultaneously) in clinical decision making may more precisely estimate a woman's risk of cancer recurrence than standard characteristics normally used to assess recurrence risk (tumor size, tumor grade, etc.). This may spare women unnecessary treatment if chemotherapy is not likely to be of substantial benefit.

The Trial Assigning IndividuaLized Options for Treatment (Rx), or TAILORx, was launched to examine whether assigning patients to treatment based on the level of expression in the tumor of genes that are frequently associated with risk of recurrence for women with early-stage breast cancer will lead to the most appropriate and effective treatment. Women recently diagnosed with estrogen receptor and/or progesterone receptor positive, Her2/neu negative breast cancer, which has not yet spread to the lymph nodes, are eligible for the study. This trial is one of the first to examine a methodology for personalizing cancer treatment, and it aims to change the way breast cancer is treated. It should improve the quality of patient's lives by identifying women who are likely to benefit from chemotherapy and those who are not. TAILORx seeks to individualize cancer treatment by using, evaluating, and improving the latest diagnostic tests.

TARGET CONTEXT AND CONDITIONS

TAILORx is sponsored by the National Institutes of Health (NIH), and is coordinated by the Eastern Cooperative Oncology Group (ECOG). Numerous clinical trials groups that perform breast cancer research studies have collaborated in the trial's development and are participating in this study. The study will enroll

over 10,000 women at approximately 700 sites in the United States, Canada, Peru and Ireland. Women will be studied for 10 years, with an additional follow-up of up to 20 years after initial therapies.

Molecular profiling with the Oncotype DX™ test will be used to analyze a specific set of genes within the breast tumor to determine a recurrence score. The recurrence score is a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of the initial diagnosis. Based on their recurrence score, women will be assigned to three different treatment groups in the TAILORx study:

- Women with a recurrence score higher than 25 will receive chemotherapy plus hormonal therapy (the standard of care)
- Women with a recurrence score lower than 11 will receive hormonal therapy alone
- Women with a recurrence score of 11 to 25 will be randomly assigned to receive adjuvant hormonal therapy, with or without chemotherapy.

TAILORx is designed primarily to evaluate the effect of chemotherapy on those with a recurrence score of 11 to 25. The trial will require 4,390 women to be randomly assigned to ensure a statistically valid assessment of the effect of chemotherapy. Because the degree of benefit of chemotherapy for women with recurrence scores between 11 and 25 is uncertain, TAILORx seeks to determine if a validated diagnostic test (Oncotype DX™) will be helpful in future treatment planning for this group.

Long Term Objective: (SRO-3.9) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.9 By 2020, identify two molecular-targeted therapies for disorders of the immune system in children. (Outcome)	*2011*	Complete phenotypic characterization of both patient cohorts. *(Baseline):* Phenotypic characterization of patients is needed in newly formed cohorts.	N/A
	2010	Begin accrual of two patient cohorts presenting in childhood, one with a monogenic autoinflammatory disorder and one with a genetically complex autoinflammatory disorder. *(Baseline):* No single cohort currently has sufficient numbers of patients to identify genetic differences associated with disease.	N/A

BACKGROUND

A number of illnesses affecting the immune system in children tend to run in families. They include relatively common illnesses such as juvenile idiopathic arthritis (JIA) as well as rare conditions such as the recently discovered deficiency of IL-1 receptor antagonist (DIRA). These types of illnesses may present with either excessive or impaired immune responses, and may lead to significant disability and even death. In certain instances, the pattern of inheritance suggests a single underlying gene, while in other cases the pattern is more consistent with the involvement of multiple genetic loci.

Recent advances in human genetics permit the identification of causative genes both for monogenic and polygenic diseases. The products of such genes present potential opportunities for the development of new therapies that may appropriately attenuate pathologically excessive activity of the immune system, or augment immune responses that are deficient.

Prevalence/Incidence

Although there are no data on the overall prevalence of immunologic diseases in children, some of the more common illnesses, such as JIA, are seen in as many as 0.1% of the pediatric population.

Disease Burden

While the specifics vary with the individual diseases, the immunologic diseases of childhood often leads to significant absence from school, disruption of parental work schedules, physical disability, and sometimes even death.

Rationale

Molecular genetic studies of children and families with disorders of the immune system could result in the identification of molecules that can be the targets of novel treatments. For example, if studies indicate that a specific molecule is responsible for excess inflammation in a particular illness, then inhibitors of that molecule may reduce disease burden. In some cases, these novel treatments might entail the use of already available drugs or biologics for previously unrecognized indications, while in other cases the treatment may be totally new. This process might also lead to the development of better therapies for other immune-mediated illnesses that share abnormalities in the same pathways. Such molecular discoveries have the potential of bringing

effective treatments to patients for whom there is currently no treatment, or developing new treatments that are more specific and have fewer side effects than current therapies.

Two recent examples of the success of this approach are neonatal-onset multisystem inflammatory disease (NOMID) and the deficiency of IL-1 receptor antagonist (DIRA). NOMID is characterized by daily fevers, skin rash, bone deformities, and chronic meningitis that can lead to blindness, deafness, and mental retardation. DIRA presents in infancy with a diffuse pustular rash, inflammation of the bones, and sometimes inflammation of the blood vessels. Both diseases can be fatal. Research conducted at the NIH has demonstrated that these illnesses are caused by two distinct genes, both of which lead to excessive signaling through a molecule called interleukin 1 (IL-1). Researchers have shown that daily injections with an inhibitor of IL-1 nearly completely block symptoms in most patients with either disease. In part based on these successes, this medication is now under study in other illnesses.

TARGET CONTEXT AND CONDITIONS

It is necessary to recruit patients presenting immune system disorders in order to identify specific genetic differences between individuals with disease and those without disease. In the case of relatively rare, single-gene autoinflammatory diseases, patients will be recruited to participate in ongoing natural history protocols at the NIH Clinical Center, and will visit the NIH Bethesda campus one or more times. In the case of more common, polygenic diseases, a national or international consortium will be established to recruit patients and obtain blood samples. Some of these patients will be seen at the NIH Clinical Center, and some will be seen at collaborating centers.

In order to identify genetic variations related to disease risk, the clinical findings must be carefully documented for patients with the relevant disorders. For example, this could include cataloging the clinical symptoms, physical findings, and relevant immunological laboratory tests for patients, in order to define subsets that may be more or less amenable to current treatments. The goal is to confirm the clinical diagnosis, but also to gather sufficient information that may eventually permit correlation of clinical findings with molecular, biochemical, or cellular abnormalities that can be targets for treatment.

In order to select molecules that could be targeted by a new treatment, it is necessary to identify the key pathways leading to disease through the completion of genetic, biochemical, or cellular studies. These may include linkage studies in the case of rare Mendelian disorders and genome-wide association studies (GWAS) for the genetically complex illnesses. In addition, focused immunologic assays, such as flow cytometry, cytokine determination, and gene expression profiling, will be used where appropriate.

The identification of specific molecular pathways helps researchers to develop new therapies tailored to the needs of the patient population under consideration. In some cases, if known molecules associated with inflammation are implicated in pathogenesis, already existing inhibitors or potentiators of these molecules will be tested. In other cases, where no such agents are available, or where the molecular targets are novel, it may be necessary to screen appropriate libraries of small molecules or biologics for activity.

Long Term Objective: (SRO-3.10) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-3.10 By 2017, advance two candidate medications for treatment of substance use disorders to clinical studies in humans. (Outcome)	*2011*	Conduct preclinical studies on one candidate compound. *(Baseline):* TBD FY10 Research Results	N/A
	2010	Identify one potential molecular target and/or potential candidate compound. *(Baseline):* Additional potential molecular targets or candidate compounds are needed to support drug development.	N/A

BACKGROUND

For decades, approaches to treat alcohol use disorders (defined as alcohol abuse and dependence) relied almost exclusively on behavioral therapies. In recent years, more attention has focused on the complementary use of medications for treatment. Although several medications have been approved for treatment of alcohol dependence in the U.S. and other countries, these agents are effective with some patients and less effective with others. This may be explained by the growing body of evidence that indicates response to treatment is influenced by a variety of genetic and environmental factors that vary among individuals. This underscores the need for a greater number and range of available medications.

Treatments for addiction to other substances, with the exception of opioids and nicotine, have also relied mostly on behavioral therapies, with limited success. In fact, there are no FDA-approved medications for the treatment of stimulant or cannabis use disorders, despite the identified need.

Recent developments in neuroscience, such as new brain imaging technologies, and greater understanding of the biological underpinnings of substance abuse and dependence have enhanced the capability to discover and develop a diverse range of pharmacotherapies. Pursuing a diverse range of therapies improves the likelihood of developing effective treatments for substance dependence and paves the way for personalized medicine.

Prevalence/Incidence

According to the 2007 National Survey on Drug Use and Health (NSDUH), there were an estimated 22.3 million persons aged 12 or older (9 percent of the population) meeting criteria for substance abuse or dependence—the great majority of whom did not receive treatment. The number meeting abuse or dependence criteria for alcohol was 18.7 million and for any illicit drug was 6.8 million, with 3.9 million meeting criteria for marijuana and 1.6 million for cocaine. In terms of comorbidity, 3.2 million were classified with dependence on or abuse of both alcohol and illicit drugs, 3.7 million were dependent on or abused illicit drugs but not alcohol, and 15.5 million were dependent on or abused alcohol but not illicit drugs.

The Centers for Disease Control and Prevention (CDC) report that excessive alcohol consumption is the number-three cause of preventable death in the United States. The WHO also ranks alcohol third among preventable risk factors for premature death in developed nations. Children also are at risk for alcohol related problems. 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.

Disease Burden

Problems related to alcohol use disorders cost U.S. society more than $235 billion each year due to lost productivity, medical costs and other factors based on research published in 2009 on the global burden of alcohol use and alcohol use disorders. Unlike other drugs of abuse, excessive alcohol consumption may induce toxic effects on any organ system in the body. These medical conditions include addiction as well as alcohol-induced organ damage such as liver disease (hepatosteatosis, inflammatory disease, alcoholic hepatitis and cirrhosis), pancreatitis, cardiomyopathy (disease of the heart muscle), fetal abnormalities, and brain damage. Excessive alcohol use is also associated with an increased risk for some types of cancer.

Illicit drug abuse and addiction are also major burdens to society. The Office of National Drug Policy estimated in 2004 that the total overall costs in the United States - including health and crime-related costs, as well as losses in productivity- are $181 billion per year. Moreover, drug use is inextricably linked to the spread of HIV/AIDS and other infectious diseases. This extends beyond needle sharing by injection drug users, to anyone under the influence of drugs (or alcohol), which impair judgment and can lead to impulsive high-risk sex, or to risky behaviors driven by addiction, such as sex for drugs. Staggering as these facts may be, however, they do not fully describe the breadth of the deleterious public health—and safety—impact, which include family disintegration, loss of employment, failure in school, domestic violence, child abuse, and other crimes.

Rationale

Substance dependence is a chronic disease subject to relapse. Current medications used for treatment are not effective for all patients. A variety of genetic and environmental factors contribute to substance use disorders and response to medications. For example, some patients possess a genetic predisposition that influences specific brain systems, such as those regulating stress or rewarding sensations, resulting in molecular and cellular variations. Others are more vulnerable to environmental stimuli. Developing a diverse repertoire of effective medications requires (1) understanding and targeting the fundamental biological and environmental variations of substance use disorders, and (2) increasing the availability of candidate medications for testing.

TARGET CONTEXT AND CONDITIONS

Three strategies have been identified that are critical to identifying candidate medications for treatment of substance use disorders, representing the natural progression of the drug development process. First, NIH will focus on identifying potential molecular targets and designing and selecting medications that merit drug development. A broad range of potential molecular targets, e.g. cellular receptors, intracellular sites and metabolic processes, will be investigated and a wide spectrum of compounds will be analyzed, including those currently in use for treatment of other disorders. Second, once a compound has been identified against a promising target, NIH will test the candidate compound in preclinical studies using animal models that mimic one or more aspects of a substance use disorder. Third, compounds that show promise in the preclinical stage will be advanced to establish proof-of-concept in humans. NIH will utilize a network of clinical trial sites to advance lead compounds to early proof-of-concept trials in humans. As potential compounds are identified and tested in humans, it will become increasingly important to identify the characteristics of patients who are most likely to benefit from the compounds. When feasible, NIH will use a pharmacogenetic approach to identify the genetic variations of individuals who are most responsive to certain compounds and the results could be used to inform further drug development.

NIH will continue to collaborate with the pharmaceutical industry in the development of medications. This includes encouraging the pharmaceutical industry to screen proprietary compounds in NIH-supported preclinical models of substance use disorders, testing promising proprietary compounds in NIH's clinical trials network, and advancing lead compounds from the NIH early proof-of-concept studies through the more extensive clinical trials that are required to develop compounds into medications.

Long Term Objective: (SRO-4.3) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.3 By 2009, evaluate the safety and efficacy of two new treatments for nonalcoholic steatohepatitis (NASH) in adults. (Outcome)	*2009*	Complete goal of evaluating the safety and efficacy of two novel treatments for NASH in adults. *(Baseline):* (FY08) Outcome data collected from (# TBD) patients in PIVENS trial	Vitamin E was found to be superior to placebo for the treatment of NASH in adult, non-diabetic subjects. Pioglitazone did not meet the pre-specified level of significance for the primary endpoint and resulted in weight gain, but it is superior to placebo in improving other key histological features and liver enzymes. Neither drug improved fibrosis scores over the duration of the study. (Target Met)
	2008	Retain/collect outcome data from greater than 85% of the participants in PIVENS to assess liver function. *(Baseline):* (FY07) 247 patients enrolled in PIVENS	To date, greater than 91 percent of the participants in the PIVENS clinical study have been retained and outcome data collected to assess liver function. (Target Met)
	2007	Complete total enrollment of 240 participants in PIVENS randomized clinical trial to evaluate the safety and efficacy of two new treatments for NASH in adults. *(Baseline):* (FY06) 176 participants of proposed 240 enrolled (73%)	NIH completed enrollment of 247 participants by January 2007. (Target Met)

Data Source and Validation
A Randomized Controlled Trial of Pioglitazone or Vitamin E for Nonalcoholic Steatohepatitis (PIVENS) Hepatology 2009;50(4 Suppl), Abstract LB2. Additional information is available from the NIDDK Office of Scientific Program and Policy Analysis More information on the NASH study can be found at: Nonalcoholic Steatohepatitis Clinical Research Network http://www.jhucct.com/nash/

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and the Measure has been Achieved. Clinical trial results successfully evaluated two different treatments for nonalcoholic steatohepatitis (NASH) in adults. 247 non-diabetic adults with NASH were randomized to receive pioglitazone, vitamin E, or placebo for 96 weeks. Patients underwent liver biopsy before and at the end of the treatment; the primary endpoint was an improvement in liver histology, as defined by a decrease in NAS by 2 points or more. Compared to 19% of patients in the placebo group who met the primary endpoint after 96 weeks of treatment, 43% in the vitamin E group improved and 34% in the pioglitazone group improved. The results demonstrated that vitamin E is superior to placebo for the treatment of NASH in adult, non-diabetic subjects. Pioglitazone did not meet the pre-specified level of significance for the

primary endpoint and resulted in weight gain, but it is superior to placebo in improving other key histological features and liver enzymes.

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is a common liver condition in the United States. NAFLD represents a spectrum of fatty liver conditions that ranges from simple steatosis to the more severe condition known as NASH. By definition, NAFLD occurs in the absence of alcohol consumption. The definitive diagnosis of NAFLD requires a needle biopsy of the liver. Steatosis or simple fatty liver is recognized by the accumulation of fat in liver cells known as hepatocytes. However, some patients who have steatosis also have injured hepatocytes accompanied by inflammation and scar formation that characterize the much more severe condition known as NASH. NAFLD is often associated with elements of the metabolic syndrome, a clinical constellation of obesity, hypertension, insulin resistance, glucose intolerance, and hyperlipidemia, a common and growing public health matter in the United States. The close relationship between the metabolic syndrome and NAFLD represents an opportunity to determine the cause or causes of this common liver condition. NASH can have significant medical consequences, eventually lead to scaring of the liver known as fibrosis which may eventually lead to cirrhosis, a severe irreversible condition of the liver. Once cirrhosis has developed, patients are at significant risk for two additional devastating conditions - hepatocellular carcinoma or liver cancer, and end-stage liver failure. At this stage of the disease, only liver transplantation offers any hope for improving the survival of the patient. Approximately 5% of liver transplants are due to end-stage NASH, based on 2004 research on NAFLD, NASH, and liver transplantation.

Prevalence/Incidence

Because of the need for a liver biopsy to diagnose fatty liver, the prevalence of NAFLD is estimated to be approximately 30% of the United States population basedon a 1999 study of NAFLD severity. Many cross sectional studies support this estimate according to 1999 data on cryptogenic cirrhosis. NAFLD occurs in all age groups, and is a growing concern in children given the epidemic of childhood obesity as published in a 2001 article on cryptogenic cirrhosis and posttransplantation NAFLD. NASH accounts for about 10 percent of newly diagnosed cases of chronic liver disease, and ranks as one of the leading causes of cirrhosis in the United States.

Rationale

Given the rising prevalence of obesity in the general population, NASH is likely to contribute to the burden of liver disease in the United States and become even more significant as a cause of liver-related morbidity and mortality. There are no approved treatments for NASH or NAFLD. An effective treatment for NASH - targeting the inflammatory component of the disease - would greatly impact morbidity/mortality and health care utilization associated with this condition.

TARGET CONTEXT AND CONDITIONS

The NIH initiated a randomized clinical trial to evaluate the safety and efficacy of pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with NASH (PIVENS). The target patient recruitment of 240 was exceeded. 247 subjects have been randomized into three arms, and will be treated for 96 weeks with outcome measured by liver biopsy. The trial has significant industry sponsorship through a Cooperative Research and Development Agreement (CRADA).

Long Term Objective: (SRO-4.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.4 By 2011, identify or study additional genes involved in communication disorders in humans and animal models. (Outcome)	*2011*	Identify additional genes involved in communication disorders in humans and animal models. *(Baseline):* (FY10) Successfully mapped one new location (locus) on the human chromosome that contains a human deafness gene and identified one new human deafness gene.	N/A
	2010	Map one new location (locus) on the human chromosome that contains a human deafness gene and identify one new human deafness gene. *(Baseline):* (FY09) NIH-funded scientists have described one new gene involved with human deafness.	N/A
	2009	Identify or describe one or more genes involved with human communication disorders. *(Baseline):* (FY08) NIH has numerous repositories, gene banks, animal models, and data resources for genetics research.	Identified 8 new genetic loci that cause hearing loss and described 3 novel hearing-loss-related mutations in another gene. (Target Exceeded)

Data Source and Validation
The identification of 8 new genetic loci that cause severe to profound hearing loss is reported in this scientific journal article:" http://www ncbi nlm nih.gov/pubmed/19287372 The description of 3 novel hearing-loss-related mutations in another gene is reported in this scientific journal article:" http://www ncbi nlm nih.gov/pubmed/19576567

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and Exceeded with NIH-supported researchers identifying 8 new genetic loci that cause severe to profound hearing loss. The results were reported after researchers analyzed genetic material from 563 large blood-related Pakistani and Indian families that carry severe to profound recessive deafness.

Efficiency

The FY2009 target proposed to identify or describe "1 or more" genes involved with human communication disorders. The NIH-supported researchers exceeded this target, and described 8 new genetic loci that cause hearing loss, and in addition, identified 3 novel hearing-loss-related mutations in another gene.

BACKGROUND

The NIH conducts and supports research and research training in the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. These processes of sensing, interpreting, and responding are fundamental to the way the world is perceived and the ability to communicate effectively and efficiently.

The NIH recognizes that one of the most rapidly developing areas of research is functional genomics, which involves determining the identity, structure, and function of genes. NIH-supported researchers are actively working to understand the genes responsible for human communication disorders. NIH currently supports a broad portfolio of scientists working towards this goal, with the hope of using their knowledge to diagnose, treat, or cure communication disorders.

Prevalence/Incidence

Communication disorders affect the range of the population from birth to adulthood and a compelling need exists for research to address these areas.

Birth and Early Childhood

- A 2003 report on the prevalence of autism in US metropolitan areas show that approximately one out of every 200 American children is diagnosed with autism, a disease that interferes with normal language and social development. Recent studies from 1998-2002 focusing on the epidemiology and related conditions of autism indicate that boys are four times more likely than girls to be born with autism, however, girls with the disorder tend to have more severe symptoms and greater cognitive impairment.
- A Centers for Disease Control and Prevention workshop on early hearing detection and intervention in 1997 indicated that approximately two to three out of 1,000 babies born in the United States have a detectable hearing loss, which can affect their speech, language, social, and cognitive development.
- According to a 1997 report on the prevalence of language impairment in kindergarten children, about eight percent of American children in kindergarten have a disorder called specific language impairment (SLI). These children have difficulty developing and using language. These difficulties affect not only speaking but also reading and writing tasks.
- Through 2005, research reports on statistics of office visits, indicate that middle ear infections (otitis media) are the most frequent reason that a sick child visits the doctor. Pilot studies conducted to investigate the burden of costs for recurrent treatment concluded that the estimated total cost of otitis media in the United States is $5 billion per year. Children with otitis media can suffer temporary hearing loss during the infection as well as during treatment, and some may suffer permanent hearing loss.
- A 1999 report on stuttering concludes that approximately one million American children stutter. Stuttering affects individuals of all ages, but epidemiologic factors and focused research shows that stuttering occurs most often in young children who are beginning to develop language skills, with boys being three times more likely to stutter than girls.
- Approximately five percent of American children entering first grade have noticeable speech (phonological) disorders, ranging from a few substituted and missing sounds to serious impairments that make their speech difficult to understand according to a 1999 article on speech delay prevalence. These speech disorders are about 1.5 times more prevalent in boys than girls. The majority of these speech disorders have no known cause.
- Flavor is the primary determinant of whether children under the age of two eat certain foods. A 2004 study on infant and toddler eating habits indicates that based on taste alone, about one-fourth of American infants and toddlers between seven and 24 months consume no vegetables and about one-fourth consume no fruits on a given day, which has important nutritional consequences.

Adulthood

- Based on results from the 1999-2000 National Center for Health Statistics (NCHS) at the CDC and the National Health Interview Survey (NHIS), approximately 15 percent (32.5 million) of American adults report some degree of hearing difficulty. In addition, there is a strong relationship between age and reported hearing loss: 18 percent of American adults 45-64 years old, 30 percent of adults 65-74 years old, and 47 percent of adults 75 years old or older have a hearing impairment. At all ages, more men (18.6 percent) than women (12.6 percent) report problems with their hearing.
- Based on results from the 1999-2000 National Health and Nutrition Examination Surveys (NHANES), 10% of adults 20-69 years (22 million) in the United States have suffered permanent damage to their hearing from exposure to loud sounds or noise at work or in leisure time activities. The prevalence of noise-induced hearing loss (NIHL) is much higher in men (20% of working age men have NIHL).
- According to a 2008 report from the NIH, nearly one million American adults have aphasia, a language disorder that results from damage to the language centers of the brain, and that can occur after a stroke or other brain injury.
- Epidemiolgic studies conducted in 2005 on swallowing disorders indicated that more than six million adults over the age of 60 have swallowing problems. Many individuals with swallowing disorders, e.g., resulting from stroke are at risk for aspiration pneumonia.
- More than 55,000 Americans, each year, develop cancer of the head and neck, according to 2002 cancer research reports. Treatment for these cancers and other types of cancer may subsequently result in a loss of hearing, balance, or the ability to speak and swallow.
- Based on prevalence data from 2005 US population estimates and the existing Disability Supplement to the National Health Interview Survey (NHIS) and 2005 US population estimates, at least 3.7% of the adult population (almost eight million) report a chronic problem (lasting three months or longer) with balance, while an additional 1.1 percent (or 2.4 million) report a chronic problem with dizziness alone.
- Research data through 2005 on risk factors for falls among community dwelling elderly persons indicated that balance disorders are a major cause of falls by American older adults, and are the most common reason individuals over the age of 75 visits a primary care physician. The patient care cost for these falls is more than $8 billion per year.
- As indicated by 2002 research on prevalence of olfactory impairment in older adults, an estimated 24.5 percent (approximately 15 million) of Americans 55 years old or older suffer olfactory impairment, which increases with age. Approximately 30 percent of Americans between the ages of 70 and 80 and 62.5 percent over age 80 experience problems with their sense of smell. Impairment in olfaction can have serious consequences, such as the inability to detect the foul smelling odorants that are added to natural gas as a warning sign of leaks.
- In occupations with high voice usage, such as teaching, studies have been conducted as recently as 2004 to determine the occupational safety and health aspects. Research indicates that voice problems limit the ability to perform certain tasks at work, result in missed workdays, and can sometimes lead individuals to consider changing occupations.

Rationale

Approximately one in six Americans will experience a communication disorder to some degree in his or her lifetime. For those individuals, the basic components of communication (sensing, interpreting, and responding to people and things in our environment) can be extremely challenging.

Not only do these disorders often compromise health, but they also affect the emotional, social, recreational, educational, and vocational aspects of a person's life. The cost of these disorders in quality of life and unfulfilled potential is substantial. NIH supported research strives to reduce the costs of communication disorders, both direct and indirect, on individuals, families, and society. As the population ages and as survival rates improve for medically fragile infants as well as after injuries and acquired diseases, increases can be expected in the prevalence of communication disorders.

TARGET CONTEXT AND CONDITIONS

NIH-supported researchers are capitalizing on the wealth of knowledge available from the Human Genome Project. Researchers strive to identify and/or describe inherited genetic mutations that cause communication disorders or play a role in susceptibility to conditions that impair communication. Some areas of active investigation include hereditary hearing loss, gene variants that predispose an individual to develop age-related hearing loss or noise-induced hearing loss, genetic mutations that cause syndromes that include hearing loss, balance disorders, loss of the sense of smell and/or taste, or other communication disorders, genes inherited by individuals who stutter, and identification of genes that permit detection of tastants (sweet, sour, salty, bitter) and odors.

NIH-supported researchers are also conducting studies that examine target populations (for example, inbred families that carry deafness genes) to identify regions of DNA that may carry the mutation that causes deafness. The putative mutation-carrying regions are identified and compared with DNA from different families carrying deafness genes to published human DNA sequences found in databases. This type of comparative analysis helps them to more precisely identify which region on the chromosome carries a mutation. The scientists must then sequence the mutated gene from the target population to help identify new genes responsible for hearing and for the maintenance of the ability to hear. When important hearing genes are mutated, hearing is disrupted, resulting in hearing loss. If the studies are successful, researchers will be able to compare normal and mutated hearing genes, and describe how the protein produced by that gene functions in normal and mutated states.

Future NIH supported studies propose to map a new locus on the human chromosome where a deafness gene resides. At present, mapping a deafness locus involves screening families whose members suffer from inherited deafness, and determining if their deafness is caused by a mutation in a region (locus) of the chromosome that is already known, or if it is caused by a mutation in a region that has not been previously identified -- a new deafness locus. Researchers also propose to screen families that suffer from deafness in order to identify one novel deafness gene.

Long Term Objective: (SRO-4.5) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.5 By 2011, identify genetic and environmental factors which predispose to three complex diseases. (Outcome)	*2011*	Identify genetic and environmental factors which predispose to three complex diseases. *(Baseline):* (FY10) Genetic and environmental factors have been identified for one complex disease.	N/A
	2010	Identify genetic and environmental factors which predispose to one complex disease *(Baseline):* (FY09) Genetic and environmental factors which predispose to complex diseases have not been fully identified.	N/A
	2009	Complete genome-wide genotyping for three complex diseases, such as Type 2 diabetes or cardiovascular disease. *(Baseline):* (FY08) Few Genome-Wide Association (GWA) studies completed or replicated.	Genome-wide genotyping for studies of lung cancer, type 2 diabetes, and cardiovascular disease have been completed. Data from the lung cancer and type 2 diabetes studies have been made available to the scientific community through the (dbGaP,). (Target Met)

Data Source and Validation
Landi MT, et al. "A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma." Am J Hum Genet. 2009 Nov;85(5):679-91. PMID: 19836008 http://www ncbi nlm nih.gov/pubmed/19836008 Gene Environment Association Studies (GENEVA) Consortium, http://www.genevastudy.org/ The eMERGE Network, http://www.gwas.org Database of Genotypes and Phenotypes (dbGaP), http://www ncbi.nlm nih.gov/gap

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target has been Met. NIH supported researchers have completed genome-wide genotyping for studies of lung cancer, type 2 diabetes, and cardiovascular disease in the Gene Environment Association Studies (GENEVA) consortium of the Genes, Environment, and Health Initiative (GEI), and of cataracts and HDL-cholesterol levels in the Electronic Medical Records and Genomics (eMERGE) Network Data from the lung cancer and type 2 diabetes studies have been made available to the scientific community through the controlled access process of the Database of Genotypes and Phenotypes (dbGaP), and data from the other three studies will be posted shortly. Together these five studies provide genome-wide genotyping data for over 28,000 individuals for investigation of genetic and environmental factors predisposing to these and other complex diseases.

BACKGROUND

With the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, NIH supported researchers have provided access to a set of research tools that make it possible to find the genetic contributions to common diseases. The tools include databases that contain the human genome sequence, the HapMap, a map of human genetic variation and a set of new technologies that can quickly and accurately analyze whole-genome samples for genetic variations that contribute to the onset of a disease.

Recently made possible by the completion of the HapMap, a Genome-Wide Association (GWA) study is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. Once new genetic associations are identified, researchers can use the information to develop better strategies to detect, treat and prevent the disease.

Researchers have reported considerable success using this new strategy. For example, in 2005, three independent studies found that a common form of blindness is associated with variation in the gene for complement factor H, which produces a protein involved in regulating inflammation. Few previously thought that inflammation might contribute so significantly to this type of blindness, which is called age-related macular degeneration.

Similar successes have been reported using GWA studies to identify genetic variations that contribute to risk of type 2 diabetes, Parkinson's disease, heart disorders, obesity, Crohn's disease and prostate cancer, as well as genetic variations that influence response to anti-depressant medications.

Although genetic variation can contribute to the onset of disease, a person's environment also influences disease susceptibility. Environmental factors such as diet, activity level, and stress, have been linked to common diseases such as cardiovascular disease and diabetes.

Rationale

Recent increases in the incidence of chronic diseases such as type 2 diabetes, childhood asthma, obesity, or autism are unlikely to be due to major shifts in the human genome, and are then most likely to be a result of changes in environments, diets, and activity levels.

Both an individual's genes and environment can increase disease risk, but these risks seldom operate independently. Subtle variations in a person's genetic code may have little effect on their risk of disease unless they are exposed to a specific environmental trigger; conversely, low level environmental exposures most common in this country may have little impact on disease risk unless the person exposed is genetically susceptible. To better understand the processes by which gene-environment interactions cause common chronic diseases, the HHS Secretary proposed the Genes and Environment and Health Initiative (GEI), which will examine these interactions at the level of the individual.

The GEI will have two main components: (1) The Genetics Program, a pipeline for analyzing genetic variation in groups of patients with specific illnesses using a GWA study; and (2) The Exposure Biology Program, an environmental technology development program to produce and validate new methods for monitoring environmental exposures that interact with a genetic variation to result in human diseases. All data from this initiative will be placed in NIH databases and can be accessed by NIH-approved users.

Ultimately, the information and tools generated will be used to generate a better understanding of gene-environment interactions. In disease etiology that can translate into improved health care and early, more effective interventions.

TARGET CONTEXT AND CONDITIONS

The GEI was created to identify genetic factors which predispose complex disease, and then to investigate the

interplay between genetic and environmental factors. An initial step toward understanding genetic factors, which lead to common disease, is to perform GWA studies for diseases of interest. Subsequent analysis will determine how environmental factors impact genetic factors in the course of disease. As of 2007, only a handful GWA studies were completed, and many have not been replicated, an essential step in order to validate the results of the study. The completion of the genome-wide genotyping for complex diseases, such as type 2 diabetes or cardiovascular disease will provide the genetic information that will be investigated in concert with environmental studies.

Long Term Objective: (SRO-4.6) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.6 (RA) By 2012, develop a technology to facilitate patient-controlled, secure image sharing between medical centers and at least one clinic operating in an underserved community. (Outcome)	*2011*	Demonstrate sharing of medical images among at least 4 different medical centers with different image storage systems. *(Baseline):* Under the current standard of care where imaging is hand-carried to physician offices, there are often incompatibility issues across systems with images not integrating with hospital's image database.	N/A
	2010	Develop a patient-controlled, secure, storage system-diagnostic infrastructure to support exchange of medical image information between medical facilities. *(Baseline):* Many of the components needed to develop such a system already exist however, others will need to be developed and a secure, HIPPA compliant, integrated system that adds significant value to the health care enterprise needs to be demonstrated.)	N/A

BACKGROUND

Health care today is delivered to an individual at multiple centers ranging from the doctor's office to the clinic to the medical center. For more optimal care, patient information in the form of health records, laboratory results, and imaging studies could be readily available at all sites of care at the time care is given. This is not currently achieved for imaging studies where image transfer is based on hand-carried CDs and DVDs and suffers from multiple compatibility problems. Incompatible formats complicate moving existing medical images to another center and result in frequent repeating of imaging studies. This unnecessary duplication of imaging studies and, in the case of CT and X-ray imaging, increased exposure to ionizing radiation adds significant risk to the patient and increased cost to the system. Estimates are that as many as twenty percent of imaging studies are unnecessarily repeated.

The imaging research community has been developing a series of standards and protocols for secure and practical sharing of image data between centers. For example DICOM and HL7 have developed widely used standards for structured representation of images and other data. In addition, the Cross –enterprise Document Sharing for Imaging (XDS-I) protocol provides a core structure for transferring images between sites. These standards and protocols could be a foundation on which a robust image sharing system can be constructed. This hypothesis, though, needs to be tested and additional components need to be developed before it can be tested.

Rationale

Medical informatics research has significant potential to impact health care at many levels from personalized medicine to electronic health records. Research on sharing of medical images represents an especially prime scientific opportunity because the state of the technology appears ready to fundamentally alter image sharing and the potential clinical impact is high. The impact value is in multiple areas including improved quality of care, reducing medical errors, decreasing unnecessary duplicate studies, and improving physician efficiency. Clinics in underserved communities have been included in the proposed pilot studies because there are special

needs in this setting and it is essential to address these needs at the outset if developing an approach to image sharing that can be generalized to all appropriate settings.

Recovery Act considerations for selecting this project include creation of jobs for a research program that can realistically accomplish the majority of its goals in two years and that, if successful, can provide significant long-term improvement in quality and cost of health care.

TARGET CONTEXT AND CONDITIONS

There are three coordinated activities associated with this project. Two projects are research projects to support pilot studies of patient-controlled image sharing systems in clinical environments (including Alabama and west Carolina-east Tennessee) that will represent a range of clinical settings from the "high-tech" medical center to the "low-tech" rural clinic. The third project is research that will develop a demonstration project for imaging sharing across established medical centers (UCSF, University of Maryland, Mayo Clinic, University of Chicago, and Mount Sinai Medical Center, NY). This project will also actively develop consensus across the potential users of such a system (radiologists and health care systems) as well as the suppliers of components to such a system (imaging companies, medical Image storage (PACS) companies, etc.) for a set of open standards to ensure interoperability through the active dissemination of the research results.

Long Term Objective: (SRO-4.7) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.7 (RA) By 2011, evaluate at least one novel animal model of type 1 diabetes. (Outcome)	*2011*	At least one well-characterized pluripotent stem cell line derived from a patient with type 1 diabetes will be established. Cell line(s) will be assayed for pluripotency markers, differentiation potential, and characterization of chromosomal integrity. *(Baseline):* Induced pluripotent stem cells (iPSCs) can now be derived from human skin fibroblasts. iPSCs derived from type 1 diabetes patients could be directed to convert to cells thought to be important players in the autoimmune process underlying type 1 diabetes.	N/A
	2010	NOD-scid IL2rγnull embryonic stem cells will be generated as a resource for rapidly generating knock-in and knock-out mice on the immunodeficient NOD-scid IL2rγnull background. *(Baseline):* After years of unsuccessful attempts, the derivation of stem cells from NOD (immunodeficient) mice has recently been reported. It should now be possible to generate transgenic mice on a NOD-scid IL2rnull background that express the major human HLA genes that are important determinant of type 1 diabetes.	N/A

BACKGROUND

Type 1diabetes is a disease resulting from the autoimmune destruction of insulin producing pancreatic beta cells. It is characterized by elevations in blood sugar that may lead to severe and life-threatening complications, including cardiovascular disease, blindness, kidney failure, and nerve damage.

The challenge of finding a cure for type 1diabetes is divided into two issues: 1) the absence of suitable number of pancreatic beta cells for replacement therapy, and 2) the incomplete understanding of the autoimmune attack that destroys them. Patients with type 1 diabetes lack a sufficient supply of beta cells, and if more are supplied by either transplantation or stimulating proliferation of the individual's existing beta cells, the patient's immune system destroys the new beta cells.

Prevalence/Incidence
Based on 2007 CDC data, about 895,000 to 1.8 million people have type 1diabetes. Additional 2007 research estimates that 15,000 people younger than 20 years of age are diagnosed annually with type 1 diabetes.

Disease Burden
Diabetes mellitus is the 7th leading cause of death in the United States (233,619 in 2005). This disease can also result in complications such as heart disease, stroke, hypertension, and nerve damage. It is also the leading cause of kidney failure and non-traumatic lower limb amputation in the United States and of new cases of blindness among working-age Americans. According to the CDC, in 2007, the total cost (direct and indirect) due to diabetes mellitus was $174 billion. Of this amount, $116 billion was due to direct medical costs and $58 billion due to indirect costs such as lost workdays, restricted activity, and disability due to diabetes, according to 2009 CDC data on diabetes prevention and control.

Rationale
While there has been much research on developing beta cell replacement therapies, the molecular mechanisms underlying the events leading to type 1diabetes are still not fully understood. In particular, elucidating the autoimmune process responsible for the destruction of the beta cells is critical to developing effective therapies. One way to better understand what cells and molecules initiate and perpetuate the attack on beta cells is to create experimental mouse models to observe how human diabetes develops, and then pinpoint the molecules, genes, and cells responsible.

TARGET CONTEXT AND CONDITIONS

Through the NIH supported, Beta Cell Biology Consortium (BCBC; http://www.betacell.org/), two Recovery Act-supported projects will produce two key components required to reconstruct components of human type 1 diabetes in the mouse: 1) one project will produce human induced pluripotent stem cells (iPS) derived from type 1 diabetes patients; and 2) the other project will produce novel genetic stocks of "humanized" mice that will permit the reconstruction of key aspects of human autoimmune diabetes in the mouse hosts by using tissues derived from these stem cells, but also by replacing mouse genes coding for key component of the immune system by their human conter-parts. These "humanized" mouse models will be based on an immunodeficient stock of mice (NOD-scid IL2rγnull) that is rapidly gaining acknowledgment by the scientific community as the "gold standard" for human tissue and cell engraftment in animals. To produce mouse models that express key component of the human immune system, embryonic stem cells from the NOD-scid IL2rγnull mice must be created that allow knock-in and knock-out of genes on the NOD-scid IL2rγnull background.

The iPS cells for transplantation into the NOD-scid IL2rγnull mice will be derived from a cohort of human type 1 diabetes patients. Fibroblasts and/or keratinocytes will be isolated from skin biopsies from 10 insulin-dependent and clinically- evaluated type 1 diabetes patients. Multiple iPS cells lines will be derived from the skin biopsies by reprogramming with a defined set of factors using available methodology. The iPS cells will be evaluated by hematopoietic cell differentiation assays, gene expression studies, and flow cytometry.

Long Term Objective: (SRO-4.8) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.8 (RA) By 2011, develop and/or test at least one strategy for improving end-of-life care or palliative care. (Outcome)	*2011*	Complete development and/or testing of at least one strategy for enhancing quality of life through improved end-of-life care and/or palliative care. *(Baseline):* Research strategies supported in FY 2010.	N/A
	2010	Identify at least one strategy, and its core elements, for improving end-of-life care and/or palliative care. *(Baseline):* Preliminary findings in areas of palliative care/end-of-life research such as: pain management, patient/family/clinician communications, and patient decision-making at the end of life.	N/A

BACKGROUND

The life expectancy of the American people has reached a historic high, but along with increased life expectancy comes an increase in the number of people living with, and dying from, chronic debilitating diseases. Prolonged courses of decline at the end of life and inadequate palliative treatment options for those with chronic illness have created an urgent need for better strategies to improve quality of life and the management of symptoms, such as pain, in those with serious illness at any stage of life. Despite an increased focus on this area of research in the last twenty years, significant knowledge gaps remain in the evidence-base related to palliative care, communication, decision-making, and quality of life at the end of life.

Rationale

New, evidence-based, strategies are needed to enhance end-of-life and palliative care. Findings from this research may provide long term public health benefits by advancing knowledge of strategies that improve quality of life and quality of care for those with serious illness and/or who are approaching the end of life. For example, research findings could integrate new strategies for palliative care into the management of children with serious illness, enhance the measurement of symptom severity in critical care environments, develop strategies for facilitating decision-making and communication by clinicians and/or families in end-of-life situations, or test interventions to train caregivers in problem-solving skills for improved symptom management at the end of life. Such findings could reduce symptom burden, improve clinical practice, decrease caregiver burden, or ensure that end-of-life treatment strategies best reflect patient preferences.

TARGET CONTEXT AND CONDITIONS

This research examines multiple aspects of end-of-life and palliative care. For example, one study is attempting to improve our understanding of the behavioral mechanisms underlying racial/ethnic disparities in palliative care outcomes by using a novel technique to study differences in decision-making processes, treatment preferences, and medication adherence in African-Americans and Caucasians with cancer pain. Another study seeks to explore how older patients with advanced cancer communicate their concerns and needs for care, and will compare the decision-making and service utilization of cancer patients who have enrolled in hospice with those who have not. A third study is developing interactive, web-based training materials for clinicians that are

designed to improve the effectiveness of communication between clinicians and patients from diverse populations. A fourth study focuses on improving palliative care of adolescents and young adults with chronic, life-threatening illnesses by developing and integrating enhanced interventions on the principles and practices of palliative care in the training of interdisciplinary clinicians. These studies represent a few examples of the multifaceted approaches being employed to achieve this measure.

Long Term Objective: (SRO-4.9) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.9 (RA) By 2011, enhance the capacity of researchers to investigate genetic causes of disease by DNA sequencing of participants in well-phenotyped cohorts. (Outcome)	*2011*	Deposit results in the database (dbGaP) to enable further research and analysis. *(Baseline):* (Baseline): dbGaP data currently limited to genotyping and phenotypic information.	N/A
	2010	Develop the study protocol and begin the DNA sequencing of participants in well-phenotyped cohorts. *(Baseline):* (Baseline): Sequencing of any part of the genome for large numbers of individuals has not been previously attempted.	N/A

BACKGROUND

Although genome-wide association studies (GWAS) have been successful in identifying high frequency genetic variants of modest effect size that are associated with numerous common complex traits and diseases, including myocardial infarction, stroke, diabetes, obesity, hypertension, chronic pulmonary disease, and anemia. They are incapable of identifying actual disease-causing genetic variants, especially those of lower frequency and potentially larger effects. Finding those variants will require large-scale DNA sequencing of thousands of individuals from well-phenotyped populations. Genotyping has already been conducted for many of the study participants. The next crucial step is to begin to sequence the genomes.

Rationale

Investment of Recovery Act funds will be used to begin to sequence the genomes of the well-phenotyped cohorts in important longitudinal studies supported by the NIH. Because of previous efforts, extensive phenotypic data from NIH-supported population-based studies are already available in dbGaP. Included are not only the phenotypic data acquired through the studies themselves, but also data acquired through investigator-initiated research projects conducted with study participants. Together the populations to be addressed include multiple ethnicities (Caucasian, African American, Hispanics, and Asian American). All together the program will address the genomes of well over 10,000 persons, a population that collectively represents experience with a wide range of common diseases, including myocardial infarction, stroke, other atherosclerotic diseases, heart failure, hypertension, obesity, adult onset diabetes, metabolic syndrome, dementia, osteoporosis, chronic pulmonary disease, anemia, and a variety of clinical traits associated with aging, menopause, thrombosis, and cognitive dysfunction. The result of this effort has the potential to be an important scientific resource; one that will inform and enable further research that should lead to an improved understanding of underlying biological processes and may pave the way for future developments of improved methods of prevention, diagnosis, and treatment of disease.

TARGET CONTEXT AND CONDITIONS

The NIH plans to fund 6 RC2 grants in order to conduct DNA sequencing of the well-phenotyped cohorts for the identification of disease causing variants and understanding biological pathways. Two of the grants will fund sequencing centers. The cohorts to be studied include those from the Framingham Heart Study, the Jackson Heart Study, the Atherosclerosis Risk In Communities (ARIC) study, the Multi-Ethnic Studies of

Atherosclerosis (MESA), the Coronary Artery Risk Development in Young Adults (CARDIA) study, and the Women's Health Initiative (WHI). By initiating the sequencing of the genomes of over 10,000 people, genetic variants of lower frequency can potentially be identified, that also may have large effects in the phenotypes of common diseases. The results will be made widely available in dbGaP, thus enabling further research and analysis and leaving to an improved understanding of disease and biological processes.

Long Term Objective: (SRO-4.10) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.10 (RA) By 2011, accelerate progress toward identifying relevant genomic alterations in 10 tumor types. (Outcome)	*2011*	Complete identification of genomic alterations in 10 tumor types. *(Baseline):* Identification of genomic alterations completed in 3 tumor types.	N/A
	2010	Begin identification of genomic alterations in an additional 8 tumor types. *(Baseline):* Pilot projects have been initiated to identify genomic alterations in 2 tumor types.	N/A

BACKGROUND

Defining the genomic changes involved in cancer is critical to the fundamental molecular understanding of cancer and will improve our ability to diagnose, treat, and prevent cancer. The Cancer Genome Atlas (TCGA) was established as a comprehensive and coordinated effort to understand the molecular basis of cancer through the application of genome analysis technologies. The pilot phase assessed the feasibility of a full-scale effort to systematically explore the entire spectrum of genomic changes in cancer. To date, the TCGA network has reported results on its large-scale, comprehensive study of the most common form of human brain cancer, glioblastoma multiforme, and made available molecular characterization data sets for ovarian cancer.

Rationale

Cancer is a disease of the genes. The total genetic information contained in a cell is called the genome. Many genes are altered in cancer. Understanding the genomic changes that occur in cancer will lead to a better understanding of the disease and to the development of diagnostic tests and drugs for the treatment of cancer. Based on the initial success of TCGA, the National Institutes of Health has decided to build upon this foundation and set a goal of identifying all relevant genomic alterations in 20-25 tumor types by 2014.

The pilot project initiated the characterization and analysis of 2 tumor types. If the rate of genomic characterization remains constant, without Recovery Act support, TCGA would be able to perform similar analyses on 2 types of cancer in the next two years. New Recovery Act support will make it possible for TCGA to identify genomic alterations and perform the analysis on a total of 10 tumor types by the end of 2011, five times the number of tumor types than originally planned. This will allow TCGA to include many major tumor types such as: lung, breast, kidney or colon tumors.

The Recovery Act will support the technological innovation required by TCGA, which will lay the foundation needed to map a wide array of cancers. This research has the potential to enable more effective, individualized approaches for helping each patient with cancer.

TARGET CONTEXT AND CONDITIONS

In this Recovery Act measure, the TCGA network will accelerate progress toward its goal by identifying all relevant genomic alterations in 8 additional tumor types by 2011, allowing 10 to be completed. Sequencing and analyzing the genomes of 10 cancer types will result in many new jobs and allow the continued support of current staff. The measure will also expedite the completion of a number of pilot-phase projects, and selected sites will be required to hire individuals at all levels of the research and development continuum.

The measure will support tissue source sites for the accrual of samples from cancer patients, a biospecimen core resource for the isolation of DNA and RNA from samples, as well as extensive pathology and molecular quality control. Because every cancer type is unique, expansion into additional sites is necessary in order to impact as many cancer patients as possible. The research will be performed by a network of scientists from the most prestigious academic and biomedical research institutions in the United States. The TCGA Network expects to identify genomic changes in common cancers by working as a team to first generate data and then to perform sophisticated analysis on 500 patient tumor samples per tumor type, A data coordinating center will also further develop databases, enhance analytical and data visualization tools, and to make the data available to the research community. The data generated by the Network will be a resource, available to all biomedical researchers, to stimulate further research leading to the development of diagnostic tools and novel drug therapies.

Long Term Objective: (SRO-4.11) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.11 (RA) By 2011, analyze oral cancer genomes using high throughput methods to develop a blueprint of genetic alterations. (Outcome)	*2011*	Analyze 124 additional samples and validate and integrate data to complete blueprint of oral cancer genome. *(Baseline):* 124 samples have been analyzed.	N/A
	2010	Analyze and annotate the genome sequences of 124 samples taken from oral and tongue cancers and normal human tissue. *(Baseline):* Repository of 248 samples ready to be analyzed.	N/A

BACKGROUND

Science is advancing rapidly, and the next generation of technological innovation may greatly accelerate breakthroughs in oral, dental, and craniofacial research. Researchers have already created prototypes for bioengineered tissue replacements and developed powerful molecular imaging tools that provide a new window into complex biological systems about which we continue to learn. This emerging wave of knowledge and tools will accelerate the development of molecular-based oral health care, and thus it is vital that the NIH support a diverse portfolio of research to achieve that end.

Scientists now have the tools to understand health and disease from a powerful systems perspective. Such deep insights will enhance our ability to predict and more effectively manage many oral and dental diseases and craniofacial abnormalities; however, understanding and addressing complex oral diseases will take more than figuring out the molecular pieces of the puzzle. It will require melding these advances with clinical, epidemiological, and bioinformatics approaches to identify diseases at their earliest inception, direct individualized therapies, and predict disease outcomes. The NIH supports a variety of efforts to integrate the basic, clinical, and population sciences to help clinicians devise prevention strategies, early detection and diagnostic tools, and personalized therapies. Oral health research stands to benefit greatly from this complementary and integrated approach.

The NIH supports development of a multifaceted program that integrates several new technologies and methods into a clinical protocol aimed to improve oral cancer detection and survival. Approaches under development include devices to aid in earlier detection, rapid gene-expression measurement tools that assess suspicious lesions removed for biopsy, and integration of screening, diagnosis, and treatment.

Prevalence/Incidence

From 1996-2003, the NIH Surveillance, Epidemiology, and End Results (SEER) Program compiled data that indicated approximately 30,000 Americans are diagnosed each year with cancer that affects the mouth or pharynx with oral and pharyngeal cancers killing about 7600 Americans each year. Overall, oral cancer rates have increased approximately 15% over the last 30 years.

Disease Burden

The SEER program concluded that oral cancers carry a high burden. Treatment is difficult, particularly for the

later stages of the disease, for which the surgery is disfiguring and radiation treatment may result in serious complications. The overall five year relative survival rate for oral cancer from 1996 to 2003 was 60%, low compared with many other cancers. These deaths are particularly tragic because, in most cases, detection and treatment of early stage oral cancer results in much higher survival rates than if the disease is diagnosed and treated at late stages. Despite annual U.S. spending of approximately $3.2 billion on head and neck cancer treatment, which includes oral cancers, relative survival rates have not improved during the past 16 years and remain among the lowest of all major cancers. Oral cancer survival among African American men has actually decreased.

Rationale

The emerging science of genome-wide association studies and other rapidly evolving genome-wide technologies are producing exciting findings in oral, dental, and craniofacial health. This discovery research is aimed at characterizing the oral cancer genome, using state of the art technological approaches. Genomic approaches may yield new insights into the causes and progression of complex conditions, such as oral cancer. Genetic analysis of tumors has proved invaluable in unraveling genetically altered core pathways and key molecules involved in tumorigenesis, the development and growth of tumors. A comprehensive catalog of somatic changes in oral cancer will be a powerful driver for oral cancer research at multiple complementary levels. The research may lead to hypothesis-driven, clinical protocols designed to improve oral cancer detection and survival.

TARGET CONTEXT AND CONDITIONS

Over the last several years, researchers have made significant technological improvements in the emerging science of genome-wide association studies and other rapidly expanding genome-wide technologies. Specific advances led to high throughput sequencing methods that are faster and cheaper than earlier methods. In parallel to the technological developments has been the increasing availability of biological repositories of human tissue samples taken from patients with specific diseases, such as oral cancer. The repositories contain not only the tissue but also information about disease type and stage, treatment received, and treatment outcome. NIH's support of genomic approaches based on improved technologies and well-defined tissue samples will advance our knowledge of the causes and treatment for oral cancers.

Using Recovery Act funds, NIH supported two Grand Opportunity projects that take advantage of technological improvements in genomic analysis and have existing repositories of biological specimens from persons with squamous cell carcinoma in the oral cavity, a cancer in the upper layers of the skin. Normal tissue is also available from the same persons. These two studies will produce information about genetic alterations in unprecedented detail, including mutations, copy number alterations, chromosomal rearrangements, and tumor-specific changes in mRNA and micoRNA profiles. Moreover, the studies will be comprehensive genomic analyses that could advance the field of oral cancer research. This work will be complementary to The Cancer Genome Atlas (TCGA) program, a large, multi-center NIH initiative to characterize the cancer genome, which has not yet investigated squamous epithelial cancers.

Long Term Objective: (SRO-4.12) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-4.12 (RA) By 2011, demonstrate the feasibility of a new therapeutic strategy in a preclinical model of a neurological disease. (Outcome)	*2011*	Demonstrate the feasibility of a new therapeutic strategy in a preclinical model of a neurological disease. *(Baseline):* New therapeutic strategies for spinal cord injury, ALS, SMA, PD, and posttraumatic seizures have been identified but require optimization.	N/A
	2010	Optimize a new treatment regimen for spinal cord injury, a neurodegenerative disease, or posttraumatic seizures. *(Baseline):* New therapeutic strategies for spinal cord injury, ALS, SMA, PD, and posttraumatic seizures have been identified but require optimization.	N/A

BACKGROUND

Hundreds of disorders, both common and rare, affect the nervous system. Together, these diseases afflict people of all ages, cause an enormous burden in lost life, disability, and suffering, and cost billions of dollars each year in medical expenses and reduced productivity from people who have neurological disorders and their caregivers.

Treatments for most neurological diseases are far from adequate, but there are unprecedented opportunities for progress in therapeutics development. In recent years, there have been significant advances in uncovering neurological disease mechanisms and potential therapeutic targets. For example, researchers have identified key genes responsible for a number of neurological disorders, including spinal muscular atrophy (SMA), muscular dystrophy, and inherited forms of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Parkinson's disease (PD), and Charcot-Marie-Tooth (CMT). The molecular and cellular events that follow nervous system injury are also better understood, along with some of the pathways that control nervous system rewiring. There are many strategies now available for modifying disease pathways, as well. Partly as a result of NIH programs, such as the NIH Common Fund Molecular Libraries Screening Network, many academic researchers now can conduct high-throughput screens to identify new drug candidates. New vectors have been developed for delivering therapeutics genes into the brain. Recent discoveries about neural cell development and brain plasticity suggest new possibilities for cell transplantation therapy.

Rationale

The NIH solicited and awarded Recovery Act grants to initiate new therapeutic approaches to treating neurological diseases. A subset of these projects focus on small-molecule drug development. Screens are underway for new drugs to treat specific subtypes of CMT, FTD, and muscular dystrophy. New drug candidates and formulations are being tested in animal models for traumatic brain injury, epilepsy, muscular dystrophy, and PD, among other diseases.

A number of Recovery Act grants are supporting the development of "biologics," such as gene, cell, or hormone-based therapies. A current project is refining a gene delivery strategy for ALS and SMA, first in mouse models and then in non-human primates. Another is exploring the possibility of restoring bladder function in individuals with spinal cord injuries by transplanting neural precursor cells just below the injury site. A receptor protein that blocks an inflammatory pathway is also being investigated as a therapy for spinal cord injury. Projects are underway to test new gene therapy approaches for Huntington's disease and Parkinson's disease in animal models. The NIH is also funding a project to evaluate the feasibility of hormone-based therapies, therapeutic genes, and small-molecule compounds in cell and animal models of spinal and bulbar muscular atrophy.

All of the Recovery Act projects are to be completed within two years. Researchers who demonstrate that their therapeutic approaches are feasible can apply for funding through the translational research program to complete all of the preclinical studies required by the Food and Drug Administration (FDA) before initiating clinical testing.

TARGET CONTEXT AND CONDITIONS

Four of the Recovery Act projects will be optimizing their treatment regimens in the first year. The investigators working on the spinal cord injury project are defining the optimal donor cell population and frequency of transplantation. The group developing gene therapy for SMA and ALS is optimizing the gene delivery vector and exploring the ideal time window for treatment. For one of the epilepsy drug development projects, the first year target is to identify the most effective dose and time of treatment for the new drug TL14077. One of the PD projects involves optimizing the chemical structure of the lead compound and finding a dose range that is both neuroprotective and well-tolerated.

Long Term Objective: (SRO-5.2) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.2 By 2010, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus). (Outcome)	*2010*	Determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus). *(Baseline):* Patient follow-up data collection completed.	N/A
	2009	Complete goal of determining the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus). *(Baseline):* (FY07) The study has completed recruitment and is currently in the follow-up phase.	Final data analyses to determine the efficacy of atorvastarin treatment are underway. The final analysis was slightly delayed due to patient follow-up issues. (Target Extended)
	2008	Implement two strategies to attain study medication compliance rate of at least 80 percent. *(Baseline):* (FY06) Previous research suggests that compliance among pediatric patients receiving treatment for chronic illness can be as high as 70% due in part to factors such as family support and severity of symptoms	The sites implemented two strategies and achieved a rate of 81.4 percent study medication compliance, exceeding the goal of 80 percent study medication compliance. (Target Met)
	2007	All clinical sites will be actively enrolling/following pediatric lupus patients, to result in an overall average recruitment rate of 3 new patients per month. *(Baseline):* (FY06) Number of Clinical Sites: 20	The sites exceeded their overall average recruitment goal of 3 new patients per month, by enrolling an average of 4.2 new patients per month. This rate increased steadily from September, 2003 to November, 2006, to an average of 13.5 new patients per month at the end of the enrollment period. (Target Met)
	2006	Complete baseline data analysis on the enrolled patients, including any adverse events. *(Baseline):* (FY04) 14% of patients are enrolled and data analysis of enrolled patients is complete, including any adverse events	Baseline characteristics of the study population as of August 2006 have been analyzed and the results were shared with the Study Data and Safety Monitoring Board. (Target Exceeded)

Data Source and Validation
Director, Division of Skin and Rheumatic Diseases NIH/NIAMS/Extramural Program One Democracy Plaza 6701 Democracy Blvd., Suite 800 Bethesda, MD 20892-4872 Tel. 301-594-5032

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 measure completion is being Extended to FY 2010. Although recruitment was a challenge throughout the measure, progress was steady. The research design included follow up with patients three years after recruitment, which delayed final year data-gathering for the study. Longitudinal follow-up is challenged by some loss of patient continuity with treatment and insuring maintenance of patient contact, which affects final data analysis. Final data gathering has been completed and final study results will be available in Spring. No additional government funds will be needed to complete the study.

Researchers are using carotid artery ultrasound measurements as the primary endpoint of the study. Statin efficacy will be determined using a mixed random-effects regression model to compare the rates of change in intima-media thickness (IMT) over time between the two treatment (atorvastatin and placebo) groups. These findings are expected to determine the role of statins in preventing progression of atherosclerosis in children with 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 works 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.

TARGET CONTEXT AND CONDITIONS

A five-year study, known as the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythymatosus) trial, plans to test children diagnosed with systemic lupus erythematosus (SLE, or lupus). The double-blind, placebo-controlled trial randomizes patients to receive either statins or a placebo for 36 months. Atherosclerosis is measured at baseline and at six-month intervals using ultrasound imaging.

This is a unique study designed to investigate a clinically challenging disease: the occurrence of atherosclerosis in children with lupus. 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 they also 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). Initial plans included enrollment of a total of 280 children with recent-onset lupus, thereby establishing the largest cohort of pediatric lupus patients ever prospectively studied in the United States. There is limited information regarding the overall compliance with study medication in children and adolescents in clinical trials of long duration for chronic diseases. Compliance with study medication is important to sustain low levels of blood lipid profiles and to diminish the likely inflammation associated with the progression of arterial wall thickening in atherosclerosis. The development of strategies to better track compliance will provide valuable insights into this and other clinical trial designs.

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. For APPLE, this included (1) complete training and full certification of sonographers who are involved in establishing the degree of atherosclerosis in the children participating in the study, and (2) training for the Interactive Voice Response System that is used for trial randomization and drug kit assignment, which takes advantage of novel and efficient technologies that improve trial conduct and cost-effectiveness.

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 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 data analyses on enrolled patients were completed, including any adverse events. Data on monitoring study progress and adverse events are routinely provided from the clinical sites to NIH. Clinical sites send weekly reports to the Clinical Trials Manager and monthly calls are conducted to coordinate efforts between the sites. The coordinating center generates monthly data reports, which are shared with the site coordinators and investigators during the monthly calls. Strategies to encourage data timeliness are discussed during these calls. Follow up with individual coordinators is conducted, as needed.

Interim analysis of the data revealed that repeated measurements of fat buildup in the blood vessels varied less than researchers had expected (when they initially estimated the number of participants that would be needed to obtain a statistically meaningful result). Because this greater precision leads to a smaller standard error for statistical analyses, the investigators were able to decrease the sample size from 280 to 220 and complete recruitment ahead of schedule.

Enrollment was completed in November 2006, and participants continue to be followed. Strategies to retain participants in the study include holiday cards, newsletters and a compensation plan. The plan was distributed

among sites to encourage participant compliance and long-term retention. Additionally, it promotes positive reinforcement of preventive care concepts related to cardiovascular health and lupus. Retention efforts and plans continue to be discussed during the monthly calls. Therefore, the NIH funding components participating in this goal are fully committed to supporting efforts toward its completion as outlined in the contract and consistent with current NIH fiscal year policies in effect at the time of funding.

Long Term Objective: (SRO-5.3) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.3 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. (Outcome)	*2009*	Complete goal of expanding 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. *(Baseline):* Chemical libraries developed by CMLD centers in high-throughput biological screens were successfully used in FY 2008. The development of libraries and efforts to make them available for screening thus continued into FY 2009 in order to meet or exceed the stated overall goal of discovering 10 new and unique chemical structures that could serve as the starting point for new drugs.	The chemical libraries developed by CMLD centers were successfully used in high throughput biological screens in FY09. The range of available methods used to create, analyze, and utilize chemical libraries was expanded, resulting in the identification of 10 new and unique chemical structures that could serve as starting points for new drugs. (Target Met)
	2008	Use chemical libraries in high-throughput biological screens. *(Baseline):* (FY06) CMLD libraries under development.	The four Chemical Methodologies and Library Development (CMLD) centers synthesized chemical libraries that were provided to collaborators for high-throughput biological screening. (Target Met)
	2007	Begin development of predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds. *(Baseline):* (FY05) Current toxicity prediction models may fail to detect human safety problems with many new chemical agents.	Supported the development of predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds. (Target Met)

Measure	FY	Target	Result
	2006	Begin development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products). *(Baseline):* (FY03) Due to the expense and the time required to isolate, purify, and identify new compounds, few pharmaceutical companies include natural products in their drug discovery programs.	Supported the development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products). (Target Met)

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SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The 2009 performance target, to expand the range of available methods used to create, analyze, and utilize chemical libraries, was successfully MET. The libraries are being used to discover molecules that could lead to new medications. Specifically these chemical libraries led to the discovery of more than 10 new and unique chemical structures that could serve as starting points for the development of new drugs.

The process included the development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products). Predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds were developed. Four Chemical Methodologies and Library Development (CMLD) centers developed methodologies and synthesized the chemical libraries that were provided to collaborators for high-throughput biological screening.

The chemical libraries developed by CMLD centers in high throughput biological screens were successfully used in FY08. The range of available methods used to create, analyze, and utilize chemical libraries was expanded to find more than 10 new and unique chemical structures to serve as starting points for new drugs.

BACKGROUND

Rationale

Many 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. One approach is to increase the efficiency of isolating and screening natural products. Another 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.

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.

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.

TARGET CONTEXT AND CONDITIONS

A total of four Centers of Excellence in Chemical Methodologies and Library Development have been established and five new multi-institutional "Groups" and seven planning grants were funded to develop natural products drug discovery programs under the International Cooperative Biodiversity Groups Program. In FY 2004 and beyond, these centers and "Groups," as well as new initiatives to be supported through the NIH Common Fund Molecular Libraries and Molecular Imaging Program, will focus on (1) developing innovative methods of synthesis and library creation; (2) increasing the sharing of knowledge among researchers, (3) increasing access to research results by exploring and developing systematic means to inventory newly created chemical libraries and methods of synthesis, (4) biologically screening the libraries and inventorying the

outcomes of these screening procedures as new libraries are created, and (5) coordinating and setting priorities for these initiatives through the use of scientific advisory groups.

Long Term Objective: (SRO-5.6) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.6 By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction. (Outcome)	*2009*	Complete goal of identifying at least two new medications to be further developed and tested for the treatment of tobacco addiction. *(Baseline):* (FY07) 2 of 3 new medication candidates identified for tobacco addiction treatment are being tested in clinical trials.	Four medications were identified as possible treatments, and are now in clinical trials or protocol development --a glycine antagonist GW468816, a D3 dopamine antagonist called 809, a GABA medication Pregabalin, and a nicotine vaccine NicVAX. (Target Met)
	2008	Analyze results from the FY 2006 clinical trial (Phase II) to determine whether an additional clinical trial should be initiated. *(Baseline):* To be determined by results in FY06 and FY07.	Analysis of the Phase II nicotine vaccine trial showed that the vaccine assisted smokers to quit, supporting continuation of the project. (Target Met)
	2007	Develop and test 1-2 potential new compounds for tobacco addiction in animal models. *(Baseline):* (FY06) Preclinical work on compounds that target nicotinic or GABA receptors is continuing based on preliminary positive results.	Four candidate medications are now being tested. (Target Exceeded)
	2006	Begin at least one clinical trial of a candidate medication for tobacco addiction. *(Baseline):* (FY05) NicVAX shows promise in pre-clinical or early clinical trials.	Three candidate medications are being tested in: Phase II clinical trials, multi-site trials, and human laboratory studies. (Target Exceeded)

Data Source and Validation
NABI Biopharmaceuticals News Release Boca Raton, FL., November 7/PRNewswire-FirstCall: "Nabi Biopharmaceuticals Announces Successful Completion of NicVAX(R) Phase 2b Trial: Drug Shows Statistically Significant Rates of Smoking Cessation and Continuous Long-Term Smoking Abstinence at 12 Months" . http://phx.corporate-ir net/phoenix.zhtml?c=100445&p=irol-newsArticle&ID=1074098&highlight= Clinical Trials.gov: Efficacy of NicVAX in Smokers Who Want to Quit Smoking http://clinicaltrials.gov/ct/show/NCT00318383?order=1 http://www nida nih.gov/newsroom/09/NR10-30 html. Validation Contact NIDA Office of Science Policy and Communications 301-443-6036

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and the Measure was Achieved. Four compounds were identified and are in various stages of clinical development:

- A nicotine vaccine for smoking cessation has shown efficacy in early clinical trials, and is now progressing to a Phase III clinical trial.
- The D3 dopamine antagonist, called 809, was identified as appropriate for clinical testing, and a protocol is now under development. It is anticipated that subject enrollment will begin in mid-2010;
- A study of Pregabalin, a GABA medication, is ongoing and near completion. Pregabalin is being tested in humans for its ability to decrease smoking and cue reactivity – which often prompts relapse; and
- The glycine antagonist, GW468816, was compared to bupropion or placebo for efficacy in a smoking relapse prevention clinical trial. Although all data have been collected, data analyses are not yet complete;

Measure

At the completion of this measure, four medications were identified for further development and/or testing as possible treatments for nicotine addiction: a glycine antagonist GW468816, a dopamine D3 antagonist (809), a GABA agonist (Pregabalin), and a nicotine vaccine (NicVAX). Research on these medications is on-going and each is in clinical trials or various stages of protocol development.

The most successful of these was the nicotine vaccine (NicVAX) for smoking cessation that showed efficacy in early clinical trials designed to assess its safety, immunogenicity, and clinical efficacy, and to determine the dose and scheduling of immunizations required for the Phase III trial. The concept for the vaccine is to induce the production of antibodies to nicotine, thereby reducing its entry into the brain, and blocking its rewarding and other psychoactive effects. This strategy could facilitate smoking cessation, and prevent relapse--a major stumbling block for the great majority of smokers. The results of the Phase II and IIb trials showed efficacy among smokers who achieved high antibody levels—even following extended follow up periods of 6 and 12 months. The Phase III trial is being initiated now, with partial support from NIH using Recovery Act funds.

Two other compounds that were tested have been ruled out—selegiline (an MAO inhibitor) did not show efficacy in a clinical trial; and tiagabine, a GABA agonist, received an FDA warning for side effects, making it a less than optimal target medication. Pregabalin (another GABA agonist) has been substituted and is continuing in human laboratory studies to assess its effects on cue-induced relapse and smoking behavior.

Advances or Other Highlights

Based on the results of earlier pre-clinical and clinical research, a clinical trial was designed and conducted as to assess the safety, immunogenicity, and clinical efficacy of a nicotine vaccine (NicVAX) among smokers, and to determine the dose required for the Phase III trial. The hypothesis is that vaccination will induce the production of antibodies to nicotine, thereby reducing its entry into the brain, and blocking it's rewarding and other psychoactive effects. If successful, this strategy could facilitate smoking cessation, and prevent relapse--a major stumbling block for the great majority of smokers. The completed Phase IIb clinical trial found a 24.6% continuous abstinence rate at the 6 month time point in subjects who achieved a high antibody response, compared to 14% for placebo. The 12-month data showed that one specific vaccination schedule with a high dose of vaccine yielded a better antibody response, associated with a significant increase in the percentage of patients who remained abstinent (compared to placebo). The Phase IIb clinical trial showed positive results for the safety, immunogenicity, and clinical efficacy of NicVAX, and determined the optimal dose and schedule of vaccination for a pivotal Phase III trial. This work is continuing with partial support using Recovery Act funds to conduct a phase III clinical trial.

BACKGROUND

Tobacco use in the United States is a major cause of death and disability. Approximately 440,000 deaths in the U.S. each year are attributed to cigarette smoking as reported by the 2008 CDC Morbidity and Mortality Weekly Report for the years 2000-2004. The high failure rate reported for smoking cessation efforts (75-80%) challenges health care professionals to explore innovative approaches to treating the highly addictive behavior of tobacco use according to the 2000 US Surgeon General's report on reducing tobacco use**.**

The agent largely responsible for maintaining tobacco addiction is nicotine. In addition to animal studies that have shown the addictive properties of nicotine, studies in humans show that smokers adjust their smoking behavior to maintain a relatively stable concentration of nicotine and that the reinforcing effects of nicotine are blocked by pretreatment with the nicotinic receptor antagonist, mecamylamine. Nicotine addiction perpetuates itself by enhancing the release of multiple neurotransmitters to produce stimulation, pleasure, and reward. Tolerance to elevated nicotine levels develops over time, as does the dependence upon nicotine to maintain brain function. Withdrawal symptoms after abstinence result from a return to subnormal levels of some of these neurotransmitters. Withdrawal symptoms, such as depressed mood, anxiety, insomnia, irritability, difficulty concentrating, increased appetite, and decreased heart rate, usually peak at one week after abstinence and taper off over time. Relapse to tobacco use is often associated with exposure to cues that have been previously associated with nicotine, which can elicit craving for months, or even years, after tobacco cessation.

Besides behavioral interventions, the Public Health Service Consensus Panel on Clinical Practices Guidelines has recommended three primary types of pharmacotherapies for treating tobacco use and addiction: nicotine replacement therapy (NRT) with nicotine gum, patch, inhaler, or nasal spray; bupropion sustained release (SR), and varenicline. NRT works by supplying an alternate source of nicotine that has a much slower rate of absorption than the nicotine found in cigarette smoke, hence reducing the potential for its abuse. A meta-analysis on the efficacy of NRTs published in 1994 showed that each NRT increased the odds of smoking cessation by 1.5 to 2-fold compared to control conditions. Bupropion SR (Zyban), an inhibitor of norepinephrine and dopamine reuptake, also interacts with nicotinic receptors, and has been approved by the FDA for use in both smoking cessation and treatment of depression (under the trade name Wellbutrin). Clinical trials suggest that bupropion SR may be more effective than NRT for smoking cessation. In a study that compared nicotine patch, bupropion, or bupropion plus patch to placebo control, the 12-month cessation rates were 15.6 percent in the placebo group, as compared with 16.4 percent in the nicotine-patch group, 30.3 percent in the bupropion group, and 35.5 percent in the group given both bupropion and the nicotine patch, as found in a controlled trial published in 1999. Varenicline (under the trade name Chantix), is a partial agonist at the alpha4beta2 nicotinic receptor site that received FDA approval in May 2006. In a 2006 study that directly compared varenicline, bupropion and placebo, 23%, 15% and 10% of study participants, respectively, were continuously abstinent to 52 weeks. As was noted earlier, and again in more recent research presented in 2009 on the comparative effectiveness of smoking cessation pharmacotherapies, combination use of these medications may increase successful tobacco cessation**;** however, new medications and approaches are clearly needed to help the large percentage of tobacco-addicted individuals who do not respond to currently available treatments**.**

Prevalence/Incidence

Forty-two years after the Surgeon General's first report on smoking and health, tobacco use continues to pose an enormous public health threat to the United States and the world**.** In 2008, the prevalence rate of current cigarette smoking by adults among the different states comprising the United States was 20.8% according to data for 2008 as reported by the CDC in 2009. This prevalence rate is substantially higher than the nation's year 2010 Healthy People goal of 12% as shown by data in the 2000 US DHHS report on tobacco use. (In 2007 the highest reported rate for a minority sub-group of the population (American Indian or Alaska Native) was 32.4%, and prevalence rates for youth are also very high according to CDC report in 2008 on trends in smoking cessation among adults.

Disease Burden
Cigarette smoking causes approximately 440,000 deaths annually in the United States, or more than 1,000 deaths per day. The annual economic cost (from medical expenses and lost productivity) attributable to tobacco use in the United States is approximately $193 billion (based on data from 2004-2006). The cost of exposure to secondhand smoke was estimated at $10 billion per year according to a 2005 CDC Morbidity and Mortality Weekly report on smoking-attributable mortality for 2000-2004.

Rationale
Tobacco addiction is a preventable cause of disease and death. Therefore, it is crucial that more effective treatments for this condition be developed. Despite almost two decades of tobacco treatment research, treatment options for tobacco addiction remain limited and only moderately effective.

Modifying existing compounds to increase their selectivity is one promising strategy for the development of new medications for smoking cessation. As mentioned previously, the nicotinic receptor antagonist mecamylamine has been shown to block the reinforcing effects of nicotine. Its use as a smoking cessation agent, however, is hampered by its peripherally mediated side effects, possibly due to its nonselective action at multiple nicotinic receptor subtypes. Therefore, the development of nicotinic receptor subtype selective antagonists may prove useful for treating tobacco addiction.

Another promising avenue for the development of novel medications is the development of a nicotine vaccine. If successful, this approach would elicit the formation of antibodies that would bind nicotine and prevent it from crossing the blood-brain barrier and reaching the brain. Pre-clinical trials have demonstrated the feasibility of this strategy for reducing nicotine uptake in the brain, and attenuating its behavioral and cardiovascular effects. A vaccine has now been developed and tested in humans. It was shown to be safe and well tolerated in Phase I studies, and showed efficacy in Phase II and Phase IIb clinical trials in those smokers who generated a sufficient antibody response to the vaccine. A Phase III clinical trial is needed to further determine the efficacy of this vaccine as a treatment for tobacco addiction. If proven effective, the nicotine vaccine could be a novel approach to improve smoking cessation rates and prevent relapse.

TARGET CONTEXT AND CONDITIONS

Knowledge gaps hinder the ability to treat tobacco addiction optimally. NIH supported research to identify new medications and targets to improve treatment. The basic (pre-clinical) and clinical research currently being conducted to identify new and better treatment options, included:

Pre-clinical approaches: To identify new compounds for potential use as smoking cessation medications, several studies are being supported that use medicinal chemistry to modify existing compounds to increase their selectivity for their targets (e.g. selective nicotinic receptor antagonists) and to evaluate these compounds in animal models of nicotine self-administration, withdrawal, and nicotine-induced reinstatement (relapse prevention).

Clinical studies of a Nicotine Vaccine (NicVAX): Based on the results of earlier pre-clinical and clinical research, this project a Phase IIb trial was designed and conducted as a proof of concept study to assess the safety, immunogenicity, and clinical efficacy of NicVAX among smokers, and to determine the dose for the pivotal Phase III trial. The hypothesis is that vaccination will reduce the reinforcing effects of nicotine and result in smoking cessation, as well as be effective in preventing smoking relapse.
The Phase IIb trial trial was a multi-center, randomized, double-blind, placebo-controlled study to assess efficacy in 301 heavy smokers who wanted to quit. The purpose was to determine whether vaccination would result in a higher continuous abstinence rate than without it. The primary measure of outcome was eight weeks of continuous smoking abstinence from weeks 19-26 (following the first vaccination) of the study. At the six-month time point, a 24.6% continuous abstinence rate was found in high antibody responders compared to 14% for placebo. The 12-month data showed that one specific vaccination schedule with the high dose of vaccine

yielded a significant increase in the percentage of patients who could remain abstinent (compared to placebo injections).

Clinical trial of a Glycine Antagonist: This clinical trial compared a novel glycine antagonist to bupropion or placebo for effectiveness in smoking relapse prevention. It started with an 8-week, open smoking cessation intervention in adult smokers with nicotine replacement therapy (NRT) and a behavioral intervention. Participation was limited to females, with males excluded at the request of the FDA. Those participants who demonstrated 7-day point prevalence abstinence after 7 weeks open label treatment with NRT were eligible to enter the 8-week, double-blind, placebo-controlled, relapse prevention trial which had follow-up at the 6 month mark. The primary outcome measure was prevention of smoking relapse. Of the 263 subjects that enrolled in the open treatment phase, 99 continued into the 8-week relapse prevention trial. Of those, 64 completed the 8-week trial and 38 completed the 6 month follow up. Although all data have been collected, data analyses are not yet complete and data have not been published.

Long Term Objective: (SRO-5.7) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.7 By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy. (Outcome)	*2010*	Validate and compare 3 imaging methods of assessing lung cancer response to therapy. *(Baseline):* Preliminary analysis of results from FDG/FLT-PET lung cancer trial initiated.	N/A
	2009	Initiate accrual in FDG/FLT-PET comparison lung cancer trial. *(Baseline):* (FY08) Performed final analysis of test-retest reproducibility of functional imaging scans.	Accrual has been initiated in this trial which is being expanded to a multi-site trial. (Target Met)
	2008	Correlate patient outcome data from the lung cancer therapy trial with serial functional imaging scan results to determine the efficacy of this imaging technique. *(Baseline):* (FY06) Performed preliminary analysis of test-retest repeatability data from 1st year of trial.	One lung cancer imaging trial will be completed within 6 months and interim results have been submitted for presentation. Reproducibility for two techniques has been evaluated. Another trial will open for patient accrual this fall. (Target Met)
	2007	Initiate lung cancer therapy trial with serial functional imaging scans and perform preliminary analysis of test-retest repeatability data from 1st year of trial. *(Baseline):* (FY05) Test-retest (repeatability) data not currently obtained in a standardized manner.	Launch of the public-private partnership responsible for conducting the lung cancer therapy trial was delayed, which led to delays in initiating the study and collecting test-retest repeatability data. Preliminary analysis of the test-retest repeatability data was conducted in 2007. (Target Met)
	2007	Perform additional analysis of test-retest repeatability data from 1st year of trial. *(Baseline):* (FY05) Trial not complete.	Additional analysis of patient data from the FDG-PET lung trial has been conducted. (Target Met)

Measure	FY	Target	Result
	2006	Initiate lung cancer therapy trial with serial functional imaging scans and perform preliminary analysis of test-retest repeatability data from 1st year of trial. *(Baseline):* (FY05) Test-retest (repeatability) data not currently obtained in a standardized manner.	Launch of the public-private partnership responsible for conducting the lung cancer therapy trial was delayed, which led to delays in initiating the study and collecting test-retest repeatability data. Preliminary analysis of the test-retest repeatability data will be conducted in early 2007. (Target Extended)

Data Source and Validation

Trial completed accrual: http://www.clinicaltrials.gov/ct2/show/NCT00083083 and http://www.acrin.org/TabID/155/Default.aspx
Newly initiated multicenter clinical trial comparing FDG/FLT: http://www.clinicaltrials.gov/ct2/show/NCT00963807
WIKI for imaging has links to the various phantom collections for public use: https://wiki nci.nih.gov/display/Imaging/RIDER

The quantitative data links to NBIA
https://imaging nci nih.gov/ncia/home.jsf
Download on NBIA by searching Collection name: RIDER Lung CT and Phantom

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SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. Accrual has been initiated in the FDG/FLT-PET comparison lung cancer trial, as part of the validation and comparison of 3 varying functional imaging methods that could serve as more

sensitive approaches to the measurement of early drug response than standard or conventional anatomic imaging techniques that are based on significant tumor shrinkage. The availability of such sensitive measurement methods or modalities could significantly streamline clinical trials and, hence, accelerate new drug approvals. The imaging methods to be evaluated are F-18-labelled-fluorodeoxyglucose positron emission tomography (FDG-PET), F-18-labelled-fluoro-L-thymidine (FLT-PET), and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).

Advances or Other Highlights

The trial testing the use of Positron Emission Tomography to assess patients for locally advanced non-small cell lung cancer completed enrollment in FY 2008 and is currently in follow-up. Patients will be followed for 3 years after accrual for survival. Validating imaging methods as potential biomarkers for tumor response to treatment requires demonstrating a high degree of test-retest reproducibility for the imaging method, and a strong correlation with the biologic parameter of interest. Reproducibility is important because it determines the minimum change that can reliably be detected in a tissue of interest. Therefore, test-retest reproducibility will be an element of all research conducted for this goal.

Quantitative imaging information:
The following data were posted on the National Biomedical Imaging Archive (NBIA) Wiki for the public in the summer of 2009. These data can be used to develop computer-aided diagnostic software

- Repeat CT measurements of lung lesions in humans from MSKCC (reference)
- Repeat measurements on PET/CT phantoms
- Longitudinal PET/CT studies of lung cancer patients

BACKGROUND

Lung cancer is one of the leading causes of death in the United States, with an estimated 160,000 deaths occurring annually and an estimated incidence of 173,000 newly-diagnosed cases each year according to recent statistics reported by the Centers for Disease Control and Prevention (CDC). Current data from the American Cancer Society further supports that only one-third of newly diagnosed cases are diagnosed at a stage early enough to allow for effective therapeutic intervention while more advanced stages of the disease are characterized by a median survival rate of less than one year. The development of new drug treatments for lung cancer has been slowed by difficulty in both early detection and measurement of early therapeutic drug response as indicated by translational based research reports in December 2009. Currently, standard anatomic CT imaging is the primary modality for measuring lung tumor response to therapy. Since this modality measures drug responses only in terms of significant tumor shrinkage, it is not an adequate method for evaluating drug responses that precede significant tumor shrinkage. The goal of this proposed research is therefore to evaluate, validate and compare varying functional imaging methods that could serve as more sensitive approaches to the measurement of early drug response than standard or conventional anatomic imaging techniques that are based on significant tumor shrinkage. The availability of such sensitive measurement methods or modalities could significantly streamline clinical trials and, hence, accelerate new drug approvals. The imaging methods to be evaluated are F-18-labelled-fluorodeoxyglucose positron emission tomography (FDG-PET), F-18-labelled-fluoro-L-thymidine (FLT-PET), and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).

Rationale

Clinical trials in non-small cell lung cancer (NSCLC) have demonstrated that FDG-PET images can provide an early indication of therapeutic response. Thus, FDG-PET has the potential to improve patient management by signaling the need for early therapeutic changes in non-responders, thereby avoiding the side effects and costs associated with ineffective treatments. Furthermore, as an early indicator of therapeutic response, the modality also has the potential to facilitate oncologic drug development by both shortening Phase II trials and detecting response to therapy at an earlier stage in Phase III investigations. Studies to further explore and validate these approaches can be conducted in parallel with those employing endpoints currently used for oncologic drug

approvals.

Uptake of FLT-PET is an indicator of DNA synthesis. FLT-PET, therefore, has potential to be more accurate than FDG-PET in distinguishing lung malignancies from inflammation or non-proliferating cells. It is highly promising as a detector of early disease or as an early indicator of response to drug therapy as manifested by a decrease in cellular proliferation.

Dynamic contrast enhanced magnetic resonance imaging is sensitive to the development of new blood vessels (angiogenesis) required to support tumor growth. It is, therefore, a potentially sensitive measure of responses to antiangiogenic drug therapy. The evaluation of antiangiogenic agents could be very important to lung cancer therapy as suggested by the recent promising increase in survival of advanced NSCLC patients treated with the anti-vascular endothelial growth factor (VEGF) drug bevacizumab (Avastin).

Validating imaging methods as potential biomarkers for tumor response to treatment requires demonstrating a high degree of test-retest reproducibility for the imaging method, and a strong correlation with the biologic parameter of interest. Reproducibility is important because it determines the minimum change that can reliably be detected in a tissue of interest. Therefore, test-retest reproducibility will be an element of all research conducted for this goal.

TARGET CONTEXT AND CONDITIONS

Clinical Trials

To lay the foundation for accepting an imaging method as a potential biomarker for drug development, the proposed or putative imaging method should be tested in one or more clinical trials where patients receive therapy known to be effective for the disease under study. The method in question should not be initially evaluated in a trial studying novel therapies due to the high number of unknown variables inherent in such trials. Therefore, patients in clinical trial protocols will receive standard, accepted platinum-based chemotherapy for lung cancer and imaging measurements (FDG-PET, FLT-PET, or DCE-MRI) will be obtained before and after therapy to be subsequently correlated with patient outcome.

Test-Retest Reproducibility

Test-retest reproducibility is a measure of the variability of the test result when it is administered to the same patient at different times or under different conditions but during a period of time when the biologic process being measured is constant. This reproducibility will be rigorously tested in a pre-clinical setting where repetitive measures can be obtained on tissue-simulating phantoms. In addition, clinical trial data with duplicate testing of individual patients will be analyzed

Electronic Infrastructure

Another necessary part of our implementation strategy is to create an electronic infrastructure so that all sites in a multi-site trial can submit images to a central archive. Centralizing the images is necessary for quality assurance evaluation, for analysis (data extraction or interpretation), to facilitate blinded reads, and for secure storage (archiving) to enable secondary analyses. The FDA requires such procedures to establish confidence in the validity and robustness of the data supporting a proposed biomarker and to permit audits of the data, if needed.

Consensus Standards

Finally, an essential part of this implementation strategy is the development of consensus standards for interpreting or extracting quantitative data from the imaging studies.

Implementation

Therefore, the implementation strategy consists of several parts. In FY 2005 a clinical trial protocol was written to include serial FDG-PET scans in Stage III and IV lung cancer patients before and after therapy. Therapy

would be standard, not experimental, therapy. Scans would be done on state-of-the-art combined PET-CT scanners. The trial was initiated during FY 2006 by the NIH-funded imaging cooperative group known as ACRIN (www.ACRIN.org). Half of the patients were to receive duplicate FDG-PET scans prior to treatment, and half to receive duplicate FDG-PET scans after treatment. The duplicate scans would allow us to assess test-retest reproducibility. This trial has had significant difficulty in accruing patients as of mid-2008, due in part to a shift in the standard of care (adding Avastin to platinum-based doublet therapy).

A second ACRIN trial supports the completion of this measure. This trial is comparing FDG-PET before and after chemoradiation in non-small cell lung carcinoma to determine if the post-treatment glucose uptake as measured by FDG-PET is a useful predictor of long term clinical outcome (survival) after definitive chemoradiotherapy.

A trial to compare FDG-PET with FLT-PET for lung cancer was initiated in FY 2007. Accrual is expected to begin in 2008 with an interim analysis after one year of patient accrual.

In FY 2006, 2007 and 2008, programs to evaluate test-retest reproducibility both of available clinical data and of tissue simulating phantom were established. These are multiple and include FDG-PET CT longitudinal studies, multi-site phantom repeat studies, multi-imaging platform study using a PET CT phantom, DCE-MRI lung patient studies, DCE-MRI phantom for lung and other organs, and CT measurements of the lung. In FY 2005, plans for the electronic infrastructure to capture all the images in a central archive were initiated. This infrastructure was implemented in FY 2006.

To develop consensus standards and quantitative tools for image assessment, workshops of relevant experts on PET and MRI scanning have been held. The resulting recommendations and the proposed clinical trial protocols will be reviewed with FDA staff.

Achievement of this goal is conditional on recruiting a sufficient number of patients to conduct the required test-retest reproducibility analyses.

Long Term Objective: (SRO-5.8) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.8 By 2012, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies. (Outcome)	*2011*	Complete 80% of planned study subject accrual and continue quantitative data collection. *(Baseline):* (FY11) Number of subjects enrolled in FY11 and total number for study (180)	N/A
	2010	Complete 40% of planned study subject accrual and collect data on hot flash frequency, duration, and impact on daily activities. *(Baseline):* (FY09) Number of subjects enrolled in FY08 and total number for study (180)	N/A
	2009	Complete 20% of planned study subject accrual. *(Baseline):* (FY08) Total number of subjects for study TBD	83 candidate women (46%) were screened and 77 (43%) were successfully enrolled into the trial. (Target Exceeded)
	2008	Initiate 1 clinical study that includes a treatment for hot flashes in which the investigators would use a sternal skin conductance monitor to measure hot flash frequency. *(Baseline):* (FY07) No clinical studies of hot flashes using user-friendly sternal skin conductance monitors exist.	NIH-supported researchers have initiated a clinical trial assessing the effectiveness of hypnosis in treating menopausal hot flashes. (Target Met)
	2007	Continue validation of at least 2 devices to measure hot flash frequency. *(Baseline):* (FY06) Prototype device from FY05 target should be available for additional validation testing.	NIH-supported researchers continued validation of three sternal skin-conductance monitors to measure hot flash frequency. (Target Met)
	2006	Develop and validate improved devices to measure hot flash frequency. *(Baseline):* (FY05) Improved devices not yet available.	NIH funded three projects to further validate new sternal skin conductance monitors. (Target Met)

Data Source and Validation
The study progress report can be obtained from the NCCAM Office of Policy, Planning and Evaluation 301-451-8876

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and Exceeded with 83 candidate women screened and 77 successfully enrolled into the trial. The clinical trial has a target enrollment of 180 women who experience 7 moderate to severe hot flashes per day or 50 per week. The researchers will use the sternal skin conductance monitor, developed under an NCCAM supported small businesses grant, to validate if hypnosis treatments are effective in reducing the frequency and severity of hot flashes.

Efficiency

Enrollment of candidates for the trial has exceeded the target of 20%.

BACKGROUND

Vasomotor symptoms, including hot flashes and night sweats, are symptoms frequently reported by menopausal women as well as breast cancer survivors and men undergoing androgen deprivation therapy. Until recently, estrogen and other forms of hormone therapy were used to treat vasomotor symptoms among menopausal women. However, the findings of the NIH-funded Women's Health Initiative, released in 2004, indicated that the benefits of hormone-based therapies for hot flashes are outweighed by the risks of heart disease, stroke, and pulmonary embolism. Furthermore, hormone therapy is not an appropriate treatment for hot flashes in individuals with a history of hormone-dependent tumors.

Studies indicate that other means to manage hot flashes, including complementary and alternative medicine (CAM) therapies are being sought out by the public. There is a long history of using CAM therapies for this purpose, but the empirical base to assess their safety and efficacy is neither extensive nor very strong. Moreover, the FDA now recommends when hormones are used for the treatment of hot flashes, they be used at the lowest effective dose and for the shortest possible period of time. However, little is known about risks and benefits for smaller doses, shorter treatment times, and different routes of administration. Thus, it is likely that researchers will be investigating both hormone and CAM treatments to reduce hot flashes in the years ahead.

In January 2004, NIH convened a meeting to assess current approaches to measuring hot flashes. A limited number of studies conducted in research laboratories and ambulatory settings have used sternal skin conductance monitors for these measurements. The meeting participants determined that (1) sternal skin conductance devices were limited in the amount of data that can be collected and for use under ambulatory conditions; and (2) improved devices were needed to assess new therapeutic approaches including complementary and alternative medicine (CAM). The criteria for an improved device include accuracy in measuring sternal skin conductance with increased device data storage capacity. Usability under ambulatory conditions is another important criterion, as some devices are too bulky or heavy and interfere with daily activities and sleep. Once device development is complete, clinical studies will be undertaken to assess both CAM and conventional therapies for the treatment of hot flash symptoms.

Rationale

In light of the aging U.S. population and the findings of the Women's Health Initiative, further clinical trials of interventions for hot flashes will undoubtedly need to be conducted. Some treatments are likely to be relatively weak when compared with estrogen, but many women may find partial relief acceptable if the benefits of treatment outweigh the risks. Given the large placebo effects that have been reported in many studies, the instability of self-reported measures of hot flashes, and modest treatment effects; important choices in the conduct of future trials must be made. Investigators can either conduct very large studies to accommodate the limitations of subjective self-reported measures, or they can develop more sensitive and reliable objective measures for use in smaller studies, which could provide substantial economies in time and resources. For these reasons, the scientists convened by NIH to consider issues surrounding the measurement of hot flashes recommended improvements in sternal skin conductance monitors.

TARGET CONTEXT AND CONDITIONS

Menopausal hot flashes disrupt a women's overall health and affect activities such as sleep patterns. However, it wasn't until 1975 that hot flashes came under scientific scrutiny. A study documented physiological changes that occurred during hot flashes - skin temperatures rose and fell, sweating occurred, and the heart rate increased by 13% at the beginning of a hot flash. The 1975 study finally put to rest the notion that hot flashes were more imagined than real.

Beginning in 2005, the NIH supported several Phase I clinical trials of an external skin conductance monitor to record menopausal hot flashes. Prior to the development of the NIH-supported skin conductance monitor, hot flashes were typically self reported. Two skin conductance monitors, the Bilog and the Freedman, were available for study, however each had pitfalls. The Biolog monitor is bulky, only has a 24-hour duration time, and is often inaccurate. The Freedman monitor has a time duration of 24 - 60 hours, but is also often inaccurate.

During Phase I studies, focus groups were assembled to define optimal characteristics needed for each type of monitor, which included 7-day record ability; small, easily attachable and removable; and accuracy in measuring hot flash occurrence (i.e., ability to distinguish between sweat produced from exercise rather than a hot flash episode). Once these steps were accomplished and a prototype developed, the monitors moved into Phase II studies for testing. Three of the NIH Phase I studies moved into Phase II clinical studies during 2006 and 2007. Of the three monitors in Phase II studies, one provided strong data for accuracy and durability (the Bahr monitor), enabling it to move forward into Phase III clinical trials.

The Bahr monitor allows for more accurate and objective measurements, improving validity and reducing variances and needed sample size. The initial prototype optimized electrodes to measure skin impedance. The device was tested to measure skin conductance, ability to run data on multiple computer platforms, and ease of downloading data. Further improvements have made the device smaller, with a longer lasting battery, and electrodes imbedded in the hardware. Currently the Bahr monitor is being utilized in one NIH-supported study and will be used in two other studies once subject recruitment begins.

The Bahr monitor is in the final stages of development to move into commercial production, which will make it more accessible to a larger number of studies and potentially into clinical settings. The monitor will provide more accurate readings and evaluation of hot flash episodes, allowing for better interpretation of data as to whether a therapy is able to reduce severity and/or frequency of menopausal hot flashes.

Long Term Objective: (SRO-5.9) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.9 By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations. (Outcome)	*2010*	Establish the role of genetic factors in three major diseases for which health discrepancies are noted between populations. *(Baseline):* (FY09) The role of genetic factors in major diseases for which health discrepancies exist are not yet clear.	N/A
	2009	Begin biologic assessment of the most likely diabetes/obesity susceptibility genes in regions of linkage/association. *(Baseline):* (FY08) One hundred candidate genes screened on 1q21-23; 1000 SNPs in the 11q23 region genotyped in ~1000 Pimas.	Biologic assessment of the most likely diabetes/obesity susceptibility genes have been initiated in regions of linkage/association. (Target Met)
	2008	HapMap III: Analyze data from samples from additional populations to assess how well the genome-wide HapMap applies to additional populations, as well as to figure out how to choose HapMap SNPs to make them most useful for additional populations. *(Baseline):* (FY07) HapMap III not started	HapMap III analyzed data from additional populations allele frequencies and haplotypes (Target Met)
	2007	Release Phase 1 core pooled data with documentation to the public, create a web utility for sharing Family Blood Pressure Program data and hold a training workshop for the scientific community. *(Baseline):* (FY05) No FBPP data publicly available to the scientific community.	The program data center successfully completed a Public Access Data Training Workshop on March 13 -14, 2007. (Target Met)
	2007	Perform initial whole genome scan for prostate cancer susceptibility genes in the C-GEMS study. *(Baseline):* (FY06) Scientific infrastructure established and RFP for initial scan released.	NIH performed initial whole genome scan for C-GEMS study. (Target Exceeded)

Measure	FY	Target	Result
	2006	Release Phase 1 core pooled data with documentation to the public, create a web utility for sharing Family Blood Pressure Program data and hold a training workshop for the scientific community. *(Baseline):* (FY05) No FBPP data publicly available to the scientific community.	The pooled data with documentation and web utility were made publicly available in September 2006. Public data training is scheduled for March 2007. (Target Extended)

Data Source and Validation
Common variation in SIM1 is reproducibly associated with BMI in Pima Indians. Traurig M, Mack J, Hanson RL, Ghoussaini M, Meyre D, Knowler WC, Kobes S, Froguel P, Bogardus C, Baier LJ. Diabetes. 2009 Jul;58(7):1682-9. Epub 2009 Apr 28. http://diabetes.diabetesjournals.org/content/58/7/1682.long Association analysis of variation in/near FTO, CDKAL1, SLC30A8, HHEX, EXT2, IGF2BP2, LOC387761, and CDKN2B with type 2 diabetes and related quantitative traits in Pima Indians. Rong R, Hanson RL, Ortiz D, Wiedrich C, Kobes S, Knowler WC, Bogardus C, Baier LJ. Diabetes. 2009 Feb;58(2):478-88. Epub 2008 Nov 13. http://diabetes.diabetesjournals.org/content/58/2/478.long Lower metabolic rate in individuals heterozygous for either a frameshift or a functional missense MC4R variant. Krakoff J, Ma L, Kobes S, Knowler WC, Hanson RL, Bogardus C, Baier LJ. Diabetes. 2008 Dec;57(12):3267-72. Epub 2008 Oct 3. http://www ncbi nlm nih.gov/pmc/articles/PMC2584132/?tool=pubmed PCLO variants are nominally associated with early-onset type 2 diabetes and insulin resistance in Pima Indians. Ma L, Hanson RL, Que LN, Guo Y, Kobes S, Bogardus C, Baier LJ. Diabetes. 2008 Nov;57(11):3156-60. Epub 2008 Jul 22. http://www ncbi nlm nih.gov/pmc/articles/PMC2570415/?tool=pubmed

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. The biological assessment of the most likely diabetes/obesity susceptibility genes have been initiated in regions of linkage/associations including: SIM1, FTO, CDKAL1, SLC30A8, HHEX, EXT2, IGF2BP2, LOC387761, CDKN2B, MC4R, and PCLO.

BACKGROUND

NIH supports research to establish the role of genetic factors in three major diseases for which health disparities are noted. The element of unplanned discovery in research makes it virtually impossible to predict accurately when significant scientific advances will be made in the genetics of any specific disease. Thus, the focus will be on programs that seek to determine genetic factors across the genome and specifically on research in disease areas that are likely candidates for genetic advances in the next few years.

Comparable to a drug discovery in which many compounds are screened and tested to yield a small subset to pursue, to identify genetic factors in three major diseases, NIH is pursuing many more than three areas of disease research. Ultimately, NIH will support three areas of research in which it is likely that important genetic factors related to disease will emerge by 2010.

Building on the foundation of the Human Genome Project (HGP), NIH, as part of the International HapMap Consortium, has developed a way to scan large regions of chromosomes for variants (called SNPs, or single nucleotides polymorphisms) associated with an increased risk of disease. Researchers can use the HapMap to

find genes and variants that contribute to many diseases; it is also a powerful resource for studying the genetic factors contributing to variation in individual response to disease, drugs, and vaccines. Understanding the role of genetics in major diseases that have been noted for disparities, and thus achieving this goal, will rely on such tools.

Prevalence/Incidence

Virtually all diseases have a genetic component, even though the vast majority of human genetic information is the same for all people. Indeed, any two individuals share 99.9% of their DNA sequence. However, this translates to approximately 10 million DNA sites where people commonly differ, many of which may be medically important. Some of these variations affect an individual's risk for disease; others influence how an individual may respond to drugs. Most genetic variations, including those that are medically important, are shared by all racial, ethnic, and cultural groups. Thus, much of human genetics research applies broadly to all groups of people, regardless of which individuals are studied.

A disease may be said to be 'common' if its incidence is high and it is seen in many populations, although not necessarily at similar frequencies in each population. Many diseases that have a genetic component affect populations in different ways. For example, CDC research from 2009 on prevention and control of population based chronic diseases indicates that diabetes is a debilitating disease that affects an estimated 18.2 million people in the United States and is the sixth leading cause of death and that Type 2 diabetes (noninsulin-dependent diabetes mellitus, or NIDDM) is the most common form and occurs more frequently among minority groups. Overall, Hispanic/Latino and African Americans are nearly twice as likely, and American Indians are 2.6 times more likely to develop type 2 diabetes than are whites.

Similar comparisons exist where:

- Deaths due to cerebrovascular diseases are highest among African Americans and lowest among American Indians and Alaska Natives, with whites at an intermediate risk.
- In 2009 a CDC report on high blood pressure showed that over 60 million Americans, or approximately 20% of the population, have hypertension. Many minorities have higher rates of hypertension, tend to develop hypertension at an earlier age, and are less likely to undergo treatment to control their blood pressure than whites.
- In 2007, the CDC reported the racial and ethnic disparities in risks of developing and dying from a number of different cancers from 1975-2004. Within the U.S, Caucasian people have the highest rates of breast cancers, Asian Americans have the highest rates of liver and stomach cancers, and Native Americans have the highest rates of gall bladder cancers. Cancer facts and figures reported by the American Cancer Society as recently as 2008 indicate that African Americans are at the highest risk of a number of different cancers, including those of the esophagus, lung, colon, pancreas and prostate. Prostate cancer is the most common non-skin cancer and the second leading cause of cancer-related death in U.S. men. Thus, the 60% higher rate of development of prostate cancer and a two-fold higher risk of death from it among African American men is a major health problem.

Rationale

Understanding how genetic variations contribute to various diseases will hopefully lead to a better understanding of why individuals are at particularly high risk of developing health problems. Genetic variations associated with a disease are identified through analyses of large study groups; only these offer the statistical power needed to identify and confirm genetic and environmental contributors to complex diseases.

Although many of the large population studies such as Framingham and the U.S. Physicians Health Study have had a major impact on the health of all U.S. population groups, these studies do not have appropriate minority representation across the U.S. population. For serious but less common diseases such as cancer, these studies may not be able to uncover specific genetic reasons for the differences in disease rates for minority

populations. Because of this, the NIH has developed specialized study populations to collect large amounts of data on minority populations to combine with the data from other large cohorts. These studies will provide great insights into the genetic factors in diseases for which health disparities are noted, but it is currently unknown which studies will bear specific results. It is expected that supported research will yield knowledge about the genetic factors in diseases such as hypertension, prostate cancer, and diabetes, but overall, research into other diseases may develop additional results.

TARGET CONTEXT AND CONDITIONS

Genomic research is rapidly producing new opportunities for understanding disease biology, and promises to enhance health care and health outcomes significantly through improved strategies for prediction and prevention, targeted drug treatment, and innovative molecular-based therapies. The NIH, a world leader in genomic research, will fund research to identify genetic factors across the genome that play a role in three major diseases for which health disparities are noted. Examples of some of the diseases currently under investigation include diabetes, hypertension, and prostate cancer. A major concern in the era of genomic health care is to insure that all racial, ethnic, and cultural groups can benefit fully from genomic technology.

Finland-United States investigation of type 2 diabetes (FUSION) involves the phenotyping and DNA analysis of 2400 individuals with diabetes living in Finland. The Finnish population provides an ideal basis for studies of complex genetic diseases such as type 2 diabetes due to its relative genetic and environmental homogeneity, excellent data sources, and a population strongly supportive of biomedical research. Researchers at NIH have been engaged in FUSION, a large collaborative study of more than 2400 individuals with diabetes from Finland, using careful detailing of diabetes and diabetes associated traits, and genome-wide genetic linkage and association. The majority of the samples have already been subjected to a genome scan using microsatellite markers, and several regions of interest have been identified. Those samples are now being genotyped in order to map these areas finely, in an effort to identify the specific genetic variants that contribute to risk for this common illness.

The Family Blood Pressure Program (FBPP) is a multidisciplinary project, with a goal of locating and characterizing genes that contribute to hypertension and related conditions in multiple racial and ethnic groups (non-Hispanic whites, African Americans, Hispanics, and Asians). Investigators involved in the FBPP have recently identified many hypertension susceptibility genes and regions of the genome that are likely to contain them. Pooled data generated by the FBPP have been made available to the scientific community, and data training workshops will be held to facilitate research in this area. The goal of the FBPP is to enable improvements in hypertension prevention and treatment.

To help meet the challenge of eliminating suffering and death from cancer, it is important to capitalize on the extraordinary momentum generated by advances in human genetic research. Currently, a comprehensive study of hormone related gene variants is planned, utilizing a coalition of investigators involved in population follow-up studies (Consortium of Cohorts). In addition, a study entitled the Cancer Genetic Markers of Susceptibility (C-GEMS) will use the latest genomic technologies to perform dense whole genome scans to identify and validate susceptibility genes in the induction and progression of prostate cancer and clarify gene-gene and gene-environment interactions. Specific regions of human chromosome 8q24 have been associated with the risk of prostate cancer in African Americans. To further understand the genetic basis for the increased risk of prostate cancer in this region, high-density sequencing of the 8q24 region is underway on a study focused on prostate cancer in West Africans from Ghana. The data from the first round of replication has been analyzed and second stage replication of the remaining positive associations (~150 SNPs) is ongoing. The second stage replication study sample set is enriched with several ethnic populations, with a particular focus on African Americans. In the future, intramural scientists will perform the second stage validation on positive genetic variants associated with increased susceptibility to prostate cancer from an extramural GWAS being planned on several ethnic groups. This group will have a particular focus on African Americans and will be carried out through an intramural/extramural collaboration. Positive findings from this study will be the focus of further

investigation across the scientific community. This work will provide new insights into mechanisms of carcinogenesis and point the way to novel strategies for accelerating the prevention, early detection, and treatment of prostate cancer.

The first phase of the HapMap Project, a comprehensive catalog of human genetic variation, was completed in 2005 and identified 1 million SNPs, markers of genetic variation, in four population groups. The second phase of the project will provide researchers with a denser map to narrow gene discovery more precisely to specific regions of the genome. In the third phase of HapMap, ten carefully chosen regions will be genotyped in additional populations to assess how well the HapMap and its tag SNPs work in other groups. This will aid in exploiting the utility of HapMap across the range of populations in the US.

The Pima Indians of Arizona have the highest reported prevalence of type 2 diabetes mellitus (T2DM) of any population in the world. This population also has high rates of obesity. Studies have shown that both T2DM and obesity are heritable diseases. The goal is to identify and characterize susceptibility genes for T2DM and obesity among this American Indian population using positional cloning in chromosomal regions identified through linkage studies. Results from the linkage study in Pima Indians indicate a locus linked to both obesity and T2DM on chromosome 11, and a second locus linked to T2DM alone on chromosome 1. In its next phase, a high density single nucleotide polymorphism map will be pursued which will facilitate identification of genetic variations associated with both obesity and T2DM.

Long Term Objective: (SRO-5.10) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.10 By 2011, conduct studies of girls aged 6 through 8 years to determine the associations between the age of onset of puberty and progression through puberty with 12 environmental exposures. (Outcome)	*2011*	Determine the associations between the age of onset of puberty and progression through puberty with 12 environmental exposures. *(Baseline):* (FY10) Collected Year 4 data on cohort.	N/A
	2010	Conduct year 4 follow-up clinical exams and data collection for at least 75% of the cohort to examine the presence of specific markers of exposure and correlate with signs of puberty. Perform chemical analyses of year 1 samples to assess levels of biomarkers in blood and urine. *(Baseline):* (FY09) Collected Year 3 data on cohort	N/A
	2009	Conduct Year 3 follow-up clinical exams and data collection for 75% of the cohort to examine the presence of specific markers of exposure and correlate with signs of puberty. *(Baseline):* (FY08) Collected Year 2 data on cohort	Conducted Year 3 follow-up clinical exams and data collection for 84% of the cohort. Collected samples have been chemically analyzed for comparison with national averages. (Target Exceeded)
	2008	Conduct Year 2 follow-up clinical exams and data collection for 75% of the cohort to examine the presence of specific markers of exposure and correlate with signs of puberty. *(Baseline):* (FY07) No exams or collection.	For year 2 follow-up, over 87% of the current cohort was successfully contacted and completed questionnaires, with over 85% completing follow-up clinical exams. (Target Met)
	2007	Complete recruitment of 1,200 girls; complete pilot analysis of selected environmental exposures. *(Baseline):* (FY06) Analyzed urine specimens of 90 girls across study sites for selected exposures.	Recruited 1244 girls and completed pilot urine analysis. Yr 2 clinical exams and data collection are on target. (Target Met)

Data Source and Validation
Internal progress reports, oral presentations by investigators and data update tables obtained by program staff were used for this evaluation. Les Reinlib Senior Health Science Administrator 919-541-4998; reinlib@niehs nih.gov

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and Exceeded. Researchers completed the Year 3 follow-up with 84% of the current cohort being examined and having samples collected. Follow-up studies included data measurements of pubertal stage, anthropometry, pedometer use, diet recall, psycho-social stress measures, and questionnaires. In addition urine, blood, and buccal samples were collected for direct measurement of the chemicals of interest and of genetic variation in the cohort.

Chemical analyses of these samples are underway for phthalate, phenol and phytoestrogen biomarkers from urine and organohalogen, cotinine, perflourocompounds, from serum. The data across the collection sites has been tabulated and statistical analysis is being computed as compared to the published national averages. These data will be compared with the corresponding anthropomorphic observations, and genetic variations to determine the gene-environment interaction on pubertal stage.

Efficiency

The measure was exceeded by researcher maintaining participation and collecting data from 84% of the surveyed cohort, above the expected rate of 75%. The larger participation rate or study sample enables a more robust study and is important to achieve reliable results in determining normal distribution of values in population based studies.

BACKGROUND

Breast cancer is a complex disease, the causes of which have eluded scientists for many decades. Improvements have been made in early disease detection, surgical and medical modalities for treatment and survival for women with breast cancer. Although scientists and clinicians understand more today about the process of carcinogenesis (the process by which normal cells are transformed into cancer cells) and genetic susceptibility, effective prevention strategies targeting the causes of breast cancer remain out of reach due to the multiplex of factors involved in breast cancer causation.

Functioning as a consortium of basic scientists, epidemiologists, research translational units, and community advocates within and across centers, the Breast Cancer Environmental Research Centers (BCERC) are investigating mammary gland development in animals and young girls to determine vulnerability to environmental agents that may influence breast cancer development in adulthood and will hopefully lead to strategies that better prevent breast cancer.

Currently there are two broad areas in the BCERC – a basic science project and an epidemiology project. The basic science project is currently composed of 4 centers that are studying environmental effects on the molecular architecture and function of the mammary gland across the lifespan in rodents. The epidemiology project will recruit young girls into a study for assessing the association of 12 environmental agents – including endocrine disruptors that may leach from plastics such as bis-phenol a and phthalates – on markers of early puberty, which is a risk factor for breast cancer.

The purpose of this scientific program is to answer questions that focus on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Answering these questions will allow the translation of such findings into information that can be applied to increase awareness of the causes of breast cancer.

Prevalence/Incidence
This study is focused on early onset of female puberty and is not a disease. However, early onset of puberty is a risk factor for breast cancer, which is diagnosed in 250,000 women in America each year according to data published in 2004 and 2006 on breast cancer morphogenesis.

Disease Burden
Breast cancer results in 50,000 deaths in America each year. One third of the prevalence is in women of child-bearing age and causes significant economic and medical-system burdens. By one estimate, as noted in a recently published NIH fact sheet on breast cancer, the total economic cost of breast cancer was $56 billion dollars in 2000, making this form of cancer the most costly among cancers.

Rationale
Despite intense research over the past decade into the potential environmental influences on breast cancer, few candidate exposures have been confirmed. Only irradiation is universally accepted as a cause for breast cancer. However, genomic, post-atomic blast survivor, and international migration studies indicate that breast cancer is largely an environmental disease. Much of the data suggests that time of life exposure is a critical factor in the risk of disease development. Girls in industrialized nations are increasingly experiencing markers of onset of puberty at earlier ages. This study is a first step to determine whether puberty is a critical "window of exposure" that could predispose women to eventual disease pathogenesis (the origination and development of disease). This project will attempt to examine dietary and environmental agents that might play a role in early puberty and, thus, increased breast cancer risk, as well as improved ways of assessing traits indicative of early puberty.

TARGET CONTEXT AND CONDITIONS

This purpose of this study is to determine the risk factors associated with early onset and altered puberty in girls. The study allows for in-depth observation and analysis of the progression through puberty of girls between the ages of 6 and 14 years old.

Approximately 1200 girls were recruited in the three Centers' regions from schools and day-camps. They are examined twice annually for signs of puberty, and are asked to keep diaries, use pedometers, and answer questionnaires concerning their diet, exercise regime, and likely exposures at home and work. Blood and urine samples are collected annually at the clinics associated with the Centers and used for genome and biomarker analysis. Urine, as well as blood, is used for the regular determination of chemical to which the girls were exposed. In addition, blood samples allow for determination of gene variations that may indicate the susceptibility of an individual to a particular exposure. The samples present a unique opportunity to determine body burden for a select list of candidate exposures and to directly associate those exposures with changes in female puberty. Exposures and pubertal changes are also correlated with subtle variations in genes of interest.

Data will be collected from all active participants. However, as this study takes place over many years, some attrition is expected each year. Attrition over the whole study may reach as high as 75%. In designing this study, a 1200 girl cohort was recruited to help ensure sufficient statistical power in study results, taking into account attrition trends from previous studies.

The investigative teams met on multiple occasions and through tele-conferences for over a year in order to jointly draft protocols, questionnaires, train examiners, and create other investigative instruments for the study. Epidemiologists also met with laboratory biologists and outreach experts in the study to produce cross-cutting, transdisclipinary studies to facilitate in-depth analysis on animal models of exposures that are likely to alter female puberty, and to set the stage for translation of messages on life-style choices that can be transmitted to local and national communities.

Long Term Objective: (SRO-5.11) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.11 By 2012, develop and test at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes. (Outcome)	*2011*	Identify at least one behavior-based strategy that manages at least one candidate symptom and improves quality of life and health outcomes. *(Baseline):* Ongoing studies are exploring behavioral strategies for symptom management.	N/A
	2010	Assess the impact on patient health outcomes of a cohort of behavior-based symptom management strategies designed to manage candidate symptoms identified in FY 2008 analysis. *(Baseline):* To be determined by results of FY 2008 analysis.	N/A
	2009	Assess the impact on patient quality of life of a cohort of behavior-based symptom management strategies designed to manage candidate symptoms identified in FY08 analysis. *(Baseline):* To be determined by FY08 results of analysis.	Assessments identified that behavioral therapy may be effective in improving chemotherapy patient sleep quality, and that including family members or friends in a patient pain reporting intervention did not impact effectiveness. (Target Met)
	2008	Conduct an analysis of current literature to identify at least three candidate symptoms appropriate for assessment in studies of behavior-based symptom management strategies. *(Baseline):* (FY07) Ongoing studies are exploring behavioral strategies to enhance patient outcomes.	An analysis of current literature was conducted to identify three candidate symptoms appropriate for assessment in studies of behavior-based symptom management strategies. (Target Met)

Data Source and Validation
Berger, A. M., B. R. Kuhn, et al. (2009). "Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue." Psychooncology 18(6): 634-46. DOI: 10.1002/pon.1438 Ward, S. E., R. C. Serlin, et al. (2009). "A randomized trial of a representational intervention for cancer pain: does targeting the dyad make a difference?" Health Psychol 28(5): 588-97. DOI: 10.1037/a0015216

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. Researchers completed two studies that assessed the impact on patient quality of life of behavior-based symptom management strategies, targeting symptoms that included fatigue, pain, and sleep quality. In one study, researchers examined a behavioral strategy for reducing fatigue and improving sleep quality in women undergoing treatment for breast cancer. The study employed a randomized clinical trial that involved over 200 women with breast cancer undergoing chemotherapy. About half of the participants received a behavioral intervention that consisted of an individualized sleep promotion plan. This plan included four components: stimulus control, sleep restriction, relaxation therapy, and sleep hygiene counseling, and was implemented prior to, during, and after receiving chemotherapy. As a control, the other half of the participants received only information on healthy eating. Results indicated that sleep quality improved significantly in the intervention group immediately following the final chemotherapy treatment, and this improvement lasted for at least 30 days after the final treatment, while the control group exhibited no difference at 30 days post-treatment. However, there was no significant difference in fatigue between the two groups, indicating that the improved sleep quality in the intervention group did not translate into reduced fatigue. These findings indicate that behavioral therapy may be effective in improving sleep quality in chemotherapy patients, and that further work may be needed to refine the intervention to address issues of fatigue in those being treated for breast cancer.

In another study, scientists sought to further develop a behavioral intervention in overcoming the attitudinal barriers that often prevent cancer patients from reporting their pain and/or using analgesics. These barriers can include excessive fear of addiction, or a fatalistic attitude about controlling pain. In previous research, an educational intervention called RIDcancerPain reduced attitudinal barriers to reporting pain and using analgesics, as well as pain severity, from baseline to two months post-intervention. The present study sought to improve on these results by using a randomized clinical trial to determine whether or not the inclusion of a friend or family member in the intervention would be more effective in encouraging the patient to overcome attitudinal barriers to pain control than conducting the intervention with the patient alone. When compared with a control group that did not receive the intervention, significant decreases in attitudinal barriers were seen nine weeks after the intervention in patients who received the intervention either alone or with a friend or family member. However, the study found that the inclusion of the friend or family member made no significant difference in the effectiveness of the intervention. Overcoming barriers to reporting pain is a critical step in successfully managing an adverse symptom experienced by many cancer patients. Further refinement and generalization of interventions such as RIDcancerPain are needed to improve their usefulness in standard clinical practice in improving quality of life and health outcomes.

Ongoing research continues to develop and test strategies for managing symptoms to improve quality of life. The two studies discussed here are initial steps in developing effective behavioral strategies to reduce symptom burden caused by symptoms such as pain and fatigue. These studies provide an important foundation for future research to design new, and refine existing behavioral strategies for managing the adverse symptoms associated with acute conditions and chronic illness, with the goal of ultimately improving patient health outcomes.

BACKGROUND

Symptoms such as pain and fatigue are associated with a wide range of acute and chronic diseases, as well as treatments for such diseases. For example, people living with HIV/AIDS often experience severe fatigue, while patients being treated for various forms of cancer may experience debilitating pain as a consequence of chemotherapy. Such symptoms can have significant, adverse effects on a patient's quality of life, and ultimately, his or her health outcomes. The term "Quality of Life" refers to how a patient perceives their life and health status, and can include a patient's ability to perform daily activities or live free from pain while coping with a chronic disease. "Health Outcomes" is an umbrella category that includes the total effects of health care practices and medical/behavioral interventions on factors such as longevity, chronic disease morbidity, and physical and mental functional status. Measuring quality of life is only one part of assessing

health outcomes. Symptoms reduce functional status, may cause patients to reduce or abandon treatment, and can cause considerable psychological distress and even depression. Therefore, along with ongoing work in finding new and better ways to prevent and treat disease, NIH scientists are exploring new strategies for managing and reducing the symptoms associated with various health conditions. It is anticipated that these research efforts in symptom management will lead to a decreased burden of illness and improved quality of life for patients suffering from acute and chronic disease.

Rationale

Behavior and biology often interact in complex ways to influence health outcomes. For example, a behavior such as exercise may confer as yet undefined and far-reaching benefits to disease sufferers through a combination of biological and psychological mechanisms. NIH-supported researchers are currently clarifying these complex interactions and leveraging this knowledge to improve health outcomes. To date, NIH-supported scientists have successfully employed behavioral interventions to increase treatment adherence for those with chronic diseases such as diabetes and HIV/AIDS, and to improve disease prevention habits for those at risk of developing disease. The intimate relationships between biology and behavior point to behavioral strategies as promising avenues for reducing symptom burden. The successful development of such strategies could significantly improve the ability to reduce the effects of disease, disability, and psychological distress on quality of life and health outcomes.

TARGET CONTEXT AND CONDITIONS

Over the next several years, NIH-supported scientists will work to systematically identify and test the effectiveness of behavioral methods for improving symptom management. Efforts will initially focus on identifying candidate symptoms appropriate for assessment in studies of behavior-based symptom management strategies. Next, behavioral strategies designed to manage these candidate symptoms will be identified and assessed for their ability to impact patient quality of life. Measuring the effectiveness of these strategies could include assessments of patients' abilities to perform activities of daily living, or of patients' pain status. The initial years of this goal will thus provide an opportunity to assess the current state of research into using behavioral methods to manage symptoms and improve quality of life. Following these initial assessments of quality of life, further study will identify and assess the impact of promising behavioral symptom management strategies in reducing the effects of disease, disability or psychological distress on overall health outcomes. Assessments of health outcomes could include measurements of not only quality of life, but also factors such as longevity, chronic disease morbidity, and physical and mental functional status.

Long Term Objective: (SRO-5.12) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.12 By 2013, identify several potential targets and/or molecules that modulate or enhance the extinction of learned behaviors and conditioned associations supporting addiction, compulsion, or anxiety disorders. (Outcome)	*2011*	Confirm in replication studies the effectiveness of compounds reported to date in animal models of extinction of drug-seeking behavior *(Baseline):* At least 2 compounds or medications tested in animal models of extinction of drug-seeking behavior	N/A
	2010	Test an additional compound in animal models of extinction of drug-seeking behavior. *(Baseline):* Research findings from FY09	N/A
	2009	Test at least two compounds or medications in animal models of extinction of drug-seeking behavior. *(Baseline):* (FY07) Research is needed to identify brain mechanisms underlying extinction and to identify potential targets for medication development.	Two compounds were tested in animal models: an mGluR5 antagonist enhanced the extinction of both methamphetamine and cocaine drug taking; and D-cyloserine enhanced extinction, and interfered with the resumption of cocaine drug seeking. (Target Met)

Data Source and Validation

Gass JT, Osborne MP, Watson NL, Brown JL, Olive MF. mGluR5 antagonism attenuates methamphetamine reinforcement and prevents reinstatement of methamphetamine-seeking behavior in rats. Neuropsychopharmacology. 2009 Mar;34(4):820-33. http://www ncbi nlm nih.gov/pubmed/18800068
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Moussawi K, Pacchioni A, Moran M, Olive MF, Gass JT, Lavin A, Kalivas PW. N-Acetylcysteine reverses cocaine-induced metaplasticity. Nat Neurosci. 2009 Feb;12(2):182-9. Epub 2009 Jan 11. http://www ncbi nlm nih.gov/pubmed/19136971

Gass JT, Olive MF. Positive allosteric modulation of mGluR5 receptors facilitates extinction of a cocaine contextual memory. Biol Psychiatry. 2009 Apr 15;65(8):717-20. Epub 2008 Dec 19.7. http://www ncbi nlm nih.gov/pubmed/19100966

Nic Dhonnchadha BA, Szalay JJ, Achat-Mendes C, Platt DM, Otto MW, Spealman RD, Kantak KM. D-cycloserine Deters Reacquisition of Cocaine Self-Administration by Augmenting Extinction Learning. Neuropsychopharmacology. 2009 Sep 9. http://www ncbi nlm nih.gov/pubmed/19741593

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. Two compounds (an mGluR5 antagonist and D-cycloserine) were shown in animal models to enhance the extinction of methamphetamine and cocaine self-administration, and to interfere with the resumption of cocaine drug seeking that is a model of drug relapse. Both compounds affect glutamate neurotransmission, thought to be important in learning and memory. One is a selective antagonist of type 5 metabotropic glutamate receptors, which facilitated the extinction of methamphetamine and cocaine self-administration. The second (D-cycloserine) is an agonist at glycine receptors, which facilitated extinction and interfered with reacquisition of cocaine drug-seeking.

Extinction (or the unlearning) of learned response can be beneficial in treating drug addiction, particularly relapse. This is because conditioning or learning is a major component of addiction, and is frequently the trigger of relapse. Learned associations between cues (e.g., people, places, and things) and the drug experience can be so powerful that a person may not even be aware of their response, and yet experience the strong cravings that lead them to start taking drugs again. Thus, compounds that facilitate extinction (or unlearning) of a response—in this case, drug self administration--may prove beneficial for treating drug addiction.

BACKGROUND

Drug addiction is a chronic, relapsing brain disease that can begin with occasional drug use, and over time lead to intense craving and compulsive drug taking, and relapse following periods of abstinence. A considerable body of evidence indicates that mechanisms of learning underlie the development of addiction, as well as other compulsive behaviors, and some anxiety disorders (e.g., posttraumatic stress disorder, obsessive compulsive disorder, specific and social phobias). Thus, interventions that can interfere with or reverse such learning would be expected to enhance treatment of disorders, including relapse to drug abuse.

Prevalence/Incidence

Addiction is a common disorder. According to the National Survey on Drug Use and Health (NSDUH), in 2007 there were an estimated 22.3 million persons aged 12 or older (9 percent of that population) meeting criteria for substance abuse or dependence. Substance abuse and dependence frequently co-occur with anxiety disorders, which is the most common class of mental disorders in the U.S., affecting an estimated 40 million America adults within a given year.

Disease Burden

Drug abuse is costly to Americans, tearing at the fabric of our society and taking a huge financial toll on our resources. Beyond its inextricable link to the spread of infectious diseases, such as HIV/AIDS, sexually transmitted diseases (STDs), tuberculosis, and hepatitis C, drug abuse is often implicated in family disintegration, loss of employment, failure in school, as well as domestic violence, child abuse, and other crimes. Placing dollar figures on the problem, smoking, alcohol and illegal drugs are estimated to cost this country more than 600 billion dollars per year, with illicit drug use alone accounting for about $180 billion in crime, productivity loss, health care, incarceration, and drug enforcement according to data for 1992-2002 reported in 2004 by the White House Office of National Drug Control Policy**.** In 2008, the number of persons needing treatment for an illicit drug or alcohol use problem was 23.1 million, and only 2.3 million of them received treatment at a specialty facility based on results from 2008 NSDUH findings.**.** In 2007, there were 5.4 million adults with serious psychological distress associated with substance dependence or abuse, and of these less than half received mental health treatment or substance use treatment at a specialty facility according to results from 2007 NSDUH data.

Anxiety disorders are also extremely costly to Americans. In the 1990s,, the annual cost of anxiety disorders was estimated at just over $43 billion, or approximately $1500 per sufferer. The leading costs for this class of disorders were attributable to direct medical and psychiatric care ($36.3 billion per year) and lost workplace

productivity ($4.1 billion per year). Of the nearly 40 million American adults with a diagnosable anxiety disorder each year, only 37% seek psychiatric or medical treatment based on a 1999 study of anxiety disorder in the 1990s.

Rationale

Evidence indicates that conditioning and other types of learning play an important role in the development of addiction, and susceptibility to relapse, as well as anxiety disorders. Therefore, interventions that can interfere with or reverse such learning may enhance treatment of addictive disorders and some anxiety disorders. Extinction is an active process whereby previously learned associations are weakened and new ones formed. For this to happen, the underlying neural circuits must be modified. Thus, it should be possible to identify potential targets and molecules that enhance extinction by affecting relevant neural substrates; e.g., the prefrontal cortex--involved in cognitive and executive function, reversal learning, and attention; the amygdala--involved in emotional learning; and the dorsal striatum--involved in habit formation. Ultimately, this research could be used to guide and enhance behavioral and pharmacological interventions for the treatment of drug abuse, and other compulsive behaviors, including some anxiety disorders.

TARGET CONTEXT AND CONDITIONS

NIH has demonstrated its commitment to this area through the release of a Request for Applications entitled "Extinction and Pharmacotherapies," with the goal of stimulating research on the mechanisms underlying extinction in order to guide the development of interventions for enhancing extinction of drug-seeking behavior. However, the level of achievement from this goal is conditional on receiving applications of sufficient scientific merit. The funded research may include investigations on how manipulations of learning and memory could control drug-seeking behavior using animal models; and studies to determine the biochemical and cellular changes occurring during extinction training. Research conducted under this RFA will ultimately be used to guide and implement combined behavioral and pharmacological/molecular interventions for the treatment of drug abuse relapse.

Because of the link between learning and other types of mental disorders, e.g. anxiety disorders, including phobias, other research investigating novel strategies to assess the link between fear conditioning/extinction, behavioral expression, and neurocognitive mechanisms will also be supported in patients suffering from anxiety related behaviors, traits and disorders and in animals and other models relevant to these traits and disorders.

Long Term Objective: (SRO-5.13) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.13 By 2014, establish a process to prioritize compounds that have not yet been adequately tested for more in-depth toxicological evaluation. (Outcome)	*2011*	Complete compound analytical analyses; test main library in >50 qHTS, test >50 compound subset in at least 250 mid-throughput assays. *(Baseline):* Results from FY10 research	N/A
	2010	Establish a >7000 compound library for testing in quantitative high throughput screens (qHTS) and test in >20 qHTS, test >50 compounds (a subset of the main library) in at least 50 mid-throughput assays. *(Baseline):* 1408 compounds successfully tested, as proof-of-principle, in ~50 qHTS assays over a 2-yr period.	N/A

BACKGROUND

According to research published by the National Research Council (NRC) in 2007 on toxicity testing in the 21st century, there are an estimated 100,000 – 125,000 chemicals in use commercially. About 20% of all these chemicals have been evaluated for toxicity. Only about 2-3% have been tested for carcinogenic activity. Determining chemical toxicity, as well as danger to human health, is important for development of prevention or mitigation strategies. Identifying which chemicals may be most hazardous could provide substantial savings in both time and resources.

Current toxicity testing approaches rely primarily on a complex array of studies that evaluate observable outcomes in animals. This strategy is time-consuming and resource-intensive making it more difficult to meet the challenge posed by the large numbers of currently untested chemicals.

Environmental toxins primarily impact living systems by interacting with biological function. This can be illustrated with a toxicity pathway which illustrates how exposures may disrupt normal biological functioning and cause disease. (See Figure 1) The consequences of a biologic disruption or perturbation depend on its magnitude, which is related to the dose, the timing and duration of the disruption, and host susceptibility. The three general methods used to study aspects of a toxicity pathway include: chemical characterization, identification of toxicity pathways, and targeted testing.

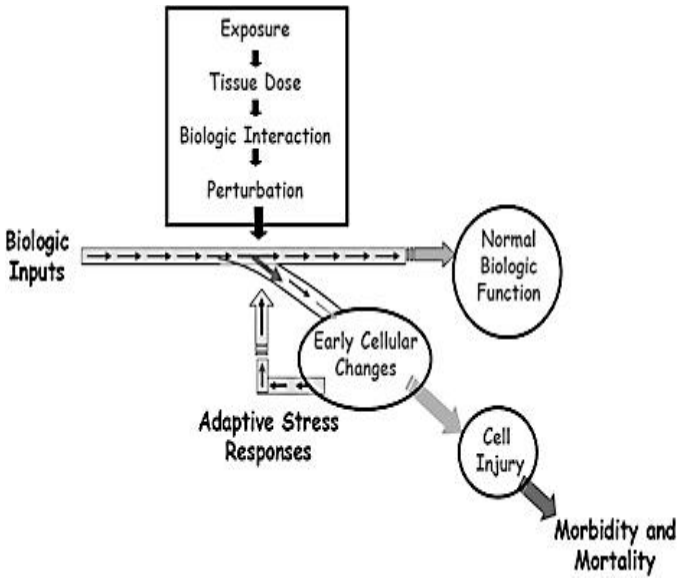


Figure 1 - From: "Toxicity Testing in the 21st Century, a Vision and Strategy" (NRC, 2007)

Chemical characterization collects data regarding physical and chemical properties, use, possible environmental concentrations, metabolites and breakdown products, initial molecular interactions of compounds and metabolites with cellular components, and possible toxic properties. A variety of computational methods might be used to predict those properties and characteristics. After chemical characterization, decisions might be made about what further testing is required or whether it is needed at all.

Identification of toxicity pathways could be the basis of new approaches to toxicity testing and dose-response modeling. In this method, suites of predictive, high-throughput assays use cells or cell lines, preferably of human origin, to evaluate relevant disruptions in key toxicity pathways. High-throughput assays are efficiently designed experiments that can be automated and rapidly performed to measure the effect of substances on a biologic process of interest. These assays can evaluate hundreds to many thousands of chemicals over a wide concentration range to identify chemical actions on gene, pathway, and cell function. Over time, the need for traditional animal testing of toxicity could be greatly reduced.

Targeted testing would be used to complement other tests and to ensure adequate evaluation. Targeted testing involves the use of in vitro or tissue-based tests. One of the challenges of developing an in vitro test system to evaluate toxicity is the current inability of cell assays to mirror metabolism in the integrated whole animal. For the foreseeable future, any in vitro strategy will need to include a provision to assess likely metabolites through whole-animal testing.

Rationale

Toxicity testing is poised to take advantage of the remarkable progress in biology and biotechnology. Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components. These changes could help scientists generate more robust data on the potential risks to humans posed by exposure to environmental agents and to expand capabilities to test chemicals more efficiently.

These scientific advances should allow the current toxicity testing system to be improved and provide a paradigm shift that would evaluate more chemicals at less cost and a faster rate, while at the same time using fewer animals. In addition, this new approach would develop a more robust scientific basis for assessing health effects of environmental agents.

Success in the Tox21 Program is expected to result in in vitro test methods for toxicity testing that are more mechanistically based, more predictive of human health effects, and more economically efficient. As a consequence, a reduction or replacement of animals in regulatory testing is anticipated to occur in parallel with an increased ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation.

A primary focus of this collaboration is to establish a process that will prioritize chemicals in regard to toxicity so that time and resources spent on further toxicological evaluation and testing will be reduced. To achieve this aim the program will identify cellular pathways (and assays for those pathways) that when perturbed are likely to result in a toxic event such as a toxicity pathway (fig. 1), establish a Tox21 library of >7000 compounds, and develop databases and bioinformatic tools needed to mine the resulting data. Ultimately, this project will enhance public health by allowing a better understanding of chemical-induced toxicity particularly for those compounds that have little or no toxicological data. As a result, prevention or intervention efforts may be developed to reduce or eliminate those hazardous substances.

TARGET CONTEXT AND CONDITIONS

In early 2008, the NIH and the EPA began a program to collaborate on the research, development, validation, and translation of new and innovative test methods that characterize how chemicals interact with cellular pathways. The goals of this Program are to investigate the use of new tools to (1) prioritize compounds for further toxicological evaluation, (2) identify mechanisms of action, and (3) better predict human health effects. A central aspect of the Tox21 Program is the application of new methodologies to evaluate large numbers of chemicals to better understand how they impact normal biological processes. This includes using mid- and high-throughput in vitro assays to rapidly screen very large numbers of compounds for potentially toxic effects. The data generated by this program will provide insights into molecular mechanisms of action for toxic compounds. These findings could be useful in identifying the many biological processes relevant to toxicity that may provide improved disease prevention or intervention strategies.

An important step in this program is developing a process to prioritize compounds for further toxicological evaluation. This process will be established using data collected on at least 7000 compounds tested in a minimum of 200 quantitative high throughput screens (qHTS) and on at least 50 compounds tested in a minimum of 500 mid-throughput assays. Initially, the project will establish a library of 7000 or more compounds for testing, and verify the identity, purity, and stability of each compound. This library will be tested in at least 100 qHTS assays. Also, a selected subset of compounds from this library (at least 50) will be tested in at least 500 mid-throughput assays that can provide more in-depth toxicological analysis.

Long Term Objective: (SRO-5.14) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-5.14 By 2013, reduce tobacco prevalence among youth by preventing initiation and increasing rates of cessation. (Outcome)	*2011*	Complete preliminary analysis of intervention data on smokeless tobacco use prevention and cessation, and for effectiveness of smoking cessation interventions and programs in low income youth and adult populations. *(Baseline):* Implemented two prevention/cessation studies.	N/A
	2010	Develop and/or test a smokeless tobacco use prevention intervention for youth, and a study to improve the effectiveness of smoking cessation interventions in low income youth and adult populations. *(Baseline):* Complete protocols for two tobacco prevention/cessation studies.	N/A
	2009	Develop clinical protocols for a study on smokeless tobacco use prevention and cessation, and for a study to improve the effectiveness of smoking cessation interventions in low income youth and adult populations *(Baseline):* Current TCRB portfolio includes 132 grants.	Clinical protocols were developed for 6 studies on smokeless tobacco use prevention and cessation, and 5 studies on improving the effectiveness of smoking cessation interventions in low income youth and adult populations. (Target Met)

Data Source and Validation
Evaluating Nicotine Lozenges for Treatment of Smokeless Tobacco Addiction http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7658239 Varenicline for Smokeless Tobacco Use http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7568685 High Dose Nicotine Patch Therapy for Smokeless Tobacco Use http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7689089 Predictors of Smokeless Tobacco and Dual Use in the US Military http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7741763 Influence of Mint Flavorings and PH on Nicotine Absorption in Smokeless Tobacco http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7742417 Exploring Current Smokers Interest in Using Smokeless Tobacco Products http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7741961 Examining the Effect of a Provider-delivered Intervention among Medicaid Smokers http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7741889 Effectiveness of Proactive Tobacco Treatment in Diverse Low-income Smokers http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7741142 Smoking Cessation Navigation for Low-income Parents: A Pilot Study http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7741408 Integrated Smoking Cessation Treatment for Low-income Community Corrections http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7742534 Culturally-tailored Smoking Cessation for American Indians http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7742113

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY09 target was Met. Clinical protocols have been developed for six studies on smokeless tobacco use prevention and cessation, and five studies on improving the effectiveness of smoking cessation programs in low-income, minority youth and adults. The clinical protocols include research on smokeless tobacco use designed to:

- Estimate the efficacy of 12-weeks of varenicline, and high does nicotine patches, for increasing smokeless tobacco abstinence rates. Varenicline (Chantix) is a novel selective nicotinic receptor partial agonist with specificity for the 1422 nicotine acetylcholine receptor that has demonstrated remarkable efficacy for increasing long-term tobacco abstinence rates in cigarette smokers.
- Assess the efficacy of high dose nicotine patch therapy for increasing long-term smokeless tobacco abstinence rates.
- Examine how novel pharmacotherapies decrease nicotine withdrawal symptoms.

The smoking cessation clinical protocols include research to:

- Test the feasibility of a physician office-delivered smoking cessation intervention targeting smokers enrolled in Medicaid Managed Care Programs in Ohio Appalachia.
- Examine the effectiveness of a proactive outreach strategy, coupled with free nicotine replacement

therapy on diverse, low income smokers.

In addition, NIH research is underway to understand why low-income and minority smokers are less likely than higher-income and white smokers to use effective, evidenced-based smoking cessation treatments that are available. The research incorporates efforts to increase cessation among these vulnerable populations, including youth and adult smokers. For example, a current study is examining the effectiveness of a novel proactive outreach strategy, coupled with free nicotine replacement therapy (NRT) at increasing the population impact of tobacco cessation treatment for diverse, low income smokers. Population impact is the product of treatment utilization (i.e., reach or exposure) and treatment efficacy (i.e., smoking abstinence rates among those who utilize treatment). The researchers' theory- driven approach, will systematically offer low-income smokers free and easy access to evidence-based treatment for tobacco dependence outside the traditional health care system.

BACKGROUND

The 2009 report on the health consequences of smoking by the US Surgeon General indicated that tobacco addiction is a preventable cause of disease and death, which contributes significantly to a wide array of medical conditions including: pneumonia, coronary heart, cardiovascular, and chronic lung diseases, various types of cancers, cataracts, sudden infant death syndrome, ADHD, and addiction. Research data from 2009 on cigarette smoking, cardiovascular disease and stroke and reports on tobacco-health effects and control also support the Surgeon General report. Statistical data from the CDC in 2004 on the burden of chronic diseases and risk factors further validates that tobacco use in the U.S. is a major cause of death and disability, with approximately 440,000 deaths each year attributable to cigarette smoking.

Research results reported as far back as 1988 substantiate what is widely known today, that the agent nicotine is responsible for maintaining tobacco addiction. Over time, tolerance develops to elevated levels of nicotine, along with a dependence on nicotine to maintain brain function. This tolerance and dependence results in a high failure rate reported for smoking cessation efforts. Almost two decades of tobacco treatment research have produced treatment options for tobacco addiction that remain limited and only moderately effective.

Prevalence/Incidence

As recently as June, 2009, the NIH reported on the use of cigarettes and other tobacco products showing that, although significant progress has been made in reducing tobacco use in the United States, many challenges remain. In 2007, approximately one in four adults (24% or about 60 million Americans), and 9.8% of youth 12 to 17 (about 2.5 million) were current cigarette smokers.

The good news is that according to the NIH 2008 Monitoring the Future Survey of 8th, 10th, and 12th graders, cigarette smoking is at the lowest rate in the survey's history. However, in 2008 nearly half (45%) of all high school students had tried smoking, and 20.4% of 12th graders reported using cigarettes in the past month. Of those adolescents who try smoking, about one in three will become regular smokers.

The US Surgeon General has reported on a number of areas focusing on tobacco use, including a 1998 report on tobacco use among US racial / ethnic minority groups which concluded that significant disparities in smoking prevalence exist, based on income, education, race/ethnicity and other factors. Anti-tobacco community and social norms against smoking are not equally distributed across populations and significant knowledge gaps exist regarding how best to strengthen and reinforce anti-tobacco social norms across diverse communities, and counteract competing pro-tobacco social norms. In addition, a 2008 update report from the NIH on tobacco and nicotine research determined that acetaldehyde, a compound found in tobacco smoke, may enhance nicotine's addictive effects, especially in adolescents.

Disease Burden

In a 2008 Centers for Disease Control and Prevention report on the mortality and morbidity of tobacco use from 2000-2004, the estimated annual cost attributable to tobacco use is $193 billion. Research data from 2005

estimate that secondhand smoke exposure has an annual estimated cost of $10 billion. The projected direct medical costs from smoking related diseases are more than $96 billion a year - a significant cost burden to the Nation as reported by the CDC in 2008.

Rationale

Today's world features a changing landscape of tobacco products, evolving tobacco industry marketing and promotion strategies, and new and emerging technologies and media channels. To ensure that tobacco use in the United States continues to decline, innovative research is needed to identify the most effective tobacco control interventions and proven evidence-based tobacco programs needs to be broadly implemented. Intervening at both the individual and population level, including policies, for all population groups is needed if we are to significantly reduce tobacco prevalence in the U.S. In addition, youth tobacco use does not take place in a vacuum. For example, children of parents who smoke are twice as likely to start smoking compared with parents who do not smoke, so that intervening with adults is necessary to impact youth smoking.

TARGET CONTEXT AND CONDITIONS

Tobacco research at the NIH works toward a world free of tobacco use and related cancer and suffering. NIH scientists conduct research and participate in diverse scientific and programmatic activities. Additionally, the NIH, sponsors conferences and symposiums, and disseminates tobacco control science.

During the next three years, NIH will support the development of novel pharmacotherapeutic agents and vaccines to treat tobacco addiction, as well as a focus on primary prevention, especially among youth; and secondary prevention to halt the progression to addiction in those that have already initiated tobacco use. This research includes developing a clinical protocol to test the effectiveness of a combination therapy Varenicline and Bupropion. Bupropion has been shown to increase cessation in adults more effectively than nicotine replacement, and because the safety of this medication has been shown in youth, it is a clear choice for investigation as a pharmacologic treatment for youth smoking cessation. NIH is also undertaking studies to evaluate clinician smoking cessation interventions in primary care community-based pediatric practices. Determining and disseminating information on the types of interventions that work best in pediatric offices will help to increase youth tobacco cessation. Other currently supported studies include testing a cessation program for adolescents, based on Acceptance & Commitment Therapy (ACT). ACT has outperformed other active treatment procedures for smoking cessation among adults. The upcoming ACT study will be the first of its kind to assess ACT effectiveness among teens.

To decrease the public health burden from tobacco use, the NIH continues to support conferences, meetings and workshops. In addition, the NIH partners with a variety of public / private organizations, and other government agencies to build foundations for research initiatives and move science into practice.

Current dissemination activities and collaborations include: Tobacco Research Network on Disparities (TReND), Smokefree.gov, the Transdisciplinary Tobacco Use Research Centers (TTURCs), the Tobacco Control Monograph series, Public Health Service (PHS) guidelines, and other tobacco related publications.

Long Term Objective: (SRO-6.1) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-6.1 By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans. (Outcome)	*2011*	Conduct Genome-Wide Association studies (GWAS) of glaucoma cohorts and make data available for research purposes. *(Baseline):* Previous GWAS do not have the statistical power to identify new genes for POAG.	N/A
	2010	Explore genetic factors involved in neovascularization related to AMD. *(Baseline):* Anti-VEGF drugs can treat 'wet' AMD; newly discovered role for inflammation genes opens new research avenues	N/A
	2009	Determine the phenotypic expression of naturally-occurring or chemically- or environmentally-induced genetic changes in animal models of glaucoma or age-related macular degeneration (AMD) to characterize the genetic mechanisms involved in disease pathogenesis. *(Baseline):* Findings from FY08	Phenotypic expression studies in multiple animal models characterized proteins and genes involved in AMD and glaucoma pathogenesis, including a potential AMD biomarker and therapeutic target, CCR3. (Target Met)
	2008	Conduct haplotype analysis to identify common risk haplotype for genes associated with primary open-angle glaucoma (POAG) through single-nucleotide polymorphism (SNP) genotyping. *(Baseline):* (FY06) Twelve genes associated with glaucoma have been mapped six genes have been cloned.	Haplotype analyses on African American populations identified key regions on chromosomes 2 and 3 associated with POAG. NIH also launched two new POAG GWAS projects in the US. (Target Met)
	2007	Conduct studies in animal models to identify potential modifier genes. *(Baseline):* (FY05) Modifier genes for AMD and glaucoma have not yet been identified.	Genes that modify risk/progression of complex eye diseases were identified and validated using animal models. (Target Met)
	2006	Develop animal models of AMD and glaucoma that closely mimic the pathologic processes underlying these diseases in humans. *(Baseline):* (FY05) Existing animal model systems for AMD and glaucoma do not closely resemble the human disease	Animal models have been established for glaucoma and age-related macular degeneration. (Target Met)

Data Source and Validation
Takeda A., Baffi J.Z., Kleinman M.E., Cho W.G., Nozaki M., Yamada K., Kaneko H., Albuquerque R.J., Dridi S., Saito K., et al. CCR3 is a target for age-related macular degeneration diagnosis and therapy. Nature (2009); 460:225–230. http://www ncbi nlm nih.gov/pubmed/19525930 Chan C-C, Ross RJ, Shen D, Ding X, Majumdar Z, Bojanowski CM, Zhou M, Salem, Jr. N, Bonner R, Tuo J: Ccl2/Cx3cr1-Deficient Mice: An Animal Model for Age-Related Macular Degeneration. Ophthalmic Res (2008);40:124-128. http://www ncbi nlm nih.gov/pubmed/18421225 Walsh MM, Yi H, Friedman J, Cho KI, Tserentsoodol N, McKinnon S, Searle K, Yeh A, Ferreira PA. Gene and protein expression pilot profiling and biomarkers in an experimental mouse model of hypertensive glaucoma. Exp Biol Med (2009); 234(8):918-30. http://www ncbi nlm nih.gov/pubmed/19491369 Anderson MG, Nair KS, Amonoo LA, Mehalow AK, Trantow CM, Masli S and John SWM, GpnmbR150X allele must be present in bone marrow derived cells to mediate DBA/2J glaucoma, BMC Genet. (2008) 9: 30-43. http://www ncbi nlm nih.gov/pubmed/18402690 Howell GR, Libby RT, John SWM. Mouse genetic models: an ideal system for understanding glaucomatous neurodegeneration and neuroprotection. Progress in Brain Research (2008) 173:303-321 http://www ncbi nlm nih.gov/pubmed/18929118 Jiao X, Yang Z, Yang X, Chen Y, Tong Z, Zhao C, Zeng J, Chen H, Gibbs D, Sun X, Li B, Wakins WS, Meyer C, Wang X, Kasuga D, Bedell M, Pearson E, Weinreb RN, Leske MC, Hennis A, DeWan A, Nemesure B, Jorde LB, Hoh J, Hejtmancik JF, and Zhang K. Common variants on chromosome 2 and risk of primary open-angle glaucoma in the Afro-Caribbean population of Barbados. PNAS (2009) 106: 17105-17110. http://www ncbi nlm nih.gov/pubmed/19805132 Schmid-Kubista KE, Tosakulwong N, Wu Y, Ryu E, Hecker LA, Baratz KH, Brown WL, Edwards AO. Contribution of copy number variation in the regulation of complement activation locus to development of age-related macular degeneration. Invest Ophthalmol Vis Sci. (2009);50(11): 5070-9. http://www ncbi nlm nih.gov/pubmed/19553609 Hecker LA, Edwards AO, Ryu E, Tosakulwong N, Baratz KH, Brown WL, Issa PC, Scholl HP, Pollok-Kopp B, Schmid-Kubista KE, Bailey KR, Oppermann M. Genetic control of the alternative pathway of complement in humans and age-related macular degeneration. Hum Mol Genet. (2009) in press. http://www ncbi nlm nih.gov/pubmed/19825847

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH researchers conducted phenotypic expression studies in multiple animal models and characterized proteins and genes involved in AMD and glaucoma pathogenesis. Investigators identified and verified the protein CCR3 as a potential AMD biomarker and therapeutic target. Researchers studying Ccl2 and CX3CR1, mutants in the chemokine protein family, observed AMD-like phenotypes in animal models, which helped them identify the potential roles of genetic factors. Additionally, mouse models of glaucoma led researchers to identify genes affected by intraocular hypertension, and also to understand the role of the Gpnmb gene in altering the immune system to confer disease susceptibility.

The ‘wet’ form of AMD in humans is characterized by the abnormal growth of new blood vessels in the eye, called choroidal neovascularization (CNV), compared to the ‘dry’, less severe, form which does not involve neovascularization. NIH researchers studying CNV in human patients with AMD discovered that the protein CCR3 is expressed in choroidal cells. However, CCR3 is not expressed in disease-free subjects, or from early stage AMD patients who do not yet demonstrate CNV (i.e., patients with ‘dry’ AMD). Therefore, CCR3 may

serve as a biomarker for detecting CNV in patients at early stages of AMD before vision loss occurs.

Researchers then tested if CCR3 stimulated blood vessel growth in the choroid. In tissue surgically removed from AMD patients with CNV, drugs that block CCR3 prevent additional vessel growth. The information gained through human testing was then transferred into a mouse model. Investigators using a laser-induced mouse model of CNV found that genetic or pharmacological manipulations that block CCR3 reduced the number of cells that lead to CNV, whereas pharmacologically stimulating CCR3 protein activity increased proliferation of these cells. Researchers found that, in mice, drugs against CCR3 are more effective than currently available therapies used to treat CNV, which means CCR3 may be a valuable therapeutic target.

NIH researchers characterized the ocular phenotypic expression (observable traits of the eye) of two genes, Ccl2 and CX3CR1, recently associated with AMD in human trials, by creating a mouse model with mutations in both genes. These mice developed pathological symptoms consistent with human AMD phenotypic expressions, such as drusen (yellow deposits on the retina), abnormal retinal cells and lesions, CNV, and accumulation of a granular pigment, lipofuscin, in ocular tissues of these animals. The researchers also discovered four proteins with significantly altered expression, including one that helps newly created proteins fold correctly. This protein, part of the chaperone family of proteins, has been reported at decreased levels in the aging retina and in AMD.

Researchers also investigated intraocular pressure (IOP) dependent changes in gene and protein expression in a mouse glaucoma model. One of the hallmark risk factors in glaucoma is elevated IOP, which leads to optic nerve damage and vision loss. The mechanism by which high IOP induces neurodegeneration is not understood. The researchers found changes in genes involved in neuronal survival, inflammation and in the function of two cellular organelles: mitochondria and peroxisomes. Another group of researchers explored the role of immune cells in another mouse model of glaucoma. The investigators were able to block the development of some glaucoma phenotypes, including increased IOP, by injecting bone marrow cells from a control mouse into the glaucoma model mouse. The researchers pinpointed a gene, Gpnmb, expressed in a type of immune cell derived from the bone marrow cells, that was necessary for the treatment to work. These findings suggest that abnormal immune cell regulation may contribute to this complex disease.

Advances or Other Highlights

Glaucoma is the leading cause of blindness among African Americans, but discovering the genetic risk factors have been elusive. Research data reported in September 2009 by an NIH-supported international team studying glaucoma in an Afro-Caribbean population in Barbados supported the discovery of a gene mutation on human chromosome 2 that accounted for nearly one-third of the genetic risk for the disease. A particularly high incidence of glaucoma on the island of Barbados pointed to a strong genetic predisposition towards the disease; 40 percent of the 249 glaucoma patients studied had a disease causing variant of the gene.

Following up on the landmark discovery in 2005 implicating an immune process known as the alternative complement pathway in AMD, investigators examined human genetic variation in some key complement genes: complement factor H, factor B and component 3. The researchers found that activation of the alternative pathway is controlled genetically, and increases with age. Genetic variation associated with increased pathway activation in the blood increased the risk of AMD. The group also looked at copy number variations for two genes related to complement factor H. In cases where both related genes were deleted, the risk of AMD decreased eightfold. Understanding the genetic risk factors for AMD and glaucoma could support more personalized medicine to reduce the burden of disease.

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. According to 2004 published data on prevalence of AMD, of the nearly 60 million people in the United States age 55 or older in the year 2000, an estimated 7.3 million are at risk of developing advanced, sight-threatening AMD in one or both eyes and 1.75 million citizens currently have AMD. This number is expected to increase to nearly 3 million by the year 2020. 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 currently, and this number will increase substantially due to the aging of the U.S. population.

Disease Burden

A 2004 NIH funded meta-analysis of eye disease epidemiology data indicated that 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. In addition, the analysis indicated that 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.

TARGET CONTEXT AND CONDITIONS

NIH began 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) enables researchers to accelerate the identification of genes that control risk for AMD and glaucoma.

Another important implementation strategy was developing standards for AMD phenotyping and agreement on precise definitions of the diverse retinal phenotypes found in macular disease. Work on AMD human genetics requires common disease descriptors and a systematic phenotyping system. This was accomplished through an existing network of reading/grading centers that review photographs of ocular pathology, both nationally and internationally. Representatives from each of these centers helped set uniform standards, examined existing descriptors to find common elements, pooled data, and determined mechanisms for sharing data. Using a consensus approach, a descriptive manual with standards was developed that will allow investigators around the world to have a 'common language' to describe different stages and forms of macular disease.

In December 2006, NIH launched the Database of Genotype and Phenotype (dbGaP) using the dataset from the Age-Related Eye Diseases Study (AREDS), a landmark study of the clinical course of Age-related Macular Degeneration (AMD) and cataracts. This database enables Genome-Wide Association Studies (GWAS), an analytic technique to assess how genetic variations across the entire human genome correlate with disease manifestation. Using these data, recent studies demonstrated an association of the complement system and inflammation with AMD, and linked two genes with the observed progression to advanced (or 'wet') AMD. In addition, the National Eye Disease Genotyping Network (EyeGENE) was created to assist in developing awareness of resources available to people affected with ocular genetic diseases, their clinicians, and researchers.

Complex diseases like AMD and glaucoma involve the interaction of multiple genetic and environmental factors. In addition, modifier genes may alter the progression or severity of a disease among affected individuals. Animal models are useful tools that allow investigators to explore complex genetic and biochemical interactions that cannot be directly tested in humans. Several candidate genes, including fibrillin-6 and Stargardt gene for AMD, and optineurin for glaucoma, have been identified in animal models. Research testing mutated forms of these genes, and other candidate genes identified in human genetics studies, is proving invaluable. Ultimately, therapies that delay, prevent, or reverse the effects of these genetic alterations in animals can be tested and may lead to studies in humans.

Also important in progress toward this goal is providing investigators with genetic material and information from well-characterized patients. Population-based resources of blood, transformed lymphocytes, and DNA from patients with AMD and glaucoma will be made available to investigators nationally. In addition, Genome-Wide Association studies (GWAS) will be conducted and the genotypic and phenotypic data will be available for research purposes. 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. Large-scale DNA collections allow geneticists to narrow in on disease-causing genes by studying haplotypes, a set of closely linked genes inherited as a unit. By using small changes in DNA called Single Nucleotide Polymorphisms (SNPs) as landmarks, geneticists can pinpoint regions of chromosomes and eventually specific genes that give rise to disease. It will also be necessary to accelerate the application of candidate gene and other genetic approaches to the study of AMD and glaucoma.

In advanced AMD, Vascular Endothelial Growth Factor (VEGF) induces abnormal neovascularization, the growth of new blood vessels, often resulting in blindness. Therapeutic strategies that block VEGF in the retina have been successfully applied to slow progression of AMD, and in some cases, reverse advanced AMD and improve vision. Recently, a genetic variant of complement factor H, important in immunity and inflammation, was shown to be associated with about half of the cases of AMD. This suggests that additional alterations of genes involved with innate immunity and vascular formation are likely to be involved in AMD. Genetic and observational studies in humans have also identified a role C-reactive protein and complement factor B, however, to date the mechanism by which inflammation impacts AMD is not well understood and few other genes have been identified and validated. Additional genetic studies using animal models might lead to new therapeutic options.

Long Term Objective: (SRO-6.2) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-6.2 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. (Outcome)	*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. *(Baseline):* Initial findings from Bari2D, ACCORD, Look Ahead, and FAVORIT trials.	N/A
	2010	Report findings of the primary results of the Bari2D Trial. *(Baseline):* (FY08) Investigators have collected data on interventions to reduce CVD morbidity in patients with type 2 diabetes.	N/A
	2009	Complete treatment and follow-up of participants in the ACCORD trial to determine effects of glycemia, blood pressure, and blood lipid treatment approaches to prevent CVD in diabetes. *(Baseline):* (FY07) 10,251 participants were randomized in the ACCORD trial.	Each of the 77 clinical sites transitioned participant care to personal physicians and established follow up strategies. The glycemia component was terminated early due to higher mortality in the intensive glycemia group compared to mortality in the control group. (Target Met)
	2008	Review and evaluate collectively, indicators of Look AHEAD's progress to date (measures such as safety-monitoring analyses, data quality, participant retention, and emerging positive or negative outcome trends) in order to determine whether the science is progressing appropriately--in accord with the clinical trial protocol--and whether the trial will be continued. *(Baseline):* (FY07) Human clinical trials require periodic review and evaluation to assess progress.	The Look AHEAD Data Safety and Monitoring Board reviewed and evaluated the raw data from the study's indicators to date, including safety-monitoring analyses, data quality, participant retention, and emerging positive or negative outcome trends, and has made a determination that the science is progressing appropriately and the trial should continue. (Target Met)

Measure	FY	Target	Result
	2007	Complete at least 90% of the total enrollment for the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial which aims to determine whether reduction of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in significant reduction in atherosclerotic CVD. *(Baseline):* (FY04) As of August 2004, a total of 2,000 study participants have been randomized into the trial.	FAVORIT enrolled and randomized the total trial population (4,000 patients) from sites located in the United States, Canada, and Brazil, by January 2007. (Target Met)
	2006	Look AHEAD aims to report outcome data on the success of the one-year intensive weight loss intervention and its impact on CVD risk factors such as diabetes control, lipids, blood pressure, and fitness. *(Baseline):* (FY05) Information is not available regarding the impact of a one-year intensive weight loss intervention on these parameters in a similar diabetic population	Initial findings from Look AHEAD were presented at the annual Society of Behavioral Medicine meeting in March 2006. One-year results from Look AHEAD on reduction in weight and cardiovascular disease (CVD) risk factors in type 2 diabetes were presented at the annual American Diabetes Association meeting in June 2006. (Target Met)

Data Source and Validation
N Engl J Med 2008; 358:2545 - 2559 http://content nejm.org/cgi/reprint/358/24/2545.pdf The ACCORD Clinical Trial www.accordtrial.org

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 Target was Met. All 77 clinical sites in the ACCORD trial scheduled and held follow-up visits with all the available ACCORD participants, final data were collected, and the clinics assisted in transitioning medical care to participants' own physicians.

Advances or Other Highlights

On February 6, 2008, the process was announced to transition participants in the intensive glycemia treatment to the ACCORD standard treatment approach due to higher mortality in the intensive treatment group. These results were published in the New England Journal of Medicine in June 2009. The trial results demonstrated that intensive glycemia lowering with a multicomponent treatment regimen increased all-cause mortality in these participants, all of whom were at substantially elevated risk of a cardiovascular event due to existing disease or multiple risk factors, and had diabetes for an average of 10 years. There was no significant reduction in the primary outcome of cardiovascular morbidity and mortality. A 5-year study will continue to follow the ACCORD participants to examine any longer-term effects.

BACKGROUND

Cardiovascular disease (CVD) is the leading cause of death in the United States according to CDC data for 2006. The rates of CVD are elevated 2- to 4-fold in people with diabetes compared with the general population. While the Nation as a whole has seen a significant decline in deaths from CVD, no decline has occurred among patients with type 2 diabetes. The importance of identifying new approaches to preventing and treating CVD in patients with type 2 diabetes has become more critical given the current national epidemic of this disease as noted in 2008 CDC diabetes alerts. The need for improved therapy to reduce CVD in chronic kidney disease patients is underscored by the fact that several million Americans have moderately decreased kidney function which places them at substantially increased risk for CVD. Moreover, in patients with kidney failure, the primary cause of death is CVD, according to 2009 data on the United States Renal Data System (USRDS).

Prevalence/Incidence

Diabetes and kidney disease are both increasing in prevalence and both diseases markedly increase the risk for life-threatening cardiovascular disease (CVD).

- In 2007, the prevalence of diabetes in the United States was approximately 24 million people, or 8 percent of the population, with approximately 90-95 percent of this number having type 2 diabetes, as reported by the CDC in 2008.
- According to the CDC diabetes data facts for 2007:
    - CVD accounts for two-thirds of deaths among people with diabetes and 7.8% of the risk of CVD is attributed to diabetes.
    - Chronic kidney disease is estimated to affect as many as 25 million Americans 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 500,000.
- Heart disease and stroke are the leading causes of death in patients with ESRD as cited in the 2009 annual data report by the USRDS.

Disease Burden

The Nation faces national epidemics of both type 2 diabetes and ESRD. In 2007, the economic cost of diabetes in the United States was estimated at $174 billion according to the CDC diabetes data facts for 2007. 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 American Indians. Among adults with diabetes, heart disease death rates are two to four times higher than in the general population. Diabetes also negates the protection gender affords non-diabetic women. 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. As rates of diabetes rose the proportion of CVD risk attributable to diabetes increased by 50% from the 3rd to 4th quarter of the 20th Century. Chronic kidney disease is also a significant health burden according to the 2007 annual data report by USRDS. In its most severe forms, it leads to ESRD, in which either dialysis or kidney transplantation is required to maintain life. About half of new cases of ESRD are as a consequence of diabetes. The number of patients with ESRD has doubled over the past decade, with the increasing disease burden most pronounced among minority populations, especially African Americans and American Indians. 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. Even among chronic kidney disease patients with a mild to moderate reduction in kidney function, CVD rates are increased twofold to fourfold. In 2005, the total cost of caring for the ESRD population was $32 billion; of this Medicare covered $21.3 billion. The ESRD population consumes 7.5 percent of program expenditures despite the fact that these patients only make up 1.2 percent of the Medicare population. According to new data for 2008 released by the NIH-supported United States Renal Data System, rates for new cases of kidney failure have stabilized after 20 years of five to ten percent annual increases; however, racial disparities in the rates of ESRD persist.

Rationale

For both diabetes and kidney disease, premature CVD is the major cause of death. This research addresses a significant public health problem by seeking to evaluate approaches for reducing CVD outcomes, such as heart attacks and strokes, in patients with type 2 diabetes and/or chronic kidney disease. Application of the results of the trials, if favorable, would extend the lifespan and improve the quality of life for persons with type 2 diabetes or kidney disease.

The research will further address a critical knowledge gap. While some clues and some promising therapies have emerged from previous epidemiologic and clinical trials, many unanswered questions remain. For example:

- Recent clinical trials established the benefit of the management of both blood pressure and low-density lipoprotein-cholesterol (LDL) in reducing CVD risk in type 2 diabetes and of glucose control in reducing CVD risk in type 1 diabetes, but a number of potential strategies to reduce CVD risk require further study.
- Although even moderate weight loss can dramatically reduce the development of type 2 diabetes among those at high risk, a benefit of intentional 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, and has recently been shown to reduce CVD in type 1 diabetes, its benefits in reducing CVD in type 2 diabetes are not fully established, and it is not known whether insulin-providing or insulin-sensitizing strategies for glucose control is more effective in reducing CVD mortality.
- Lowering of LDL cholesterol has been shown to prevent CVD in general, but type 2 diabetes is associated with a distinct lipid profile, with low high-density lipoprotein (HDL) cholesterol and increased triglycerides. 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, is a putative risk factor for CVD. Folate and B-vitamin supplementation can normalize homocysteine levels in patients with mild chronic kidney disease; however, their effect on CVD risk remains to be determined.
- Kidney transplant recipients typically have reduced levels of kidney function, thus can be considered chronic kidney disease patients.

Once individuals with diabetes develop coronary artery disease, the optimal treatment approach is not clear; for example, it is not known whether bypass surgery or artery-opening with placement of a drug-eluting stent would provide a better outcome.

TARGET CONTEXT AND CONDITIONS

The NIH has initiated research to support a set of major, multicenter, randomized clinical trials, each of which has both long term objectives and milestones that provide performance targets/measures. The set of trials is unparalleled in scope and research intensity and, collectively, could not be replicated by other organizations.

Look AHEAD [Action for Health in Diabetes] Trial. This is the largest clinical trial to date to examine the long-term health effects of intentional weight loss in patients with type 2 diabetes: specifically assessing the benefits and risks of weight loss with respect to cardiovascular events. The study will also investigate the cost effectiveness of the intervention. Over 5,000 patients with type 2 diabetes, with or without CVD, who are overweight or obese at study entry (BMI of 25 or over) are enrolled.

Note: Although the Look AHEAD clinical trial will not be completed until 2013, it will generate intermediate outcomes that will contribute to ongoing research. . For example, previous research focused on providing outcome data on the success of the one-year intensive weight loss phase and the effect of the weight loss intervention on important clinical measures such as diabetes control, lipids, blood pressure, and fitness. Significant cost savings will accrue from not having to conduct similar studies in a separate trial.

ACCORD [Action to Control Cardiovascular Risk in Diabetes] Trial. The objective of this trial is to determine whether each of three treatment approaches reduces the incidence of cardiovascular complications of type 2 diabetes. The target patient recruitment is 10,000 patients with type 2 diabetes who either have CVD or are at high risk of developing CVD. The three treatment approaches are: (1) intensive control of blood glucose compared with standard control, (2) intensive control of blood pressure compared with standard control, and (3) treatment to raise HDL cholesterol (the "good" cholesterol) and lower blood triglycerides as well as lower LDL cholesterol (the "bad" cholesterol) compared with a treatment that only lowers LDL cholesterol. The treatment approach of intensive control of blood glucose was stopped due to safety concerns and a recommendation by the DSMB. The Blood Pressure and Lipid trials are continuing to their planned completion dates.

BARI 2D [Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes] Trial. The primary long-term aim of the trial is to answer the following questions: (1) Does immediate elective revascularization reduce CVD morbidity and mortality over and above intensive medical management of the patients' coronary artery disease and risk factors? (2) Does blood glucose control that includes lowering insulin resistance reduce CVD morbidity and mortality more than comparable blood glucose control without medicines that lower insulin resistance? The target patient recruitment is 2,300 patients with type 2 diabetes and stable coronary artery disease who might be candidates for revascularization.

FAVORIT [Folic Acid for Vascular Outcome Reduction in Transplantation] Trial. This trial aims to determine whether reduction of level of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in a significant reduction in arteriosclerotic CVD (compared with a control group whose homocysteine levels are expected to remain the same over time). A total of 4,110 kidney transplant recipients were recruited.

Long Term Objective: (SRO-6.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-6.4 By 2014, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations. (Outcome)	*2011*	Characterize cellular and molecular inflammation in the distal lung that may contribute to severe disease with frequent exacerbations. *(Baseline):* Little is known about the role of inflammation in the distal lung in the pathology of severe, exacerbation-prone asthma.	N/A
	2010	(FY10) Describe phenotypic characteristics of a group of asthma patients prone to exacerbations. *(Baseline):* (FY09) Little is known about clinical/physiologic characteristics of asthma patients prone to AE compared to those who are not.	N/A
	2009	Identify single nucleotide polymorphisms (SNPs) in DNA that may be associated with AE in children. *(Baseline):* SNPs associated with asthma risk have been identified, but none have been associated specifically w/AE in children.	A SNP(-251) in the Interleukin-8 gene was identified and found to be associated with exacerbations of asthma in children. (Target Met)
	2008	Use advanced radiological and molecular imaging techniques to increase understanding of changes in pulmonary physiology associated with asthma exacerbations. *(Baseline):* (FY06) Limits of imaging methods have made it difficult to understand how AEs affect pulmonary physiology.	Advanced imaging techniques such as multiple detector (MD) CT, 3He-MRI, and FDG-PET have been performed on approximately 40 subjects with AE. (Target Met)
	2007	Analyze data from studies of molecular, cellular, and genetic causes in AE. *(Baseline):* (FY05) Little information is available on how environmental factors affect the lung and subsequently result in AE.	Investigators met to share findings from data analyses of studies of molecular, cellular, environmental, and genetic causes in AE. (Target Exceeded)

Measure	FY	Target	Result
	2006	Initiate study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history. *(Baseline):* (FY05) Little is known about the role glycosidase activity may play in modification of airway glycans and the promotion of virus-induced AE.	A study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history was initiated in July 2005. (Target Exceeded)

Data Source and Validation
The results are detailed in the final progress report for grant R01-HL080083. More information on the progress report is available from the NHLBI Office of Science and Legislation Programs.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. A particular genotype associated with a specific SNP (-251) in the Interleukin-8 gene was identified and found to be significantly associated with asthma exacerbations in children that correlate with inflammatory cells called neutrophils. This association was independent of whether the children were treated with corticosteroids for asthma. These results may provide a rationale for designing targeted interventions for the prevention of neutrophilic exacerbations in childhood asthma.

BACKGROUND

Asthma is a chronic lung disease that involves inflammation and narrowing of the airways. Patients with asthma experience recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma exacerbations (also known as asthma attacks) are defined by worsening or new symptoms and are a major cause of morbidity and mortality in asthma patients and a significant concern for the clinical management of the disease. But little is known about the pathophysiologic processes that occur during exacerbations, how exacerbations resolve, the effects of exacerbations on future exacerbation severity and frequency, and the long term effects of exacerbations on lung physiologyand function and on disease progression.

Prevalence/Incidence

According to 2009 research data from the NIH, asthma prevalence has increased significantly over the past 20 years: in 2007, nearly 11 percent of U.S. adults had been diagnosed with asthma. The 2007 Morbidity and Mortality Chart Book from the National Center for Health Statistics indicates that, for the adult population, the disease affects women and minorities disproportionately with prevalence rising to over 20 percent in some groups. Prevalence in children has reached 13 percent in the United States. Boys are more likely to be diagnosed with asthma than girls. Prevalence in boys begins to decrease around puberty at the same time that it begins to increase in girls, resulting in an overall increased prevalence in women. Clinical research published in 2009 on improving asthma outcomes in minority children shows that minority and low socioeconomic status children are disproportionately affected and are more likely to have suffered an attack in the past twelve months.

Disease Burden

In 2007, the National Center for Health Statistics reported that asthma is a major cause of lost days from work and school, sleep disruption, restricted activities, physician and emergency department (ED) visits, and asthma-related mortality. In 2007, an estimated 23 million people in the U.S. had asthma, resulting in nearly 11 million physician visits and nearly 2 million ED visits. The annual cost of asthma to the U.S. economy is estimated at

$21 billion. Hospitalizations and ED visits account for nearly 50 percent of the overall cost. According to 2007 study reports on the national estimate of the economic costs of asthma, although only 20 percent of asthmatics have been admitted to an ED or hospital, these patients account for more than 80 percent of total direct costs and the average annual cost per patient who had an asthma attack is more than three times higher than the cost per patient who did not have an attack. Asthma exacerbations (AE) contribute significantly to loss of disease control and increased healthcare costs.

Rationale

The NIH supports a comprehensive asthma program to develop new approaches to prevent, treat, and control asthma. AE cause many of the negative effects of asthma and management of AE accounts for a large proportion of the estimated annual cost to the U.S. economy. In contrast to our understanding of the basic underlying inflammatory mechanisms of asthma pathogenesis, little is known about the pathophysiologic processes that occur during an exacerbation, how exacerbations are resolved, the effect of AE on future exacerbation severity and frequency, and the long term effects of AE on lung physiology, function, and disease progression. Research is needed to develop more effective treatments to control exacerbations and to maintain or improve lung function.

Molecular pathways, chains of sequential biochemical reactions that take place inside cells, are responsible for the characteristic responses that underlie physiological states and pathophysiological states, including asthma exacerbations. The many steps that comprise a pathway can offer numerous targets for intervention with drugs or immune modulators. Defining which pathways participate in the physiological processes observed in AE is an essential prerequisite for the discovery of new therapeutic agents.

The potential relationship between exacerbations and progressive loss of lung function needs to be explored and defined. Since exacerbations often occur while a patient is receiving treatment, it is likely that the mechanisms responsible for AE are distinct from the processes in more stable asthma. Many patients with asthma experience AE that seem to resolve completely with periods of normal lung function in between each exacerbation. However, it is unclear whether changes in lung structure, function, and immune response remain following AE that lead to future episodes and ultimately contribute to disease chronicity and persistence.

TARGET CONTEXT AND CONDITIONS

Little is known about AE, one of the principal causes of asthma morbidity. In order to develop new interventions to prevent and/or help resolve AE, the NIH initiated a set of basic, clinical, and translational studies to determine the molecular, cellular, and genetic causes of AE. The long term goal is to identify and characterize two molecular pathways of potential clinical significance that may serve as a basis for discovering new medications for preventing and treating AE. The studies will address diverse areas including: the role of environmental triggers in enhancing airway hyperresponsiveness, the relationship of environmental factors to frequency and severity of AE, specific effects of initiating events on lung physiology and inflammation, genetic approaches to individual susceptibility for AE, and the role specific immune and lung cells play in the pathobiology of AE.

Glycans are molecules that may play a role in host defense, including defense against viral airway infection, one of the most common triggers for AE. An individual's 'secretor' status is defined by enzymatic activity involved in glycan biosynthesis (glycosyltransferases) and glycan degradation (glycosidases). The secretor status and frequency of viral airway infection in asthmatic patients hospitalized for management of acute asthma symptoms will be compared to asthmatic individuals without a history of exacerbation requiring hospitalization. The role of glycans and glycosidases during virus-induced AE will also be studied.

As the studies to determine the molecular, cellular, and genetic causes of AE progress, periodic review and analysis of data collected (prior to completion of the studies) is critical for determining future research direction. During the course of the studies, investigators will meet to share experiences, successes, and

concerns, as well as to assess the state of the field.

Imaging modalities have not been used effectively to study the development of AE. Future research directions could include evaluating the use of new imaging techniques to assess obstruction in the lung as it relates to the thickness of the airway wall and inflammation and to visualize the ventilated airspaces under both dynamic and static conditions. The research will contribute to the understanding of lung physiology, in general, the relationship between inflammation and lung physiology, and alterations in lung physiology that occur during AE.

Long Term Objective: (SRO-6.5) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-6.5 By 2014, develop and evaluate two new interventions for the prevention and/or treatment of HIV disease utilizing the newly restructured HIV/AIDS clinical trials networks. (Outcome)	*2011*	Complete enrollment of study examining the effectiveness of antiretroviral (ARV) therapy for prevention of HIV transmission in serodiscordant (one partner with and one without HIV) couples. *(Baseline):* Correlation between HIV viral load and HIV transmission.	N/A
	2010	By 2010, initiate studies to evaluate strategies to protect HIV-infected pregnant women from disease progression and protect their babies from becoming infected in utero, at delivery or during breastfeeding. *(Baseline):* (FY09) Strategies for MTCT in resource limited countries can lead to drug resistance in pregnant women and their infants.	N/A
	2009	Complete preliminary analysis of study to determine impact of the use of therapies to control STDs that may play a role as a co-factor in HIV-acquisition. *(Baseline):* (FY08) Some STDs that cause genital ulcerative disease (GUD) may play a role in HIV-acquisition.	Completed study analysis shows no evidence that standard acyclovir regimens prevent HIV infection; however it does reduce the occurrence of genital sores. (Target Met)
	2008	Establish 140 domestic and international clinical research sites to conduct HIV prevention and therapeutic clinical trials. *(Baseline):* (FY07) Awards were made to 6 newly restructured HIV/AIDS clinical trials networks in FY06 to address the six highest priorities in HIV/AIDS clinical research.	NIH established 184 clinical research sites and 74 clinical research units in domestic and international locations to conduct HIV prevention and therapeutic clinical trials. (Target Exceeded)

Data Source and Validation
http://www3 niaid.nih.gov/news/newsreleases/2008/hptn039 htm http://www hptn.org/research_studies/HPTN039.asp http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)60920-4/fulltext http://www hptn.org/web%20documents/HPTN039/HPTN039Backgrounder31Jan08FINAL.pdf

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH-supported researchers completed the analysis of a clinical study (HPTN 039) designed to examine whether people infected with herpes simplex virus type 2 (HSV-2), the virus that causes genital herpes, can reduce the risk of becoming infected with HIV by using acyclovir, an approved drug that suppresses genital herpes. The analysis of the clinical data showed no evidence that the standard acyclovir regimen prevents HIV infection among HSV-2 infected people. Specifically, there was a 3.9 percent HIV incidence rate (75 cases) among the 1581 participants who received acyclovir, while there was a 3.3 percent HIV incidence rate (64 cases) among the 1591participants who received placebo. This was not a statistically significant difference.

The analysis of acyclovir for suppressing genital herpes provided additional evidence that acyclovir reduces the occurrence of genital sores. The study volunteers who received acyclovir had a 37 percent decrease in genital ulcer incidence and a significantly lower proportion of ulcers due to HSV-2. An individual infected with HSV-2 who has sex with an HIV-infected individual is at a greater risk of acquiring HIV than individuals who are not infected with HSV-2. Genital ulcers, the sores or small breaks in the skin of the genital area caused by HSV-2 infection, make it easier for HIV to enter the bloodstream during sexual intercourse. Throughout the course of the study, volunteers were counseled on how to avoid exposure to HIV and were supplied with condoms.

Advances or Other Highlights

An ancillary study of HPTN 039 was conducted to determine the effect of HSV-2 suppression with twice-daily acyclovir on HIV viral set point during the first six months after HIV acquisition. The researchers also assessed the effects of acyclovir suppressive therapy on CD4 counts during the first six months after infection and described the incidence and severity of clinical HSV reactivation. The results of this ancillary study are not yet available. Another substudy is currently ongoing at select sites to examine the pharmacodynamics of acyclovir.

BACKGROUND

The main cause of HIV transmission continues to be via sexual transmission. Sexually transmitted diseases (STDs) is a primary risk factor in the transmission of HIV. The presence of infected white blood cells increase on contact areas, which compromises the body's ability to fight infection leading to increased chances for HIV transmission. Antiretroviral treatment or "cocktails" aim to keep the amount of HIV in the body at a low level. The cocktail consists of specific combination of drugs that an individual must take for the rest of their life. Antiretroviral treatment can prolong the time between HIV infection and the onset of AIDS. Over time, HIV slowly weakens the immune system to the point where it is not able to effectively fight the disease and many other health problems can develop. These health problems include, systemic infections and cancers that a healthy immune system would normally prevent. Treatment focuses on the specific health problem. The onslaught of the treatments continue to weaken the immune system, the body is unable to fight the illnesses and AIDS is eventually diagnosed.

Prevalence/Incidence

In 2007, there were an estimated 2 million deaths worldwide due to HIV/AIDS. While there has been a decline in HIV/AIDS mortality as a result of increased antiretroviral treatment, HIV/AIDS remains a leading cause of death worldwide and the primary cause of death in sub-Saharan Africa. In 2007, there were an estimated 2.7

million new HIV infections and a total of 33 million people living with HIV/AIDS globally. The number of children living with HIV/AIDS increased from 1.5 million in 2001 to 2 million in 2007, although the number of new infections per year decreased among children from 460,000 in 2001 to 370,000 in 2007.

In the United States, the most recent statistics from the Centers for Disease Control and Prevention revealed that 56,000 people became newly infected with HIV in 2006, with African-Americans continuing to face the greatest burden of HIV/AIDS. The rate of new HIV infections among African Americans in the United States is seven times the rate among whites. There is also evidence of resurging HIV/AIDS epidemics among men who have sex with men in the United States; 53% of new HIV infections in 2006 were in men who have sex with men.

Disease Burden

The impact of the AIDS pandemic is profound. Although global availability of resources to combat HIV/AIDS has increased since 2001, the populations most affected by HIV are still at greater risk of poverty, hunger and childhood mortality than those less affected by the pandemic. The AIDS pandemic continues to destroy families and communities, and thereby weaken and threaten the social stability and national security of developing nations. There is evidence of resurging HIV/AIDS epidemics among men who have sex with men in the United States and some European countries, and of similar hidden epidemics in Latin America and Asia. Sub-Saharan Africa remains the most severely affected region of world. More than two out of three (68%) of adults and nearly 90% of children infected with HIV live in this region and more than three out of every four deaths due to AIDS globally (76%) occurred in that region. These statistics reflect inadequate access to HIV prevention and treatment programs in that region.

Rationale

While a safe and effective HIV vaccine would be the optimal strategy for preventing HIV infection, control of the epidemic will likely require a combination of preventive approaches to more fully protect individuals and the public against HIV infection. Such approaches may include topical microbicides, antiretroviral therapy (ART) to reduce the ability of HIV-infected persons to infect others, pre-exposure prophylaxis (PrEP) ART treatment to reduce risk of HIV infection, treatment of sexually transmitted infections (STIs) that are cofactors for HIV transmission, drug abuse treatment as an HIV transmission modality for injection drug users, prophylaxis to prevent mother-to-child transmission (MTCT), and strategies specifically directed at individuals or communities for reducing the risk of HIV transmission associated with sexual activity and/or with substance use.

As the number of people with HIV/AIDS continues to rise worldwide, the need for simpler, more effective treatment strategies becomes more critical. Although antiretroviral therapy (ART) was shown to suppress HIV viral load to "undetectable" levels in many infected individuals, there is still a need to develop novel, more effective treatment options. ART cannot suppress the virus indefinitely, and latent virus can still persist. In addition, some infected individuals on ART never achieve adequate viral suppression, while other patients find certain drug regimens too complex and difficult to maintain. As importantly, drug resistance is also associated with some of these regimens, particularly with the prevention of MTCT in resource-limited countries. These regimens can also induce a number of serious metabolic, cardiovascular, and morphologic complications and cancers, which cause significant morbidity and mortality. The long-term effectiveness and effects of these combination drug therapies are not known, nor is it understood how to completely stimulate anti-HIV-specific immune function. Optimal strategies for long-term use of these antiretroviral regimens have not been established. Finally, the continued surge of the epidemic into resource-limited settings also necessitates the identification of simpler and less toxic regimens that can be deployed in all parts of the world.

TARGET CONTEXT AND CONDITIONS

In June 2006, the NIH funded six newly restructured HIV/AIDS clinical trials networks, with clinical research sites located in 24 states in the U.S. and 19 countries. These networks include the AIDS Clinical Trials Group (ACTG), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), the

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network, the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), and the Microbicide Trials Network (MTN). Each of these networks focuses its activities on one or more of NIH's six highest priorities for HIV/AIDS clinical research including: development of a safe and effective HIV vaccine; translation of laboratory findings into new drugs with clinical applications; optimization of the clinical management of HIV/AIDS, including co-infections and other HIV-related conditions; development of microbicides to prevent HIV acquisition and transmission; development of strategies to prevent mother-to-child transmission of HIV; and development of new HIV-prevention methods. The targets for the next three years are reflective of important studies targeting specific populations and/or HIV prevention and treatment and prevention strategies.

In addition to the restructured networks, NIH also supports research programs that will continue to collaboratively develop and conduct studies with the new NIH-funded networks. For example, the NIH Domestic and International Pediatric and Perinatal HIV Studies Network will continue to collaborate and enroll patients in trials that address issues in women, children, and adolescents such as those through IMPAACT and ACTG. Researchers at the Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions conduct research to explore promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and at-risk adolescents. The ATN conducts studies both independently and in collaboration with the other research networks, such as IMPAACT, ACTG, MTN, and HVTN. In addition, the Pediatric HIV/AIDS Cohort Study (PHACS), an observational study, addresses the long-term safety of fetal and infant exposure to prophylactic antiretroviral (ART) chemotherapy and the effects of perinatally acquired HIV infection in adolescents. Finally, research on HIV co-infections and comorbidities, including hepatitis C, hepatitis B, tuberculosis, cancers, neurological disorders, and organ-specific complications, also continues to be pursued in collaboration with other NIH institutes and Federal agencies.

In order to effectively prevent HIV infection, a broad range of prevention strategies will be required since no single prevention strategy is likely to be 100 percent effective or accepted. Toward that end, NIH is evaluating a variety of different prevention approaches through several investigator-initiated grants, the HPTN, MTN, and IMPAACT, which collaborates with the Pediatric/Perinatal HIV Clinical Trials Network on the prevention of mother-to-child transmission (MTCT). Because more than one prevention strategy will be required, NIH will continue to initiate and conduct trials to evaluate strategies to reduce co-factors associated with increased HIV infection, such as herpes simplex virus, the development of pre-exposure prophylaxis regimen, and the treatment of injection drug use. In addition, through the HPTN, the NIH is examining infection rates in serodiscordant couples (one partner is infected with HIV and the other is not) to determine if ART can prevent the sexual transmission of HIV.

Microbides are another important potential prevention tool being examined. Currently, there are no licensed microbicides. Given that women make up nearly half of all people living with HIV worldwide, a microbicide would provide a valuable means for women to protect themselves from HIV infection. The MTN is currently conducting a large, multi-site trial examining the safety, acceptability, and preliminary effectiveness of two candidate topical microbicides to prevent HIV infection.

The IMPAACT network conducts studies assessing strategies to prevent MTCT of HIV as well as studies aimed at optimizing the treatment of HIV-infected children. It also collaborates with the ATN to conduct HIV prevention studies in adolescents. Studies in this network will: evaluate strategies to prevent MTCT during breastfeeding; and evaluate approaches to optimize ART and reduce drug resistance in women and infants who are exposed to short-term ART to prevent MTCT. While the results of NIH-funded research have led to the dramatic reduction of MTCT, particularly in developed countries, the problem remains how to optimize maternal treatment. And, in resource-limited countries, the use of Neviripine as the standard for preventing MTCT often results in drug resistance which can compromise subsequent treatment for the mother and possibly the infant. The PHACS is also examining the long-term consequences of in utero ART exposure on children.

The ACTG and INSIGHT clinical trials networks focus primarily on treatments for HIV-infected adults and adolescents. The two networks have ongoing and/or planned studies of anti-HIV therapies (including studies of therapeutic vaccines) and/or anti-HIV multi-drug regimens that will help identify treatment regimens with increased efficacy, diminished toxicity and side effects; improved bioavailability; and minimal development of drug resistance. The purpose of these studies is to optimize regimens that facilitate treatment compliance. These networks are also undertaking studies to identify treatment regimens for use in resource-limited settings, as well as studies for patients who have failed all available treatment options and/or present with significant clinical problems as a result of AIDS disease.

Long Term Objective: (SRO-6.6) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-6.6 By 2015, provide at least one new or significantly improved minimally-invasive treatment for clinical use in patients using image-guided interventions. (Outcome)	*2011*	Support translation of at least two additional image-guided interventions. At least one additional IGI system will be developed to the point of "first-in-human" pilot studies. *(Baseline):* Feasibility testing has been completed on image-guided intervention technologies for treatment of epilepsy and corrective hip surgery, as well as the "first-in-human" pilot studies for MR-guided prostate biopsy.	N/A
	2010	Conduct feasibility testing of at least two additional new image-guided interventions. At least one IGI system will be developed to the point of "first in human" pilot studies. *(Baseline):* (FY09) Feasibility results on image-guided intervention technologies for treatment of cardiac arrhythmias and for prostate biopsy.	N/A
	2009	Demonstrate prototype feasibility of at least two new image-guided intervention systems that have the potential to advance into new clinical applications. *(Baseline):* (FY08) Ten technology development projects supported to demonstrate the feasibility of new IGI technologies.	Two new image-guided intervention prototypes are undergoing feasibility testing: MRI-guided focused ultrasound (MRgFSU) system for thermal ablation and MRI-Guided, Robotically Controlled Cardiac Ablation. (Target Met)
	2008	Test at least one image-guided intervention in humans from the baseline of 17 active grants in FY07. *(Baseline):* (FY07) Image-guided interventions are currently being tested in animal models and phantom studies.	Two new MRI related techniques from the baseline of 17 active grants were tested in humans to assist with neurosurgery or in the treatment of uterine fibroid tumors. (Target Met)

Data Source and Validation
Progress Report Summary Information - R21EB007715-02 Progress Report Summary Information - 5R01EB008999-02 McDannold N, Ziso H, Assif B, Hananel A, Vykhodtseva N, Gretton P, Pilatou M, Haker S, Tempany C. MRI-guided focused ultrasound (MRgFUS) system for thermal ablation of prostate cancer: Pre-clinical evaluation in canines. SPIE Photonics 2009 http://www ncigt.org/publications/item/view/1726

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY09 target was Met. The two new image-guided intervention prototypes undergoing feasibility testing are MRI-guided focused ultrasound (MRgFSU) system for thermal ablation and MRI-Guided, Robotically Controlled Cardiac Ablation.

Thermal ablation has been pursued as an alternative to surgery for treatment of prostate cancer. It can destroy tumors with little or no effects to the surrounding tissue. It can also be used along with radiotherapy and chemotherapy and can be reapplied in the case of recurrence. Focused ultrasound has shown potential as a non-invasive alternative to existing prostate cancer treatments. MRI offers substantial potential improvements in target identification and control over current focused ultrasound treatments. In addition to its superior image quality, it has the ability to quantify the heat deposition in near real-time, providing a means to control to treatment and tailor the ultrasound exposures to the patient's tumor and individual differences in anatomy. Investigators have completed pre-clinical tests of a prototype transrectal MRI-guided focused ultrasound to ablate prostate tumors. Results of these tests, suggest that this device will be capable of ablating tumors within the prostate while sparing surrounding healthy tissue.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. It increases a patient's risk of stroke and has a significant negative impact on quality of life. It is a significant public health problem incurring substantial health care costs. Current drug treatment of AF is temporary, expensive, and has well-recognized limitations such as relatively low efficacy and often poorly tolerated systemic side effects. Ablation techniques have been used to replace invasive surgical treatment; however, current ablation technologies are not optimal for epicardial ablation due to potential damage to surrounding tissue. High intensity focused ultrasound (HIFU) has the potential to overcome the limitations of current technologies to achieve better ablation outcome. Investigators are developing and demonstrating the feasibility of innovative imaging technologies to monitor cardiac ablation conducted with high-intensity focused ultrasound. Additional work has demonstrated progress in feasibility studies of MRI-guided, robotically-controlled ablation.

BACKGROUND

Image-guided interventions (IGI) have the potential to replace some invasive treatments that are commonly used today, such as more invasive surgical techniques. IGI techniques are potentially faster, safer, and less expensive than traditional invasive procedures, and recovery time from minimally-invasive IGI procedures is shorter. An image-guided intervention is often a treatment or procedure that is also more precisely targeted. In the case of interventions such as image-guided neurosurgery, this may decrease risk of damage to normal surrounding tissue and increase the ability to assess complete tumor resection. For diagnostic procedures, such as biopsies, this means better targeting of smaller masses. These improved capabilities are particularly important in light of the shifting trend in medicine towards a model of early, pre-symptomatic detection of disease.

Furthermore, image-guided technologies may involve robotic manipulators that can operate in small and difficult-to-reach spaces, such as the inner ear, within the chambers of the heart or on a fetus in utero. Thus, IGI increases the variety of interventions at the clinician's disposal. In addition, image-guided interventions can be done remotely, bringing clinical expertise to underserved communities and remote locales.

Image-guided procedures have the potential to improve health care by enabling less invasive, more precise, and faster biopsy and treatment procedures, minimizing unintended damage to healthy tissue, decreasing incidents of medical error, producing fewer complications, and allowing for clinical intervention at a distance.

Feasibility testing of new image-guided interventions is being done in a variety of areas including neurosurgery, cardiovascular surgery and cancer treatment. Co-registering and fusing images from complimentary imaging techniques including MRI, CT, ultrasound, nuclear (PET), or optical imaging, for real-time use can guide treatment in the surgical environment or interventional suite. For example, robot-assisted therapeutic and diagnostic procedures, under MRI guidance, are being developed for the treatment of prostate cancer. Also, better visualization techniques are being developed to minimize the time required for catheter-based treatment of abnormal heart rhythms.

Rationale

The need to support research and development in the area of image-guided procedures has been identified at workshops sponsored by NIH and other Federal agencies. Recent Biomedical Imaging Research Opportunities Workshops (BIROW) have established the need for research into the design, development, deployment and evaluation of the new methods, devices, and procedures for image-guided interventions.

Minimally-invasive treatment will be implemented using image-guided interventions. IGIs are potentially disruptive technologies that, in some cases, may completely replace conventional surgery or more invasive procedures. For example, non-invasive treatments using high-intensity focused ultrasound technology, combined with image-guidance (e.g., MRI or ultrasound) may lead to substantial changes in the treatment of uterine fibroids, cancer, and other diseases. In order for these changes to occur, research is needed to develop and validate these integrated imaging and treatment systems for specific applications.

TARGET CONTEXT AND CONDITIONS

The development of a new drug is often characterized as an ever narrowing funnel where the testing of thousands of compounds leads to hundreds of promising compounds and, potentially, to one successful therapy. The development of an image guided intervention goes through a similar path but with significant differences in scale. Typically, tools and techniques are developed to evaluate the feasibility a small number of potential interventions. Interventions that are found to be feasible, often after several separate procedures or techniques have been developed and integrated, then need to be prepared for clinical use and validated in a first in human demonstration. Finally, an image guided intervention that makes it to this point needs to be further developed to make it practical, cost-effective, safe and effective.

Currently, 17 projects in the area of image-guided interventions are being conducted. These include four cardiac and four neurosurgical interventions, as well as nine image-guided interventions for the treatment of cancer. In addition, the National Center for Image-Guided Therapy at Brigham and Women's Hospital in Boston is being supported.

The NIH has developed an initiative to foster research on image-guided intervention technologies that create minimally-invasive, image-guided procedures that may replace some traditional surgeries and more invasive techniques. This goal will be accomplished in two phases of investigator initiated research. During FY 2007, NIH supported technology development demonstrating the feasibility of new IGI technologies. In FY 2009, NIH supported the continued development of the most promising IGI technologies.

In FY 2010, NIH will support the translation of minimally-invasive, image-guided interventions to replace some traditional surgeries and more invasive techniques. During FY 2009, NIH continued to support technology development demonstrating the feasibility of new IGI technologies, and pilot tests in humans of one IGI system.

Long Term Objective: (SRO-7.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-7.4 By 2009, create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis. (Output)	*2009*	Create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis. Survey and clinical data from the 24-month clinic visits for the remaining 2,110 participants will be available for download from the OAI Web site. X ray and MR images from the 24-month clinic visits for all participants also will be available upon request. *(Baseline):* Researchers can access baseline and 12-month survey and clinical data and images from all 4796 participants, and 24-month survey and clinical data and images from 2686 participants.	Completed the osteoarthritis dataset and provided access to survey, clinical, and x-ray and MR image data for 4,796 participants across 3 years (baseline, 12 month, and 24 month) (Target Met)
	2008	Image data from baseline and 12-month clinic visits of remaining 2,110 OAI participants will be available from the OAI Web site. Survey and clinical data from the 24-month clinic visits for the initial 2,686 participants also will be available. *(Baseline):* (FY07) Baseline images, 12-month survey and clinical data, and 12-month images are available for 2,686 participants. Baseline survey and clinical data are available for all 4,796 participants.	Survey, clinical, and image data are available from three clinic visits by 2,686 participants. Baseline and 12-month image data for the remaining 2,110 participants also are available. (Target Met)
	2007	Survey, clinical, and image data from baseline and 12-month clinic visits of 2,500 OAI participants will be available from the OAI Web site. *(Baseline):* (FY06) Baseline survey and clinical data for ~2,000 participants, baseline x rays and MR images for 200 participants, and 12-month x rays and MR images for 160 participants are available to researchers.	Researchers can access baseline survey and clinical data for all 4796 participants and baseline images, 12-month survey and clinical data, and 12-month images for 2686 participants. (Target Exceeded)

Data Source and Validation
Hospitalizations for Osteoarthritis Rising Sharply. AHRQ News and Numbers, September 3, 2008. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/news/nn/nn090308 htm (accessed 10/16/09). Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008 Jan;58(1):26-35. PMID: 18163497 http://www ncbi nlm nih.gov/pubmed/18163497 OAI data are available to researchers through http://www.oai.ucsf.edu/datarelease/ Two-year incidence and predictors of future knee arthroplasty in persons with symptomatic knee osteoarthritis: Preliminary analysis of longitudinal data from the osteoarthritis initiative. Riddle DL, Kong X, Jiranek WA. Knee. 2009 May 4. [Epub ahead of print] PMID: 19419874 http://www ncbi.nlm nih.gov/pubmed/19419874 The relation of femoral notch stenosis to ACL tears in persons with knee osteoarthritis. Stein V, Li L, Guermazi A, Zhang Y, Kent Kwoh C, Eaton CB, Hunter DJ; for the OAI Investigators. Osteoarthritis Cartilage. 2009 Oct 2. [Epub ahead of print] PMID: 19835830 http://www ncbi.nlm nih.gov/pubmed/19835830 Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. Lo GH, McAlindon TE, Niu J, Zhang Y, Beals C, Dabrowski C, Hellio Le Graverand MP, Hunter DJ; for the OAI Investigators Group. Osteoarthritis Cartilage. 2009 Jun 26. [Epub ahead of print] PMID: 19583959 http://www ncbi nlm nih.gov/pubmed/19583959 The knee pain map: reliability of a method to identify knee pain location and pattern. Thompson LR, Boudreau R, Hannon MJ, Newman AB, Chu CR, Jansen M, Nevitt MC, Kwoh CK; Osteoarthritis Initiative Investigators. Arthritis Rheum. 2009 Jun 15;61(6):725-31. PMID: 19479703 http://www.ncbi.nlm nih.gov/pubmed/19479703

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and the measure was Achieved. Through the Osteoarthritis Initiative (OAI), researchers developed an osteoarthritis database that is freely available to scientists who require information about the natural progression of the disease, risk factors, joint changes, and outcome measures for their hypothesis-driven research. By the end of FY 2009, data collected over a 3-year period from 4,796 men and women aged 45 years or older at high risk for developing knee OA, or those with early stages of the disease, were freely available to the entire research community. Specifically, the research community has access to the survey, clinical, and image data that OAI investigators collected from participants at the baseline, 12 month, and 24 month visits.

Actual numbers of participants for which certain data elements are available (and expected numbers for data elements that were not released as specified in the targets):

	Baseline ***Survey and Clinical Data***	***Baseline Image Data***	***12-month Survey and Clinical Data***	***12-month Image Data***	***24-month Survey and Clinical Data***	***24-month Image Data***
FY 2006	2000	200				
FY 2007	4796 (2500 expected)	2686	2686	2686		
FY 2008	4796	4796	4796	4796	2686	2686 (0 expected)
FY 2009	4796	4796	4796	4796	4796	4796

Use of OAI data by the scientific community
The OAI is a long-term effort, developed with support from across NIH and the private-sector, to create a publicly available scientific resource to identify and evaluate biomarkers of OA for use in clinical research. By the end of FY 2009, more than 1,350 researchers from 54 countries had registered to access OAI data through the OAI Web site, and had downloaded a total of 4,100 clinical datasets. In FY 2009, at least 18 articles using OAI data were published or accepted for publication in peer-reviewed journals, bringing the total number of articles about the OAI to 29. The OAI data also were featured in posters and oral presentations at major scientific conferences, such as the Osteoarthritis Research Society International and the American College of Rheumatology annual meetings.

Research by non-OAI investigators included findings that can improve a surgeon's ability to advise patients about their probable need for knee replacement surgery. Other investigators have used the OAI data to predicting which patients are at risk of anterior cruciate ligament (ACL) injuries because of their knee anatomy and, therefore, could benefit from lifestyle changes to preserve their knee health.

To further encourage researchers to integrate the OAI into their studies, the Osteoarthritis Research Society International reserved time at its 2009 annual meeting for a session to introduce its members to OAI resources. The session, titled the NIH Osteoarthritis Initiative Public Data User Workshop, provided an overview of OAI design, subject characteristics, data, and images; an introduction to the OAI Web site and the OAI data access policies; information about the image data that are available to researchers; and an opportunity for participants to ask questions.

Research advances
OAI investigators demonstrated that some joint changes observed through MR imaging, unlike data collected from x-ray films, correlate with patient symptoms. Studying images collected through the OAI, researchers observed that bone marrow lesions and swelling (effusion) observed through MR imaging were strongly associated with weight-bearing knee pain, and somewhat associated with non-weight-bearing knee pain. Therefore, scientists should consider these changes to non-cartilaginous tissue when developing new knee OA treatments. Combined with a new, rigorous, and reliable method that researchers developed to better define painful regions of knees, the finding will facilitate studies better predict worsening of disease and development of disability and may be reflected in the inclusion criteria for future clinical trials.

Ongoing activities and next steps
OAI investigators have conducted quantitative and semi-quantitative analyses of baseline, 12, and 24 month x ray and MR images for approximately 300 participants. Investigators posted the data on the OAI Web site for use by others in the research community who are identifying and evaluating biomarkers for surrogate OA endpoints. These images were the basis for some of the research referenced above.

The American Recovery and Reinvestment Act (ARRA) allowed the NIH to further enhance the utility of the OAI as a research resource. Under ARRA, the NIH awarded a "Grand Opportunities" grant to a team of researchers who are systematically examining the genetic underpinnings of radiographic knee OA (NIH grant number RC2 AR058950). The researchers will make all genetic data that emerge from their genome-wide association study publicly available. When combined with the structural, clinical, and functional characteristics measured in OAI participants, the new genetic component of the OAI is expected to provide additional opportunities for researchers who are searching for OA biomarkers and therapeutics. Specifically, the discovery of genetic variants that protect against or increase a person's risk of developing OA is likely to suggest targets for the development of disease-modifying agents. Moreover, investigators could use genetic markers to identify appropriate participants for clinical trials. For example, a drug that acts on a particular molecular pathway might not benefit patients whose OA is caused by another mechanism; therefore, enrolling them in a study may not be scientifically appropriate, or even ethical.

In summary, the multi-million dollar effort described in this measure has demonstrated how the combined resources of the Federal government and private sector can quicken the study of a chronic, debilitating disease. The OAI has served as a model for other partnerships between the NIH and industry and, as a testament to its success, its sponsors are continuing the program for another five years.

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. A degenerative disease, it is caused by a breakdown of cartilage, the hard but slippery tissue that covers the ends of bones where they form a joint. Healthy cartilage allows bones to glide over one another, and it absorbs energy from the shock of physical movement. In OA, the surface layer of cartilage breaks down and wears away due to biochemical and mechanical factors. This results in bones under the cartilage rubbing together, causing pain, swelling, and stiffness. The body attempts to repair the damage, which may result in the growth of new bone along the side of existing bone. These attempts at repair are usually imperfect, and result in bony lumps, tenderness, pain, and swelling in the joint that permanently change the joint's shape.

A limited number of therapies exist for OA treatment. Most are designed only to relieve pain and reduce the disability caused by bone and cartilage degeneration. However, no existing treatment inhibits the degenerative structural changes that are responsible for disease progression.

Prevalence/Incidence

OA is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. An estimated 12.1 percent of the U.S. population (nearly 27 million Americans) age 25 and older have OA. By 2030, about 72 million Americans will have passed their 65th birthday and will be at high risk for the disease.

Disease Burden

According to the Agency for Healthcare Research and Quality (AHRQ), hospitalizations for OA rose from 443,000 in 2000 to 735,000 in 2006. The large increase is due primarily due to the increase in knee replacement surgery, the principal treatment for people who have debilitating knee OA.

Rationale

One barrier to the development of drugs that block joint degradation, the underlying cause of painful and disabling OA symptoms, is the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. To help address this barrier,the NIH—with input from the U.S. Food and Drug Administration—partnered with private sponsors to create the Osteoarthritis Initiative (OAI), a publicly available research resource that investigators can use to identify and evaluate osteoarthritis biomarkers.

Potential biomarkers might include structural characteristics that can be observed with magnetic resonance (MR) imaging; proteins or substances in the blood or urine that indicate a breakdown or rebuilding of bone or cartilage; and genetic markers that suggest susceptibility to, or protection from, joint degradation. Once validated, the biomarkers will improve the efficiency of clinical research on OA and potential interventions. Depending on the marker, it could be used to identify appropriate participants for clinical trials of disease modifying agents, or even be validated as a surrogate endpoint of disease progression or recovery.

For example, clinicians currently rely on x rays to monitor joint damage even though the technology is insensitive for uncovering changes in joint structure that may have clinically meaningful effects on OA symptoms. However, if researchers could use MR scans to track heretofore undetectable joint changes and could link these small but measurable changes in joint structure with patient function, such findings would enable earlier and more accurate assessment of OA, identification of potential targets for interventions, and ultimately the more efficient development of disease modifying agents to treat OA.

The OAI relates directly to the HHS Strategic Plan for FY 2004-2009:

- *Objective 4.1*—Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. As a public-private partnership facilitated by the Foundation for the National Institutes of Health, the OAI also addresses —Accelerate private sector development of new drugs, biologic therapies, and medical technology.
- *Objective 4.2*—Accelerate private sector development of new drugs, biologic therapies, and medical technology.

TARGET CONTEXT AND CONDITIONS

This measure has been fulfilled through the OAI, a public-private partnership established in FY 2002 to develop a prospective, natural history cohort of approximately 4,800 participants. Researchers have collected, de-identified, and archived biological specimens, images, and clinical data from 4,796 men and women aged 45 years or older at high risk for developing knee OA, or those with early stages of the disease, over a 3 year period. At the end of FY 2009, data were freely and publicly available to the research community through the OAI Web site, http://www.oai.ucsf.edu/datarelease/.

The OAI resource includes a variety of data elements that can be used for a range of scientifically rigorous studies that are being proposed by investigators studying OA. The project was designed to have participants provide fasting blood samples and urine specimens for use in genetic and metabolic studies, answer questions about their health and behavior, undergo both clinical and functional exams, and receive x rays and MR scans at regularly scheduled clinic visits. Examples of information being collected follow.

- Survey data: Includes answers to questions about OA symptoms; pain severity; walking ability; endurance; balance and strength; nutrition; quality of life; co-morbidities; and prescription medicines and alternative therapies used by the participants.
- Clinical data: Includes weight, body mass index, blood pressure, heart rate, balance, and strength.
- Image data: Includes x rays of participants' knees, hands, and hips, and MR images of participants' knees.

The data elements noted above are only a few examples of the information collected about each OAI participant. Now that three years of data are available, the OAI provides an unparalleled state-of-the-art database showing both the natural progression of the disease and information on risk factors, joint changes, and outcome measures. The breadth of information that the OAI contains allows researchers to develop hypotheses about possible OA biomarkers of disease onset and progression, test their theories, describe the natural history of OA, and investigate factors that influence disease severity and progression. It also allows scientists to identify potential disease targets, and to develop tools for measuring clinically meaningful improvements. All data and images collected are freely available to researchers worldwide to help quicken the pace of scientific studies related to OA.

Long Term Objective: (SRO-7.7) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-7.7 By 2011, assess community-based methods for facilitating cancer research and providing patients access to optimal cancer care. (Outcome)	*2011*	Provide assessment of community-based methods for facilitating cancer research and providing patients with access to optimal cancer care. *(Baseline):* Community-based research methods are implemented.	N/A
	2010	(FY10) Begin implementation of the assessment of community-based research program components *(Baseline):* Program components are not in existence	N/A
	2009	Identify and define metrics used for the assessment of community-based research methods. *(Baseline):* (FY07) Suitable metrics not available.	Metrics, surveys, and tracking forms were developed to assess community-based research methods, including health disparities, quality of care, and implementation of clinical trials. (Target Met)

Data Source and Validation
Evaluation Design Report for the Community Cancer Centers Program This document may be accessed through the NCCCP Evaluation Project Officer. Executive Plaza North, Room 4086 6130 Executive Boulevard Rockville, Maryland 20852 Phone: 301-451-4402 Fax: 301-435-3710 http://outcomes.cancer.gov/

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY09 target was Met. NIH developed and defined metrics, surveys, and tracking forms that will be used to assess community-based research methods of exploring health disparities, quality of care, and clinical trials in NIH Community Cancer Centers Program (NCCCP) communities. To assess Health disparities, participant race and ethnicity, and access to care will be included. Quality of care assessments will include the types of multidisciplinary conferences that are regularly attended; the percent FTE for the Physician Director; and the implementation of the conditions of participation. To assess research on clinical trials, data will be collected on the number of patients accrued to trials; the number and types of trials open; and the number of early phase trials. The assessment of multiple areas will be supported by data on general factors such as the number of cancer screenings provided; the number of cancer patients provided navigation; and the number of community partners.

These metrics will be used in conjunction with other data gathering tools such as interviews, to enable the assessment of the NCCCP programs. The development of metrics and methods for this assessment was guided by overarching questions about the NCCCP and the need to analyze this pilot program at different levels of intervention.

Three overarching questions guide this NCCCP evaluation plan:

1. What changes in each program component and for the cancer service line overall seem to be facilitated by the NCCCP?
2. What organizational requirements are necessary to effectively manage/implement the NCCCP?
3. What changes and elements are sustainable and potentially replicable?

The evaluation has been designed to address key evaluation questions at five possible levels of intervention:

1. National - through the network or learning collaborative being developed by NIH to administer the NCCCP;
2. Organizational - within the systems and hospitals that the program is being implemented;
3. Programmatic - for the impact on delivery of the cancer service line;
4. Individual - in terms of the impact on patients' perceptions of the quality of care they are receiving within each participating hospital;
5. And with regard to each program component of the NCCCP.

These questions informed the metrics analysis and helped ensure that the appropriate metrics are being used for the assessment of unique community-based research methods.

BACKGROUND

Significant advances in cancer treatment in recent years have made possible the concept of a community hospital-based cancer network. When the NIH-designated Cancer Centers were being established in the 1960s, there was a need for special care units in large hospitals to manage the side effects of the highly toxic chemotherapies of the day. Today, these treatments –and the newer generation of immunotherapies and other regimens – are less toxic, making it possible to administer more advanced care at community hospitals, often in an outpatient setting.

Rationale

It is estimated that that 85 percent of cancer patients in the United States are diagnosed at hospitals in or near the communities in which they live. The other 15 percent are diagnosed at NIH-designated Cancer Centers, a network of 65 academic research institutions located in largely urban areas across the country. Many patients are not treated at the major cancer centers because of the distance from their homes, or for other personal or economic reasons.

TARGET CONTEXT AND CONDITIONS

The NIH is launching the NIH Community Cancer Centers Program (NCCCP) as a pilot program to bring the latest scientific advances and the highest level of innovative and integrated, multi-specialty care to a much larger population of cancer patients.

The program is intended to complement other NIH initiatives in seeking to:

Draw more patients into clinical trials in community-based settings. Clinical trials provide access to cutting-edge advances and state-of-the-art care, and help develop new preventatives, diagnostics, and treatments. Yet only 3 percent of adults with cancer participate in clinical trials. In underserved urban and rural communities, the adult accrual rate is even lower. These groups include populations with disproportionately high cancer rates, so their absence from clinical trials is a significant factor in ongoing healthcare disparities.

Reduce healthcare disparities. The disparity problem is complex. The NIH is working through this pilot program and a range of other programs to better understand the problem and address the causes. Research confirms that equal treatment at the same stage of disease yields equal outcomes across all populations. Equal access to optimal care could dramatically reduce cancer mortality in the United States.

Prepare sites for standardizing the collection and storage of biological specimens for cancer research. Biospecimens play an important role in translating basic science into cancer treatments because biospecimens allow researchers to study cancer cells at the molecular level. Implementation of a national standard for how these samples are collected and stored is critical; standardization and making biospecimens more widely accessible would accelerate the translation of research into more effective treatments for patients, including treatments that are personalized for greater efficacy and fewer side effects.

Link sites to national databases supporting basic, clinical, and population-based cancer research. Explore implementation of electronic medical records. The use of electronic medical records opens broad new avenues for data-intensive research in understanding cancer. Assessing the ability of sites to create and utilize IT infrastructures that are compatible with NIH's Cancer Biomedical Informatics Grid (caBIG™) could lead to a nationwide repository of data on screened patients, high-risk patients on prevention trials, cancer patients actively being treated, and cancer survivors.

In 2009, NIH will develop metrics suitable for assessing the NCCCP pilot. The goals of NCCCP have been defined; the next step in the assessment is to identify suitable metrics that can help determine if the program is successful. This will involve a review of metrics used in similar studies, consultation with program experts, and an analysis to determine what metrics may be best suited for measuring performance of community-based research and care. Defining appropriate metrics is a critical step that may be complicated by the diversity of the communities and facilities involved in the pilot. To overcome such complications, a logic map will be created to explain how unique structures and processes may impact outcomes. This information will be used during the metrics analysis to ensure that the appropriate metrics are being used for the assessment of unique community-based research methods; ultimately leading to a high quality assessment of community-based methods for facilitating cancer research and providing patients access to optimal cancer care.

Examples of program components that will be implemented during the pilot phase of the NCCCP include:

- expansion and/or addition of integrated multi-specialty cancer care, clinical research, palliative care, and genetics and molecular testing programs;
- increased use of evidence-based guidelines for cancer care;
- enhanced linkages with NIH-designated Cancer Centers for referrals and research support;
- introduction of survivorship plans into initial patient care plans; increased use of navigation and outreach programs to reduce cancer health disparities;
- appropriate medical and administrative staffing;
- and assessment of infrastructure requirements for IT integration with caBIGTM and biospecimen resource compliance with the First Generation Guidelines for NIH-Supported Biorepositories.

Long Term Objective: (SRO-7.8) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-7.8 (RA) By 2011, create genomic resources to identify rare genetic variants that contribute to primary open angle glaucoma. (Outcome)	*2011*	Apply recently developed genome sequence capture and high throughput sequencing to a subset of 200 POAG patients and 200 control subjects to discover rare genetic variants within exons and flanking intronic sequences that contribute to POAG. *(Baseline):* Novel technologies to capture exomic regions of genomes and new computational analysis methods have become available.	N/A
	2010	Complete SNP-based GWAS from 2,000 POAG patients and 2,000 healthy controls. *(Baseline):* Genetic samples and clinical phenotypes of POAG cases and age- gender-, and ethnically matched controls have been collected in NEIGHBOR.	N/A
	2009	Establish NEIGHBOR consortium and collect and harmonize clinical POAG phenotypes and genetic samples in preparation for large-scale GWAS. *(Baseline):* Initial small-scale GWAS have identified loci important for POAG.	NEIGHBOR consortium established with 22 investigators at 12 institutions, collecting genetic samples and phenotypes using harmonized definitions and standardized methodologies. (Target Met)

Data Source and Validation
Genetic Resources and Information for Vision Researchers http://www nei nih.gov/funding/gen_resources.asp NEIGHBOR Program Director 5635 Fishers Lane Rockville, MD 301-451-2020

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY2009 target was Met. NIH established the NEIGHBOR consortium, which consists of 22 investigators at 12 institutions throughout the United States collecting genetic samples and phenotypes using harmonized definitions. The consortium collaborates with and extends the ongoing GLAUGEN project to collect and

genotype additional POAG cases and age-, gender-, and ethnically matched controls. The consortium first developed a consistent clinical definition for POAG to be used by all the centers. It also developed a common technology for processing genetic samples. These steps will facilitate data sharing and subsequent analyses within the consortium and with GLAUGEN.

BACKGROUND

Glaucoma is a family of diseases characterized by progressive optic neuropathy (optic nerve degeneration diagnosed by visual field defects). Most forms of glaucoma are associated with elevated intraocular pressure (a build-up of fluid in the eye) commonly attributed to impaired drainage of aqueous humor fluid through the outflow pathways known as the trabecular meshwork. The increased pressure can lead to death of retinal ganglion neurons, the cells that transmit visual signals from the eye to the brain. Glaucoma causes irreversible blindness that can be prevented by therapeutic intervention if patients are treated at early stages of the disease. Unfortunately, since quality of life is not significantly affected until latter stages of the disease process, a significant proportion of individuals remain either undiagnosed or untreated.

The most common form of glaucoma, Primary Open Angle Glaucoma (POAG) occurs mainly in adults. The disease incidence is consistent with a significant genetic predisposition (first-degree relatives have risk about 10 times that of the general population). Despite the high heritability of POAG, susceptibility cannot be linked to a single underlying gene or simple mode of inheritance. Traditional genetic approaches (parametric linkage using large pedigrees affected by POAG) have led to the identification of 14 major genetic loci associated with POAG. Genes that contribute to rare (mendelian) forms of glaucoma have been identified in three of these regions. Large-scale genome-wide association studies (GWAS) are needed to identify genetic variants that are biologically relevant to this genetically complex disease.

Prevalence/Incidence

Glaucoma affects more than 2 million adults 40 years and older in the United States. It is the leading cause of blindness among Hispanic and African Americans and is the third most prevalent cause of visual impairment and blindness among Caucasian Americans.

Rationale

Primary Open Angle Glaucoma is a complex disease of the eye with interacting genetic, environmental, and aging-related risk factors. Recently developed high-throughput genomic methodologies coupled with large-scale genetic epidemiologic consortia provide investigators with extremely valuable resources to explore the biological processes underlying this significant cause of blindness. The identification of genes responsible for glaucoma could have a substantial impact on diagnosis and treatment as current therapy treats the symptoms of the disease, but the causes for most forms of glaucoma are not known. The projects outlined in this goal forms the core of NEI's signature Recovery Act project.

TARGET CONTEXT AND CONDITIONS

The manifestation of complex diseases such as POAG depends on the interaction of many genes as well as environmental factors. Although classical genetic linkage analyses identified several chromosomal regions potentially involved in POAG, little progress has been made in explaining the genetic contributions to the disease. In 2005, a new genomic approach, genome-wide association studies (GWAS), led to the identification of a variation of a gene, an allele, found to confer increased risk for a major ocular disease, age-related macular degeneration (AMD). The gene, not previously associated with AMD, opened the door to studying a new molecular pathway and potential therapies for the disease. Since that proof-of-principle advance, GWAS has been applied to many other complex diseases and conditions, which necessitates collecting large sample sizes for sufficient statistical power to identify the disease causing genes. This measure develops resources to support and conduct GWAS to identify rare genetic variants that contribute to POAG.

Instead of looking at genes one-by-one, GWAS compares the total genetic make-up from individuals with a disease to those without. Many individuals are needed in order for the statistical methods to provide significant results. Furthermore, clinicians must accurately describe symptoms and other diagnostic characteristics that may be related to the condition. Some undiagnosed individuals may nonetheless exhibit some early stages of the disease. Therefore, to understand the impact of gene variants on disease etiology, it is important that clinicians record phenotypes (the hereditary characteristic associated with the condition) as accurately as possible, according to a common set of definitions used by all doctors participating in the study. To build on the opportunities created by preliminary glaucoma GWAS investigations, the NIH launched initiatives to design and conduct large-scale GWAS for POAG. The success of GWAS in discovering genes for POAG will depend on multiple factors including the study design, the careful harmonization of phenotype definitions, the appropriateness of control subjects, and the sample size employed in the study.

To conduct large-scale GWAS, the NIH started to assemble networks of investigators focusing on glaucoma. The NEI Glaucoma Human genetic collaBORation (NEIGHBOR) is a consortium of clinicians and geneticists who will ultimately contribute data from more than 4,000 individuals (2,000 POAG cases and 2,000 controls). The investigators will use harmonized clinical definitions for glaucoma phenotypes and the same technology for genotyping subjects thereby increasing the statistical power for discovering genetic factors associated with glaucoma. The DNA samples will be genotyped using a high-density single nucleotide polymorphism (SNP) array platform and analyzed for genome-wide associations.

NEIGHBOR will also incorporate glaucoma data from a separate consortium, GLAUGEN (Gene-Environment interactions in glaucoma). GLAUGEN collects data from 2,400 individuals (1,200 POAG cases and 1,200 controls) to help identify the relationships of environmental exposures to gene-trait associations in common, complex diseases. NEIGHBOR and GLAUGEN will use standardized definitions for glaucoma thus enabling researchers to combine data across the consortia. Together, these two consortia will initiate large-scale GWAS for identifying both gene-gene, and gene-environment interactions.

Recovery Act funding creates an opportunity to explore genomic causes of POAG at a higher resolution that the standard GWAS. This research leverages the existing NEIGHBOR and GLAUGEN data by subjecting subsets of these samples to further analysis that enhances and extends the SNP-based GWAS. The proposed gene resequencing uses the new, cutting edge technologies of genome sequence capture methods and high throughput sequencing to discover POAG-associated regulatory variants residing within the protein-coding exons as well as flanking introns. Gene resequencing will begin with samples from 200 POAG patients and 200 control subjects.

Establishing the NEIGHBOR infrastructure is resource-intensive, particularly in ascertaining and phenotyping POAG patients and carefully matched control subjects, collecting and genotyping their DNA, and then applying state-of-the-art analysis methods. Recovery Act funds support and extend unique, timely scientific opportunities. The funds accelerate NEIGHBOR's efforts to coordinate the collection of clinical phenotypes and preparation of DNA samples for genotyping for GWAS. After initial GWAS results are identified, genetic variations will be replicated and validated in separate and distinct study populations. The resulting NEIGHBOR genotype data and clinical phenotype, along with associated epidemiologic and environmental exposure data, will be made available as a resource to the research community through the NIH database of Genotype and Phenotype dbGaP. The high resolution DNA sequence data will also be made available for further analysis as a resource to the research community. The overriding goal of NEIGHBOR is to create genomic resources that will afford identification of genetic risk factors for POAG, through GWAS and other cutting-edge genetic and genomic methodologies.

Long Term Objective: (SRO-7.9) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-7.9 (RA) By 2011, enhance understanding of the characteristics of differentiated heart, lung, and blood cells derived by reprogramming human embryonic and induced pluripotent stem cells. (Outcome)	*2011*	Refine cell lines for use in analytical studies. *(Baseline):* Specific cell lines need refinement in order to develop cell-based disease models and molecular signatures of disease.	N/A
	2010	Initiate characterization studies of stem and progenitor cells. *(Baseline):* Information currently is lacking comparing iPS and ES cells	N/A

BACKGROUND

Recent advances in stem cell research, including the induction of pluripotent stems cells from adult somatic cells and the directed differentiation of stem cells into a variety of cellular derivatives, hold great promise for future therapeutic application. However, important gaps remain in our understanding of stem and progenitor cell characteristics, the mechanisms of their differentiation, and the unique attributes of resultant differentiated states. In addition, the degree to which differentiation of stem cells in the laboratory recapitulates the in vivo characteristics of tissues and organs remains unclear, and fundamental knowledge of cardiovascular and pulmonary stem and progenitor cell biology lags behind that of hematopoietic cell biology.

Rationale

Recovery Act funds will be used to enable identification and characterization of stem cells and progenitor lineages of the heart, lung, vasculature, and blood. Cardiac and pulmonary lineages in particular require additional genetic, epigenetic, and functional characterization. Key questions in stem cell biology include whether induced pluripotent stem (iPS) cells are equivalent to embryonic stem (ES) cells and whether iPS cells can serve as stable, safe cell sources for basic and future clinical research. Funded investigators will compare cells derived from ES cells and iPS cells to each other and to tissue-derived progenitor cells. Investigators will also create iPS cells from individuals with heart, lung, and blood diseases to develop cell-based disease models and molecular signatures of disease.

TARGET CONTEXT AND CONDITIONS

Development of model experimental systems and eventual safe and effective therapeutic use of stem and progenitor cells require solutions to a number of questions. In order to address gaps in our understanding of stem cells, the NHLBI plans to support 4 RC2 grants. The efforts will entail:

- Creation of iPS cells from lung disease patients and comparison to ES cells to define the genetic and epigenetic programs of the earliest stages of human development
- Using the human hematopoietic system as a model to compare differentiated iPS cells and ES cell progenitors and red blood cells with normal human progenitors and red blood cells. An assay for tumorigenic potential will also be investigated. The well-studied hematopoietic system may be the best-suited for making these critical comparisons.
- Using iPS cells to study normal and pathological hematopoeisis. Blood development will be studied in cell lines derived from subjects with disease, and thus hold promise for important insights into normal hematopoiesis and into myeloproliferative disorders.

- Conducting a comprehensive comparative analysis of multiple human and mouse ES and iPS cell lines using molecular and functional criteria.

These research efforts will address key gaps in our understanding of stem and progenitor cells. The studies will begin to determine stem cell characteristics, mechanisms of differentiation, and characteristics of differentiated cells. The research will address important gaps in knowledge of iPS cells, including equivalency to ES cells and if the iPS cells can be used in the future for clinical research.

Long Term Objective: (SRO-7.10) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-7.10 (RA) By 2011, create a publically accessible database of novel and highly-detailed cell images, videos, and animations from a variety of organisms. (Outcome)	*2011*	Populate the database with approximately 15,000 cell images. *(Baseline):* No cell images in the library.	N/A
	2010	Create a comprehensive, publicly available database (i.e. Image Library) of images, videos and animations of cells from a variety of organisms. *(Baseline):* No existing comprehensive and publicly accessible database available.	N/A

BACKGROUND

With the recent explosion of sophisticated microscopic techniques, much discovery in biology is currently in the form of images and videos that appear as figures or supplementary data in research journals. This information is not organized for easy access, and much of it is difficult to find. The creation of a library of image data depicting cellular structures, functions and events across a range of biomedical topics, will provide researchers easy access to primary data on the architecture and dynamic behavior of cells. The Library's images, videos, and animations will be vetted and annotated by scientists, and instantly accessible and searchable for a wide range of users. By developing a systematic protocol for acquiring, reviewing, annotating, and uploading the images, an efficient platform for building the library at a rapid rate will be created.

Rationale

The purpose of the image library database is to advance research on cellular activity with the ultimate goal of improving human health. Cells are the building blocks of tissues and undergo dynamic rearrangements and changes in shape and motility during human embryonic development; abnormalities in these processes underlie some birth defects and diseases such as cancer. The proposed Image Library creates a publicly accessible database of images, videos, and animations of cells from a variety of organisms. The images depict cellular events, processes and structures, providing primary data for scientists and clinicians attempting to understand human cell biology. Because such a database does not currently exist, the project will have a significant impact on biomedical research. The Library will become immediately useful to a broad range of research scientists – including cell biologists, geneticists, immunologists, and pathologists, as well as students, teachers, and the general public. During the two year timeframe, surveys, use analyses, and benchmark attainment will be used to provide periodic checkpoints on progress. By the completion of the project in 2011, some 15,000 images will populate the Image Library, which is expected to expand as the project continues with funding from other sources or large-scale collaborations.

The long-term goal is the construction of a library of image that will serve as primary data for research. Such a library would have a significant impact on research in health-related fields, an impact comparable to the changes wrought by access to a library of genome sequence data. By visualizing the structure and dynamic behavior of a broad range of cells, scientists and clinicians will be better able to understand the nature of specific cells and cellular processes, both normal and abnormal. These will likely lead to new discoveries about diseases and drug targets in the future. Because the project creates the electronic infrastructure and a protocol for acquiring, reviewing and annotating new cellular images, the number of images available to researchers

will continue to increase beyond the two-year lifetime of the grant. The project meets the goals of the Recovery Act by creating and retaining jobs, and accelerating the pace of research by making primary data easily accessible to scientists and clinicians.

TARGET CONTEXT AND CONDITIONS

A comprehensive and publicly available library of cell images does not currently exist. To create the image library, the following steps will be taken: 1) design and implement the electronic architecture needed for the Image Library; 2) begin populating a database of reviewed cell images so that in two years nearly 15,000 images exist; 3) assess the effectiveness of the preliminary database and incorporate feedback-based modifications continuously; and 4) seek long-term support for the library and explore option for linking the library with other databases.

The proposed library will make a large number of images depicting cellular events, processes, and structures available to researchers, teachers, and the public at large. Researchers will use this collection to correlate observations from different laboratories and for different cell types under various physiological conditions. Such studies are expected to facilitate consensus development about the interpretation cellular images and lead to the recognition of previously ill-defined cellular structures, states, and processes. This work will engage and benefit a broad range of research scientists – including cell biologists, geneticists, immunologists, and pathologists. The library will provide data that can be used by computational biologists interested in simulating cellular activities to better understand cellular regulation. Teachers will use the images to enhance student learning. Clinical care of patients may eventually benefit from increased understanding of normal and diseased states of cells, better understanding how these states are reflected in images, and advances in automating image analysis to assist pathologists in diagnosing disease. Overall, the library will make publicly funded NIH research broadly and readily available to the public for use by government, industry, and private citizens.

Long Term Objective: (SRO-7.11) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-7.11 (RA) By 2012, gather sufficient data to support the development of a national standard for normal fetal growth. (Outcome)	*2011*	Recruit at least 50% of the study participants needed. *(Baseline):* Completed the study protocol for twin pregnancies and launched recruitment for twin pregnancies.	N/A
	2010	Expand the study protocol and recruitment to include twin pregnancies, in addition to singleton pregnancies, to conduct a series of ultrasound exams, nutrition surveys, body measurements, and blood collection. *(Baseline):* The study protocol for singleton pregnancies has been completed and recruitment has been launched.	N/A

BACKGROUND

A healthy pregnancy that leads to a healthy newborn requires, among other factors, that the fetus grows at a normal rate. Some babies that do not grow at a normal rate are at risk for complications during delivery, which also puts the mother at risk for adverse health outcomes. At other times, small or large babies reflect the stature of the parents and are born without complications. So at what point do physicians determine whether a fetus is too small or too large and whether additional treatment support may be needed during delivery or after birth?

Currently, there is no standard for optimal fetal growth. The most commonly used method of estimating fetal growth is to use charts based on birthweights and gestational ages, including those of premature infants. Babies born prematurely, however, are likely to have birthweights outside of the normal range because of abnormal fetal growth or of a maternal complication. These infants do not represent all unborn fetuses. To overcome this limitation, a standard needs to be developed based on longitudinal ultrasound data throughout pregnancy and a sufficient sample size representative of the U.S. population which is growing in its racial and ethnic diversity. Data on race, ethnicity, fetal size by gestational age, and fetal growth rate by gestational age are needed so that clinicians may construct optimal fetal growth rate curves. These fetal growth curves could then be personalized by incorporating maternal and fetal genetic and physiologic factors.

Rationale

The health and lifestyles of Americans are changing. A national standard for normal fetal growth is urgently needed, given the high prevalence of obesity, couples waiting to have children later in life, and an increasing number of twin pregnancies achieved with the help of artificial reproductive technologies. In addition, normal fetal growth curves would complement the Institute of Medicine's recent report and guidelines on weight gain during pregnancy. With a commonly accepted standard to define normal and abnormal fetal growth, physicians will be better able to detect potential problems during pregnancy. Furthermore, the standard would be a valuable measure in perinatal research.

With funds through the American Recovery and Reinvestment Act (ARRA), researchers are poised to speed the establishment of a U.S. national standard for normal fetal growth, expand it to include twin pregnancies,

and collect additional data on nutrition, social, and behavioral factors that can affect fetal growth. To achieve this goal, additional personnel will be hired at a greater number of research sites. Additional staff would include ultrasound technicians, nurses, laboratory staff, data monitoring, and analysis professionals.

TARGET CONTEXT AND CONDITIONS

NIH scientists are aiming to establish the first U.S. national standard for normal fetal growth. Researchers recently launched an effort to develop a national standard for normal fetal growth in singleton pregnancies. Building on this effort with funds through ARRA, researchers will expand the study to include twin pregnancies, add more research sites, conduct detailed nutrition surveys for all of the study participants, and increase representation of races and ethnicities across the country. Women in their first trimester of pregnancy will be recruited from at least ten hospitals across the country to include African American, Asian, Hispanic, and Caucasian populations. Clinical and anthropometric data will be collected from the pregnant women participating in the study and from the newborns. Anthropometric data are comparative measurements of the body, and includes, height, weight, body mass index, and waist-to-hip ratio. In addition, ultrasound exams will be conducted throughout pregnancy to collect data on fetal size and fetal growth. A data coordinating center will manage the data and coordinate the study among the sites. A central sonology team will train, certify, and conduct continuous quality control for the ultrasound measurements. These research efforts will generate more detailed information on risk factors for abnormal fetal growth, and investigate biological, social, and behavioral factors that affect fetal growth.

Long Term Objective: (SRO-8.2) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-8.2 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. (Outcome)	*2009*	Complete goal of identifying and characterizing two molecular interactions of potential clinical significance between bone-forming cells and components of bone. *(Baseline):* (FY07) Research on interactions between bone-forming cells and bone continues.	Researchers identified DMP-1 as a critical factor in bone formation and control of minerals in the blood and discovered a robust network of matrix proteins that regulate bone turnover. (Target Met)
	2008	Determine the properties of bone-forming cells and bones from mice in which fibrillin-2 is absent. *(Baseline):* (FY06) Although fibrillin proteins have been studied as structural components of the matrix, it has only recently been recognized that they may influence the function of bone cells.	Fibrillin-2-null mice have reduced bone formation, and the bones show significantly altered material and mechanical properties. The abnormalities reflect defects in their response to TGF-beta. (Target Met)
	2007	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. *(Baseline):* (FY03) Information is incomplete on where thrombospondin-2 is produced; mouse model can provide this data.	Researchers determined that the fluorescent mouse was not going to provide useful information and are pursuing a different strategy to identify sites of TSP-2 production. (Target Not Met)
	2007	Determine the characteristics of the skeleton in mice deficient in dentin matrix protein 1 (DMP-1), and assess the consequences of DMP-1 deficiency for bone cell function. *(Baseline):* (FY06) The skeleton of a mouse lacking DMP-1 exhibits complex defects. It is unknown how this is related to bone cell function.	DMP1 is needed for bone cell differentiation and maturation. Bones of mice lacking DMP1 are soft and, at a cellular level, are poorly organized like bones found in a rare form of rickets. (Target Exceeded)

Measure	FY	Target	Result
	2006	Generate a genetically modified mouse in which only bone-forming cells are deficient in fibronectin, and identify the cell surface molecule mediating interaction between bone-forming cells and connective tissue growth factor. *(Baseline):* (FY04) Mice wholly deficient in fibronectin are not viable. Molecules interacting with CTGF are unknown.	Researchers produced a mouse in which only bone-forming cells are deficient in fibronectin and identified integrin alpha v beta 5 as the cell surface molecule that mediates interactions between the cells and connective tissue growth factor. (Target Met)

Data Source and Validation
Osteoporosis Overview - National Institutes of Health. May 2009 (http://www.niams nih.gov/Health_Info/Bone/Osteoporosis/default.asp). The matrix protein DMP-1 (dentin matrix protein-1) influences bone cell maturation, controls bone mineralization, and regulates phosphate metabolism. Pathogenic role of Fgf23 in Dmp1-null mice. Liu S, Zhou J, Tang W, Menard R, Feng JQ, Quarles LD. Am J Physiol Endocrinol Metab. 2008 Aug;295(2):E254-61. Epub 2008 Jun 17. PMID: 18559986 http://www.ncbi.nlm.nih.gov/pubmed/18559986 Multiple matrix components regulate bone formation and resorption by modulating the activity of growth factors. Extracellular microfibrils: contextual platforms for TGFbeta and BMP signaling. Ramirez F, Rifkin DB. Curr Opin Cell Biol. 2009 Oct;21(5):616-22. Epub 2009 Jun 12. PMID: 19525102 http://www.ncbi.nlm nih.gov/pubmed/19525102 Do osteocytes contribute to phosphate homeostasis? Feng JQ, Ye L, Schiavi S. Curr Opin Nephrol Hypertens. 2009 Jul;18(4):285-91. Review. PMID: 19448536 http://www.ncbi.nlm nih.gov/pubmed/19448536 TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, Zhao L, Nagy TR, Peng X, Hu J, Feng X, Van Hul W, Wan M, Cao X. Nat Med. 2009 Jul;15(7):757-65. Epub 2009 Jul 5. PMID: 19584867 http://www ncbi nlm nih.gov/pubmed/19584867 Advances or other highlights Fibronectin binds and enhances the activity of bone morphogenetic protein 1. Huang G, Zhang Y, Kim B, Ge G, Annis DS, Mosher DF, Greenspan DS. J Biol Chem. 2009 Sep 18;284(38):25879-88. Epub 2009 Jul 18. PMID: 19617627 http://www ncbi nlm nih.gov/pubmed/19617627 Thrombospondin-2 regulates matrix mineralization in MC3T3-E1 pre-osteoblasts. Alford AI, Terkhorn SP, Reddy AB, Hankenson KD. Bone. 2009 Sep 8. [Epub ahead of print] PMID: 19744582 http://www ncbi nlm nih.gov/pubmed/19744582 Delany AM, Hankenson KD. Thrombospondin-2 and SPARC/osteonectin are critical regulators of bone remodeling. J Cell Commun Signal. 2009 Oct 28. [Epub ahead of print] PMID: 19862642 http://www.ncbi.nlm.nih.gov/pubmed/19862642

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and the measure was Achieved. In searching for and characterizing clinically significant interactions between bone-forming cells and the bone matrix, researchers identified DMP-1 as a critical factor in bone formation and control of minerals in the blood and also discovered a robust network of matrix proteins that regulate bone turnover. This research has substantially changed the way scientists think about this crucial aspect of bone biology. Researchers demonstrated that the interaction between cells and the matrix protein DMP-1 is critical for the organization of osteocytes within bone, the formation of fully

mineralized bone, and even the proper control of mineral concentrations in the blood. In another major advance building on the efforts of several research teams, investigators determined that the importance of several matrix components arises not so much from direct interactions with bone cells, but from the components roles in organizing and regulating other molecules that are not usually thought of as matrix proteins.

Measure

The matrix protein DMP-1 (dentin matrix protein-1) influences bone cell maturation, controls bone mineralization, and regulates phosphate metabolism

In 2005 research indicated that the skeletons of mice that did not produce DMP-1 resembled the soft, misshapen bones of people who have diseases such as osteomalacia and rickets. Early in 2007, investigators studying DMP-1's role in bone health linked defects in the protein to a previously unrecognized form of rickets. When researchers analyzed the blood and urine of the mice lacking DMP-1 and compared the results to clinical findings from members of two families who had a mysterious type of rickets, they discovered that the DMP-1 protein affects osteocyte maturation, calcium phosphate deposition in bone, and phosphate metabolism in other tissues. Genetic sequencing revealed that mutations to the gene for DMP-1 caused the patients' disease, which researchers dubbed autosomal recessive hypophosphatemic rickets.

Additional experiments revealed that the osteocytes of mice lacking DMP-1 did not mature completely as they embedded in the bone matrix. The cells also overproduced a protein, called phosphaturic factor FGF23, which regulates the amount of phosphate excreted in the urine and circulating in the blood. Although researchers and clinicians knew that increased concentrations of FGF23 caused a different form of rickets, no one had linked bone mineralization and phosphate excretion with interactions between DMP-1 and osteocytes. Expanding on their discovery, the scientists developed a strain of mice that was missing FGF23 and DMP-1, and confirmed that osteocyte-produced FGF23 influences how the kidneys process phosphate, as well as vitamin D metabolism.

This work illuminated the previously unrecognized role of interactions between osteocytes and the DMP-1 protein in the mineralization of bone. The discovery that mutations in the DMP-1 gene cause a rare genetic disease in humans shows that the effects of DMP-1 defects originally observed in mice are equally important in people. Finally, the effects of the DMP-1 mutations on blood levels of phosphate demonstrate a previously unsuspected link between bone cells and the kidney, which is a critical regulator of mineral levels in the circulation.

Multiple matrix components regulate bone formation and resorption by modulating the activity of growth factors

Since 2002, NIH-supported researchers have probed the biological importance of several bone matrix proteins, in many cases by characterizing mouse strains that they had genetically modified to lack specific proteins. In the paradigm that emerges from this work, matrix components such as fibronectin, biglycan, and fibrillin are necessary for the proper function of regulatory molecules, including transforming growth factor beta (TGF-beta) and bone morphogenetic proteins (BMPs). At the beginning of this measure, scientists had intensively studied TGF-beta and the BMPs, but did not recognize that bone matrix proteins controlled their activities. TGF-beta, in particular, has emerged recently as a critical "coupling factor" that coordinates bone resorption and bone formation. BMPs, a group of proteins related to TGF-beta, have other important functions in the development, remodeling, and repair of bones.

Under this measure, NIH investigators have demonstrated that biglycan, fibrillin, and fibronectin mediate the incorporation of TGF-beta into bone, chiefly in an inactive or latent form. Investigators also demonstrated that BMPs are incorporated into the matrix, where they are prevented from interacting with bone-building cells. Thus, the regulation of the functions of these growth factors depends on the controlled release of active factors from the matrix. Defects in this process can have serious consequences for health. In the genetic disorder Camurati-Engelmann disease, for example, failure to inactivate TGF-beta leads to skeletal deformities and

fractures.

Scientists have begun to develop integrated models that take into account the many of these findings. For example, NIH-funded investigators summarized the latest understanding of the roles members of the fibrillin protein family play in forming the bone scaffold and in regulating TGF-beta and BMP signals. In addition, a separate NIH investigator integrates the evidence that osteocytes have essential roles in bone mineralization with data, including those described above, about osteocytes' contribution to phosphate regulation.

Taken together, these insights have important implications for clinical interventions. For example, researchers already have shown that an inhibitor of TGF-beta action corrects the defects in a mouse model of Camurati-Engelmann disease. Similarly, the recognition that association with matrix components modulates the activity of BMPs could help to improve the effectiveness of these proteins in clinical applications. Orthopaedic surgeons currently can use BMPs to promote new bone formation during surgery, but the large amounts required make BMP-based interventions costly.

Advances or Other Highlights

Researchers have continued to explore the functions of bone matrix components. For example, recent results show that fibronectin controls the activity of BMP-1 and similar molecules, which are responsible for the processing of precursors into mature functional proteins involved in matrix assembly. In experiments using molecular techniques to reduce the amount of TSP-2 in bone cells, results suggest that TSP-2 may promote mineralization by facilitating proper organization of the matrix. Recent results of work on TSP-2 and osteonectin suggest that both matrix proteins positively influence bone cell function and may have similar mechanisms of action.

BACKGROUND

Skeletal health depends on the process of bone turnover, in which small regions of bone are broken down (resorbed) and replaced with new bone. The process is critical to maintaining bone mass and preventing fracture. For example, an excess of resorption over formation underlies many bone diseases, such as osteoporosis.

A major public health threat, osteoporosis affects 44 million Americans. The medical expense for treating bones that break because of osteoporosis is as high as $14 billion each year. Bone deterioration is an underlying characteristic of osteoporosis, and the Food and Drug Administration has approved several drugs that slow or stop bone loss. Because bone-building interventions also can prevent osteoporotic fractures and promote healing of broken bones, many researchers are trying to understand and harness factors that control bone formation.

Bone is more than a hard skeleton. Bones are living organs, made of cells that interact with a matrix of many different proteins. Osteoblasts are cells that form new bone. As osteoblasts embed in the bone matrix, they develop into other cells called osteocytes. When the NIH developed this performance measure in FY 2002, researchers were beginning to appreciate that osteocytes, like the bone-building osteoblasts, had an important role in skeletal health.

Rationale

Interactions between proteins in the extracellular bone matrix and other proteins on the outer surfaces of osteoblasts and osteocytes produce signals that regulate bone build-up and break-down. In FY 2002, however, researchers understood few details about cell-matrix interactions. The NIH undertook this measure because understanding the factors that stimulate bone formation could yield targets for new drugs or tissue-engineering approaches to restore lost bone.

In FY 2002, NIH identified thrombospondin-2 (TSP-2; FY 2003 and FY 2005 performance targets) and osteonectin (FY 2004 performance target) as particularly interesting candidates for cellular and animal testing under this GPRA measure. Over time, it added other bone-matrix proteins:

- small proteoglycans, such as biglycan (FY 2004, FY 2005, and FY 2006 strategic targets),
- fibronectin (FY 2004, FY 2005, and FY 2006 strategic targets, and FY 2006 performance target),
- connective tissue growth factor (CTGF; FY 2006 performance target),
- dentin matrix protein-1 (DMP-1; FY 2007 performance target), and
- fibrillin-2 (FY 2008 performance target).

Deficiency of the protein fibrillin-2, for example, causes a genetic disease called congenital contractural arachnodactyly (CCA), one feature of which is reduced bone mass. NIH added fibrillin to the GPRA performance measure because of findings which suggested that fibrillin-containing structures are necessary for normal bone cell function. Understanding the mechanism of this effect could help in the development of therapies for CCA and could also lead to new ways of stimulating bone formation in osteoporosis.

TARGET CONTEXT AND CONDITIONS

In FY 2002, researchers had identified several bone matrix proteins and knew that the rates of bone build-up and break-down depended on interactions between bone cells and these extracellular proteins. Before scientists can translate their findings into therapeutic applications, however, they need to understand how the interactions influence bone health. Between FY 2002 and FY 2009, NIH-funded researchers identified and characterized several significant molecular interactions between the bone-forming cells and protein components of bone.

Their approaches spanned the three basic building blocks of biomedical science: experiments with cultured cells; studies of genetically modified mice; and lessons from humans who have genetic bone disease. Cell cultures allow for the most detailed analysis of the molecular mechanisms underlying cell functions. However, cell cultures seldom reflect all factors governing overall physiological processes. For example, although researchers can cause osteoblasts to produce bone matrix in culture, the interaction between cells and matrix in culture is not normal, and osteoblasts do not become recognizable osteocytes within the bone produced in culture.

In contrast, genetically modified mice can provide information about consequences of the absence or excess of a specific protein in the intact organism. As a result, researchers can define the function of different matrix proteins, and the cell surface proteins that interact with the matrix. They can assess the consequences of interfering with specific cell-matrix interactions by thoroughly examining the bones of mice, which can even indicate the ultimate effect on the mechanical strength of the bones. However, the study of genetically modified mice has significant pitfalls. The effects of protein deficiency or excess can be difficult to predict. Mice lacking a particularly important protein may be born dead or die shortly after birth, limiting the information mouse studies can provide. It can be difficult to isolate the regions of the mouse chromosomes necessary to generate a desired type of mouse. Finally, mice do not always faithfully reflect human physiology. For this reason, a third building block is the study of humans: patients who have genetic diseases, and cells and tissues both from healthy people and from people with specific diseases.

Long Term Objective: (SRO-8.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-8.4 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. (Outcome)	*2009*	Complete goal of assessing 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. *(Baseline):* (FY07) IDeA/COBRE evaluation completed, and IDeA/INBRE evaluation initiated.	Through the COBRE program recruitment and retention of junior investigators have done exceptionally well obtaining NIH grant funding; with the percent of junior investigators succeeding in the quest for PHS grant increasing by 23% and R-type grants received jumping by 40%. Through the INBRE program increases in the enrollment in science and health-related programs suggest that the academic pipeline is functioning. (Target Met)
	2008	Full-Scale Assessment of the IDeA Program: -Complete the IDeA/COBRE evaluation and analyze preliminary results. *(Baseline):* (FY06) IDeA/COBRE evaluation initiated.	NIH has received the final report entitled 'Process Evaluation of the Centers of Biomedical Research Excellence (COBRE) Program.' (Target Met)
	2007	Full-Scale Assessment of the IDeA Program (Step 2): - Initiate the full-scale evaluation for IDeA/INBRE. *(Baseline):* (FY05) INBRE evaluation design.	The full-scale evaluation for IDeA/INBRE was initiated with a process evaluation on 23 sites funded between FY 2001 and FY 2002. (Target Met)
	2006	Full-Scale Assessment of the IDeA Program (Step 1): - Initiate the full-scale evaluation for IDeA/COBRE. *(Baseline):* (FY04) COBRE evaluation design	The full-scale evaluation for IDeA/COBRE was initiated when the contract to conduct the COBRE evaluation was awarded on September 28, 2006. (Target Met)

Data Source and Validation
The final report entitled "IDeA Networks of Biomedical Research Excellence (INBRE) Program-- Process Evaluation Report" is located in the Office of Science Policy, NCRR @ 301-435-0864.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and the measure has been Achieved. The process evaluation for IDeA/INBRE was commissioned to answer two broad questions: Are the networks implementing the program as planned, and Is

there evidence that various program objectives, processes, and short-term outcome goals are being accomplished? The data reported indicate that the 23 INBRE networks are successfully implementing both the required program cores and additional cores that meet the local objectives and goals for each network and the program as a whole. Over the past 5 years, the INBRE networks have largely completed the development of their planned research infrastructure, and have created a series of research laboratory cores and shared facilities that are being utilized by members within each network, and in some cases, regional utilization is beginning to occur. Each network has put into place a program for constructing an "investigator pipeline" by selecting a number of promising junior investigators, providing them with research mentoring and pilot or research subproject funding, and supporting their movement toward attaining independent status. Many of the networks have converged upon a timeline of about 3 years of project support. There remains some variability and uncertainty around whether the end result of this support should be the successful attainment of an R01 application, versus other options such as serving as a co-principal investigator (or co-investigator) on a mentor's grant. However, the networks seem to be learning from their own experiences through reviews by External Advisory Groups or outside.

Efforts to create an academic pipeline have focused primarily on undergraduate and graduate students, although some networks have begun to conduct outreach activities with local high schools and with high school graduates who are entering college. It may still be too soon to determine whether these activities are succeeding.

There is also evidence that the INBRE networks are meeting their program objectives. The focus on developing research infrastructure within the networks has shifted to developing the needed research expertise through faculty recruitments and through the selection of promising young investigators. Increasing enrollments in science and health-related programs (particularly at the associate degree levels) suggest that the academic pipeline is functioning, and it will now be necessary to find better ways to track the students who have participated in network interventions to determine whether these efforts are beginning to work.

The full-scale process evaluation for IDeA/COBRE completed in September 2008 focused on the 19 COBREs. The purpose of the evaluation was to determine if the program operations and outputs during the centers' first six years have been successful as well as the success of the junior investigators supported during this period. Some examples of the outputs that were assessed include: successful recruitment of new research faculty and technical staff, expansion of core facilities and successful implementation of 3-5 research projects. The period of performance for the 19 centers in this cohort was FY 2001 to FY 2006. The findings illustrated how effective this exploratory program project grant program has been in strengthening the research infrastructure of institutions located in IDeA states.

A major achievement was the centers' recruitment and retention of a cohort of junior investigators who have done exceptionally well. A majority of the junior investigators (65%) succeeded in the quest for a Public Health Service (PHS) grant after joining the program, a significant increase over the pre-COBRE percent of 42%. Most importantly, junior investigators new awards were primarily R-type or Research grants, with the percent receiving an R-type grant jumping from 0% to 40%. The success is especially noteworthy given the current research grant environment and the challenges of building a successful research career in an IDeA state. The study's findings are expected to be helpful to NIH administrators, COBRE program directors, and others interested in developing and evaluating multidisciplinary research center programs.

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, providing mentoring for 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 budget 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 2004, BRIN was renamed IDeA Networks of Biomedical Research Excellence (INBRE) to better reflect the purpose of the program and to avoid confusion with another program with a similar name.

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.

TARGET CONTEXT AND CONDITIONS

A database was developed for the annual progress report to collect potential indicators based on previous related NIH evaluations and findings from a pre-COBRE analysis.

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

Step 1 of the Assessment Methodology for the IDeA Program consisted 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 INBRE. Step 2 consisted of completing the evaluation design to determine a confirmed list of target indicators to measure IDeA/INBRE impact and assessing the results of the COBRE evaluation design study.

Since the COBRE began before INBRE, the two evaluations are being conducted at different intervals. The evaluation design study for COBRE was completed in FY 2004 and that for INBRE was completed in FY 2005. The full-scale evaluation for COBRE began in FY 2006 and was completed in FY 2008. The full-scale evaluation for INBRE began in FY 2007 and will be completed in FY 2009.

The purpose of each evaluation design study is to determine the best strategy for evaluating the program.

Consideration was 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

Further, the annual progress reports that collect potential indicator data validated 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 was determined by the design studies.

Following completion of these evaluation design studies, the full-scale evaluations of COBRE and INBRE began to determine the impact of the IDeA program.

Long Term Objective: (SRO-8.5) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-8.5 By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease. (Outcome)	*2009*	Complete goal of developing an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease. *(Baseline):* To be determined by FY08 results.	Eleven calibrated item banks are available to clinical researchers for assessment of pain, fatigue, and other domains in chronic disease through a free, web-based service center. The center also offers training for use of the item banks and other resources (Target Met)
	2008	Conduct primary data analyses of item responses in pain, fatigue, physical functioning, emotional distress, and social role participation domains obtained from large, diverse samples of the general population and chronic disease patients to calibrate items and refine item banks for the PROMIS instrument. *(Baseline):* (FY07) More data needed from large, diverse samples of chronic disease patients using the test item pool.	Primary data analysis has been conducted to allow release of calibrated item banks for preliminary versions of the PROMIS instrument. (Target Met)
	2007	Initiate analyses on preliminary data of pain, fatigue, physical functioning, emotional distress, and social role participation. *(Baseline):* (FY06) Preliminary data analyses undertaken.	Data analysis was initiated in April, 2007, six months ahead of schedule. Primary analyses have been completed, and additional analyses are ongoing. The result of these analyses are item banks ready for public release. Publications resulting from these analyses are in process. (Target Exceeded)
	2006	Initiate administration of instrument(s) to a large demographically diverse patient sample representing a wide range of chronic disease type and severity. *(Baseline):* (FY05) An initial item pool for assessing specified domains of symptoms and/or domains of health-related quality of life developed using FY 05 target.	Administration of the PROMIS item pool to a diverse sample representing a wide range of conditions was initiated in July, 2006. (Target Met)

Data Source and Validation
NIH PROMIS http://www nihpromis.org Publication citations that describe the primary data analysis: http://www nihpromis.org/Web%20Pages/Publications%20and%20Reports.aspx User registration to view the short forms and begin work with the CAT system: http://www.assessmentcenter.net/ac1/

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and the measure was Achieved. Eleven calibrated item banks are available at NIH PROMIS, at no charge, to clinical researchers interested in the assessment of domains of symptoms and health-related quality-of-life. These question banks include items for measuring emotional distress (anger, anxiety, depression), fatigue, pain (behavior, impact), physical function, sleep and wake disturbance, and satisfaction with social activities and social roles. The item banks can be administered as customizable short forms (hard copies), or by computerized adaptive testing (CAT).

Measure

The PROMIS performance targets were met or exceeded each year. Researchers began by reviewing questions, or items, from existing patient-reported outcomes (PRO) instruments. Then new and modified items were developed, followed by analysis, categorization, and "winnowing" to reduce redundancy. Items were tested extensively by focus groups and cognitive interviews across ethnically, racially, culturally, educationally, and economically diverse populations, in preparation for field testing of the computer adaptive testing (CAT) system. The item banks were tested using preliminary versions of PROMIS instruments, e.g., PRO short forms (hard copies) and CAT, and all were made available to clinical researchers Analysis of the data for construction of final item banks was completed six months ahead of schedule.

Advances or Other Highlights

There are over 1100 registered users of these item banks through the web-based service center A free demonstration is available of the PROMIS CAT, which allows participants to obtain instant scores and comparison information of select item banks. Training is available for both an introduction to psychometric methodologies and CAT, as well as use of other resources at the service center.

BACKGROUND

Conventional clinical and functional measures of disease status do not fully capture the ways in which chronic diseases and their treatment affect individuals. Many aspects of patients' subjective experience, such as symptom severity and frequency, emotional and social well-being, and perceived level of health and functional ability are important targets for disease intervention that are not measured by x-rays or laboratory results. Measurement of patient-reported outcomes (PROs) is particularly important in clinical trials, where changes in clinical measurements or imaging results alone may not translate into important benefit to the patients, or in trials in which two treatments may be comparable in limiting or curing disease but have different adverse effect profiles differentially affecting symptoms, functioning, or other aspects of patients' quality of life.

The last several decades have seen a proliferation of tools to measure symptoms, quality of life, functional status, emotional status, and general perception of health. Although many of these instruments have good demonstrated reliability and validity, there are many limitations to current measurement approaches. One challenge is to compare results across different studies when different measurement tools are used. These instruments may have non-comparable or non-combinable scores because each scale may use a different number of items, different response options, different reference periods, or different item content. For example,

progress in clinical pain research is slowed by the use of various pain measurement scales that are not directly comparable. The length and complexity of questionnaires and batteries can also be problematic, creating a level of respondent burden that hampers recruitment, results in too much missing data, or is detrimental to response validity and reliability. The clinical outcomes research enterprise would be enhanced greatly by the availability of a psychometrically validated, dynamic system to measure PROs efficiently in study participants with a wide range of chronic diseases and demographic characteristics.

Rationale

Increased availability of more precise, efficient and easier to use measures of quality of life and symptom indices will significantly facilitate all forms of clinical research and enhance patient care delivered on the front lines. The development of better health-related quality of life (HRQOL) and symptoms instruments would provide the needed tools for comparing the outcomes of preventive, rehabilitative, and curative interventions.

A new enabling technology, computerized adaptive (or dynamic) health assessments, can yield a more efficient and easier-to-use set of validated clinical research tools. Two critical concepts form the basis of this new technology. The first is that by collecting a large set of questionnaire items in subjects with the widest possible range of severity of disease and levels of health, one can construct reliable models (i.e., item response theory models) that predict the probability of specific responses by patients based on their answers to initial questions. The second concept uses software programs to control the specific set of questions asked of each patient. Based on the answers to initial questions, the program can focus the remaining questions to more accurately assess the patient's level of functioning. If these standardized instruments and information on their performance in reference populations were widely available, clinical researchers would be able to measure clinical outcomes far more accurately, compare across diseases or populations, account for co-morbid conditions, and ascertain the impact of nonspecific symptoms like fatigue, without the necessity of conducting or having to duplicate, previous validation efforts.

Properly constructed, this repository and supporting technology will lead to more efficient, precise and reliable assessment of quality of life and non-specific symptoms in clinical research, increasing the interoperability of clinical research, permitting the direct comparison of results even from different instruments, using different questions.

TARGET CONTEXT AND CONDITIONS

A multi-disciplinary network of cooperative agreements (PROMIS) has been funded to develop an item bank, test item response theory models of item performance, and develop a computerized adaptive testing system to measure a select number of health-related quality of life (HRQOL) domains and non-disease specific symptoms in patient with chronic illnesses. In FY 2006, the network characterized the ability of commonly used instruments to capture these domains. The strengths, deficiencies, gaps, and redundancies in the most common instruments for these domains were described. Network experts guided the process of developing a set of items to be tested, some new and some from existing instruments, with input from patients.

Data collection using this item set was initiated in a wide range of patients suffering chronic diseases and conditions, and enrollment was completed in March 2007. These data were analyzed in FY 2008 to determine a variety of item characteristics and psychometric properties, to select the most useful items for the final item bank and to develop the CAT system and hard copies (“short forms”). Additional data collection will be conducted in current domains, as well as new areas, to address any remaining questions about psychometric properties of the item banks.

Long Term Objective: (SRO-8.6) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-8.6 By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES). (Outcome)	*2011*	Report stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES). *(Baseline):* Preliminary estimates complete; survey data available for public analysis.	N/A
	2010	Conduct initial analysis of data to determine estimates of the extent and nature of vision impairment. *(Baseline):* Preliminary statistical analysis completed. Survey data verified as ready for use in determining estimates.	N/A
	2009	Complete preliminary analyses of the data to prepare national estimates of visual impairment. *(Baseline):* (FY08) Approximately 7,000 people surveyed by the end of FY08.	Conducted preliminary analysis and quality control of the NHANES vision data and released results to the public. (Target Met)
	2008	Continue collecting data for the vision component of NHANES to reach a target of surveying approximately 7,000 people in total. *(Baseline):* (FY07) Approximately 3,500 people surveyed in FY 2007.	NHANES has conducted over 6,700 vision exams, sufficient to maintain the power of the study. (Target Met)
	2007	Extend NHANES and survey approximately 3,500 people. *(Baseline):* (FY06) Very little reliable data on the prevalence of visual impairment in the U.S.	NHANES Survey is recruiting at an annual rate of 3410 respondents. (Target Met)

Data Source and Validation
Survey data released to the public for analysis: http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/VIX_E.htm NHANES results and products index: http://www.cdc.gov/nchs/nhanes/nhanes_products htm

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH performed quality control analysis on the survey data before it was released

to the public. These data will be used by government agencies and public health experts to assess target milestones for one of the vision objectives in the DHHS national health promotion and disease prevention initiative, Healthy People 2010.

The visual component of NHANES consisted of a two-part survey. First, individuals were interviewed in their homes; 10-minutes of questions pertained to visual health. Second, individuals were asked to report to a mobile examination center where trained health technicians performed a visual screening examination using a standardized protocol that included automated data collection as well as visual acuity measurements. In total, 6,917 people participated in the mobile examination portion of the survey and visual acuity data were available from 6,452 individuals.

Survey interview data were transmitted electronically from the field to the NHANES central survey database system for preliminary processing and quality control. NHANES staff conducted preliminary processing and quality control. This analysis included removal of personally identifying information and checks of the raw data to be sure they were collected and stored in a consistent manner. Data were examined for logical inconsistencies and technician or equipment errors. Edits of the data were performed when errors were detected. Based on the sampling methodology, NHANES applied statistical weights to the data so results will be a valid representation of the national burden of disease; details are available on the NHANES website. NHANES provided preliminary data to partners to conduct additional quality content review and enable any discovered issues to be addressed prior to public release.

BACKGROUND

The NIH collaborated with the National Center for Health Statistics to develop a vision component for the National Health and Nutrition Examination Survey (NHANES). After collection of baseline data through 2004, changes were made to the future survey, including revised questions to capture information on severe visual impairment, the extent of uncorrected but correctable refractive errors, the methods selected by study participants to correct their diagnosed refractive error, and vision-related quality of life questions. Additionally, a retinal component was added by the Centers for Disease Control to augment the vision component for 2005-2006, and both eye components in the survey have been extended to 2007-2008. These changes will provide better estimates of the extent and nature of vision impairment in the U.S. Knowledge about the nature and extent of visual impairment in the United States will allow public health officials to more efficiently tailor surveillance activities to identify individuals in need, health providers to better supply corrective modalities to individuals whose vision can be improved and rehabilitation services to those with uncorrected visual impairment, and health economists to allocate sufficient resources to this effort. The end result will be to provide more Americans with normal vision allowing them to more safely perform activities for which vision is required, including driving, occupational, and recreational activities.

Disease Burden

Vision impairment is one of the most feared disabilities. Although it is believed that half of all blindness can be prevented, the number of people in the United States who suffer vision loss continues to increase. The leading causes of vision impairment and blindness in the U.S. are primarily age-related eye diseases. The number of Americans at risk for age-related eye diseases is increasing as the baby-boomer generation ages. These conditions, including age-related macular degeneration, cataract, diabetic retinopathy and glaucoma, affect more Americans with age-related eye disease. The vision impairment that results is expected to double within the next three decades. As of the 2000 census, there were more than 119 million people in the United States in this age group.

Refractive errors are the most frequent eye problems in the United States. Nearsightedness (myopia) and farsightedness (hyperopia) are the most common refractive errors. Most infants have some degree of hyperopia, but vision becomes more normal with age usually leveling off by age 6. While some children may be farsighted early in life, most myopia occurs later during adolescence. Other common refractive errors include astigmatism

(uneven focus) and presbyopia (an age-related vision problem with near focus). Fortunately, almost all refractive errors can be corrected by eyeglasses or contact lenses. It is estimated that more than 150 million Americans use corrective eyewear to compensate for their refractive error. Americans are estimated to spend over $15 billion each year on eyewear, supporting an optical industry in the U.S. worth more than $30 billion. Uncorrected or under-corrected refractive error can result in significant vision impairment.

Rationale

Several studies have reported prevalence and incidence data for diseases that can cause visual impairment and blindness, but there are no solid national estimates of the prevalence or incidence of visual impairment and the attendant disability, loss of productivity, and the impact on quality of life.

The NIH collaborated with the National Center for Health Statistics (NCHS) to develop a vision component for NHANES in support of the vision objectives in Healthy People 2010. After collection of baseline data through 2004, changes were made to the 2005-2006 survey, including revised questions to capture better information on severe visual impairment, as well as extending the vision-related quality of life questions to ages 20 and older (compared to those 50 and older for NHANES 1999-2004). As a nationally represented survey of Americans with both interview and examination components, NHANES is uniquely suited to gather, in a cost effective manner, information on vision and ocular health from both a quality of life and medical perspective. Because NHANES encompasses a range of health and nutritional components, the opportunity exists to identify other health conditions that may be related in some manner to visual impairment or be experienced by individuals with visual impairment. Insights about concurrent conditions can help foster further research efforts to better understand disease and can assist in the design and implementation of comprehensive health and vision promotion programs.

TARGET CONTEXT AND CONDITIONS

NHANES is the only nationally representative survey incorporating questions about vision in a personal interview as well as an assessment of vision in an examination setting. The newly added vision component consists of questions about visual impairment and quality of life activities as well as examination data on visual acuity, refraction, and keratotomy. The medical examination now includes a retinal assessment of the optic disc and macular areas. Integrating data from these two sources allows a more comprehensive approach including differentiating causes of visual impairment for those individuals whose vision cannot be corrected to normal levels. Analysis of the vision data collected in the 2007-2008 survey cycle will provide better estimates of the extent and nature of vision impairment in the U.S., as well as allowing assessment of the impact of Healthy People 2010 on the vision health of the Nation. In order to achieve this goal, approximately 7,000 people will be sampled in a multi-stage probability sample of the US civilian, non-institutionalized population in a manner designed to be nationally representative.

NHANES has internal processes for deciding which components are included during each survey cycle as well as how survey data are acquired, managed and released to co-sponsoring agencies and to the public. At the end of 2008 survey period, NHANES staff will facilitate a preliminary analysis of the raw survey data: verifying the merge of individual responses into a secure, annotated database using unique survey participant identification numbers; checking for errors and inconsistencies; applying statistical weights based on sampling methodology; and, cross-validating data items across survey response categories. At the completion of this preliminary analysis in late 2009, co-sponsoring agencies, such as NIH, will take receipt of data for an additional quality control review of the consolidated data file and its related data documentation and will have 60 calendar days to report any issues back to NHANES staff. Vision data and related documentation from the 2007-2008 NHANES survey are expected to be publicly released by NCHS in 2010 and, once in the public domain, will be used to develop national estimates of visual impairment.

Long Term Objective: (SRO-8.7) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-8.7 By 2012, identify three (3) effective implementation strategies that enhance the uptake of research-tested interventions in service systems such as primary care, specialty care and community practice. (Outcome)	*2011*	Identify at least 3 mechanisms for tracking successful implementation within studies to improve the uptake of research-tested interventions in health care settings *(Baseline):* (FY11) 5-7 studies underway that include viable methods for tracking implementation or dissemination	N/A
	2010	Identify at least three systemic (or services) intervention studies which utilize implementation mechanisms, strategies or techniques to improve the uptake of effective interventions in healthcare settings *(Baseline):* (FY08) 5-7 studies are currently underway to test the impact of key implementation interventions	N/A
	2009	Identify and test at least three (3) key variables for measuring implementation to improve the uptake of effective interventions in healthcare settings. *(Baseline):* (FY07) 10-15 studies currently underway to test reliability and validity of measures elucidating key implementation constructs.	Variables for measuring implementation include organizational culture and climate, capacity for organizational change, dimensions of supervisory adherence to treatment principles, and adherence to clinical guidelines. (Target Met)
	2008	Identify three (3) implementation mechanisms, strategies, or techniques to improve the uptake of effective interventions in healthcare settings. *(Baseline):* (FY07) Approximately 15-20 studies are underway that may contribute to formation of effective implementation strategies.	Three mechanism, strategies, or techniques, were identified to improve the uptake of effective interventions in healthcare settings, including community-based models, evidenced-based care framework, and collaborative frameworks. (Target Met)

Data Source and Validation
Glisson C et al. Therapist turnover and new program sustainability in mental health clinics as a function of organizational culture, climate, and service structure. Adm Policy Ment Health. 2008 Mar; 35(1-2):124-33. http://www ncbi nlm nih.gov/pubmed/18080741 Bobiak SN et al. Measuring Practice Capacity for Change: A Tool for Guiding Quality Improvement in Primary Care Settings. Qual Manag Health Care. 2009 Oct/Dec; 18(4):278-284. http://www ncbi nlm nih.gov/pubmed/19851235 Schoenwald SK et al. Clinical supervision in treatment transport: effects on adherence and outcomes. J Consult Clin Psychol. 2009 Jun; 77(3):410-21. http://www ncbi nlm nih.gov/pubmed/19485583 Kurian BT et al. A computerized decision support system for depression in primary care. Prim Care Companion J Clin Psychiatry. 2009; 11(4):140-6. http://www ncbi nlm nih.gov/pubmed/19750065

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH researchers identified variables for measuring implementation to improve the uptake of effective interventions in healthcare settings, including organizational culture and climate, capacity for organizational change, dimensions of supervisory adherence to treatment principles, and adherence to clinical guidelines.

NIH researchers examined therapist turnover and new program sustainability in mental health clinics as a function of organizational culture, climate and services structure. This study interviewed mental health clinic directors and administered an on-site survey of the therapists using the Organizational Social Context (OSC) measurement system. The OSC is designed to assess latent constructs of culture, climate and work attitudes in mental health clinics. According to the results of the OSC survey, organizations most effective in implementing and sustaining new treatment and service programs were those which had the best climates, low turnover rates, and best culture profiles. The findings suggest that organizational characteristics may serve as mediators to adoption and implementation of mental health treatments and services within the organization. For this reason, strategies to support the implementation of new programs should give consideration to organizational context and the compatibility of organizational service structures.

NIH researchers also developed a new construct based on the development of the Practice Change Model, to measure organizational capacity for change in primary care settings. This study reviewed previous conceptual and empirical studies to generate a 25 item instrument to assess organizational culture, climate and structure. Using information from direct observation and key informant interviews, a research team member rated these items for 15 primary care practices engaged in a quality improvement intervention. Results demonstrated that the instrument had excellent reliability and correlated well with a summary assessment of each practice's capacity for change suggesting good convergent validity. The ability to quantify capacity for change may enable better recognition of organizations likely to be successful in their implementation efforts and those first requiring capacity building prior to interventions.

Several NIH studies have used clinical adherence models and guidelines to assess adoption and implementation of mental health interventions. For example, one study used Mixed-Effects Regression Models (MRMs) to examine relations among supervisor adherence to a clinical supervision protocol, therapist adherence, and changes in the behavior and functioning of youth with serious antisocial behavior. MRM results showed one dimension, supervisor focus on adherence to treatment principles, predicted greater therapist adherence. Two supervision dimensions, adherence to the structure and process of supervision, and focus on clinician

development, predicted changes in youth behavior. Another study established feasibility and efficacy of implementing a computerized decision support system to treat major depressive disorder (MDD) in primary care. The study used a computerized decision support system (CDSS) guideline to assess adherence among physicians acutely treating patients with MDD compared to usual care. Measures of implementation were based on adherence to key elements of evidence-based depression care (i.e. appropriate dosage, outcomes-informed medication switching, and medication augmentation). Results indicate that patients treated by physicians employing CDSS had significantly greater symptom reduction than patients treated with usual care, and render the CDSS superior to usual care for patients with MDD in primary care settings.

BACKGROUND

The Nation spends billions of dollars yearly on medical research. Yet, despite this enormous investment, it is estimated that only a relatively small percentage of scientific findings actually impact clinical practice (an estimated 14%), and this impact occurs slowly (an estimated 17 years after the initial publication of a clinically-relevant finding). Medical research has provided a wealth of knowledge leading to any number of innovative approaches to prevention, early detection, diagnosis, and treatments of a host of diseases and conditions. Yet, little is known about how to best ensure that the lessons learned from biomedical and health behavior research inform and improve the quality of health and human services and the availability and utilization of research-tested interventions in service systems such as medical practices, schools, the criminal justice system, and community health organizations. NIH has recognized that closing the gap between research discovery and program delivery is both a complex challenge and an absolute necessity in ensuring that all populations benefit from the Nation's investments in new scientific discoveries.

Significant barriers exist that prevent the adoption and implementation of newly devised and research-tested interventions into service systems. These barriers may occur at the individual level, practice level, or broader organizational level. For example, an evidence-based program may require extensive clinical training and additional resources, or staff may consider their existing approaches sufficient to address the majority of problems they encounter. There may be few incentives for service providers to train clinical staff in new practices. There may be financial barriers, such as an inability to get reimbursed for providing a specific intervention, or costs associated with becoming a "certified" provider of a specific evidence-based intervention. There may also be constraints that stem from the nature of a system's function and the population it serves, for example the criminal justice system, where unmet treatment needs contribute to the vicious cycle of drug abuse and criminal recidivism.

Organizational barriers, such as frequent turnover of staff or poor supervision, can also threaten the sustainability of an effective intervention, or the ability to know whether a practice is being delivered as it was designed. There may also be assumptions, rather than empirical knowledge, that the program will not work for the specific population that a service provider is working with. In addition, even if barriers to implementation are overcome, few models ensure effective implementation. Programs may be used in ways that undermine effectiveness, such as when staff adapts a program without an understanding of which components are essential for its effectiveness. Few efforts may be made to involve all staff in the implementation process, and little may be done to ensure sustainability of the program. New approaches are needed to overcome these barriers and to improve the use of strategies, to adopt and integrate evidence-based health interventions, and to change practice patterns within diverse service settings.

Rationale

More research is needed to develop new implementation models for intervention and service delivery. Recognizing this need, NIH has undertaken an initiative to broaden its portfolio in implementation research by encouraging trans-disciplinary teams of scientist and practice stakeholders to work together to develop innovative approaches for identifying, understanding, and overcoming barriers to the implementation of research-tested interventions in service settings. The initiative should lead to new implementation models that account for the diverse audience of stakeholders involved in health service delivery, including consumers,

caregivers, practitioners, policymakers, employers, administrators. These implementation models will be measured and tested within real-world practice settings with the hope that these models will ultimately bridge the gap between public health, clinical research and everyday practice.

TARGET CONTEXT AND CONDITIONS

The identification of research-based implementation strategies to enhance the uptake of evidence-based interventions into clinical practice depends upon several important research efforts. Research is needed to better delineate the barriers preventing effective implementation of evidence-based practices. This understanding will lead to new theories of implementation and the generation of novel approaches to integrate effective interventions into clinical practice. A sound methodology for testing the effectiveness of these approaches will need to be further refined, including the development of valid and reliable common measures of implementation effectiveness. New approaches to implementation of diagnostic, preventive, and treatment interventions will need to be systematically studied in a variety of existing care systems. Processes to implement new treatment interventions may require changes in clinical or administrative infrastructure and practices. Thus, an essential component of implementation research is understanding the organizational changes needed to improve the quality of care, to adopt new technology, and to sustain practice improvements over time. Implementation questions will need to be better integrated into all clinical research efforts. Finally, new and improved implementation strategies will need to be disseminated to the many stakeholders that provide public health and clinical services.

Achievement of this goal is dependent on the influx of new investigators to the field, each building the theoretical, methodological and empirical skills to enable comprehensive trials of dissemination and implementation strategies.

Long Term Objective: (SRO-8.8) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-8.8 By 2012, identify at least one candidate intervention that extends median lifespan in an animal model. (Outcome)	*2011*	Measure effects of selected intervention(s) on physical parameters that could affect lifespan. *(Baseline):* Measurement of health-related parameters will be feasible in test animals.	N/A
	2010	Begin Phase II testing of the most promising potential interventions from Phase I. *(Baseline):* (FY08) Further testing of promising candidate interventions is needed to validate results and extend the findings to specific aging phenotypes.	N/A
	2009	Begin Phase I testing of at least three potential interventions and design approach for the first Phase II pilot testing. *(Baseline):* (FY08) 14 interventions are undergoing Phase I testing (as of 5/08).	Began Phase 1 testing on acarbose, methylene blue, and 17-α-estradiol and designed the approach for Phase II testing of rapamycin. (Target Met)
	2008	Identify at least three potential interventions to extend lifespan in an animal model, and begin Phase I testing with these interventions. *(Baseline):* (FY07) 14 interventions are currently undergoing Phase I testing.	NIH identified three potential interventions but did not begin Phase I testing. (Target Not Met)

Data Source and Validation
Phase I results of rapamycin treatment: Harrison, D. E., Strong, R., Sharp, Z. D., Nelson, J. F., Astle, C. M., Flurkey, K., Nadon, N. L., Wilkinson, J. E., Frenkel, K., Carter, C. S., Pahor, M., Javors, M. A., Fernandez, E. and Miller, R. A. (2009) Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460:392-395. http://www nature.com/nature/journal/v460/n7253/pdf/nature08221.pdf For further information on Phase I testing of the three new compounds, contact Chief, Biological Resources Branch, Division of Aging Biology, National Institute on Aging; or 301-402-7744.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. Phase 1 testing began on three new compounds: Acarbose, methylene blue, and 17-α-estradiol.

- Acarbose is used in diabetes therapy, and may confer some of the same benefits as caloric restriction (known to extend life in model systems) by preventing use of specific forms of carbohydrates.
- Methylene blue, used to treat malaria, has antioxidant activity and has been show to delay cellular senescence in cell cultures.
- 17 α-estradiol is chemically related to 17 b-estradiol, a hormone with documented neuroprotective effects. Compared to17 b-estradiol, however, the ability of 17 α-estradiol to bind to estrogen receptors in the body is greatly reduced, limiting undesirable side effects while still providing significant neuroprotection.

In addition, an approach has been designed, and the mice are being bred, for planned Phase II testing of rapamycin, a drug that is already used in humans for a variety of indications. In Phase I testing, this drug was found to robustly extend lifespan in both male and female mice when treatment was initiated at either 9 months or 20 months of age. Rapamycin-treated and control mice showed similar pathology at death, suggesting that rapamycin treatment did not act simply by reducing one form of prevalent pathology in the mice. This research shows that it may be possible to extend lifespans even with treatments that begin later in life. Phase II testing is scheduled to begin in FY 2010.

Advances or Other Highlights

The Phase I finding that rapamycin extends life span in a mammalian model represents a significant breakthrough in the science of life extension. NIH researchers found that in mice, rapamycin works as an inhibitor of the TOR enzyme, which was already known to be linked to the aging process in invertebrates; investigators had not known whether or to what extent TOR was involved in mammalian aging. With these findings, TOR becomes the first protein known to modulate lifespan in each of the four model organisms most commonly used to study aging: yeast, worms, flies and mice. Although investigators do not recommend use of rapamycin to slow the aging process in humans – among other things, it's a powerful immunosuppressant – the discovery that rapamycin works by inhibiting TOR activity opens the door to discovery of new compounds that may also inhibit TOR, without rapamycin's potentially dangerous side effects.

BACKGROUND

A better understanding of the nature of aging and the mechanisms controlling longevity in animal models could enable the development of interventions to extend not only the length but also the quality of life for humans. The recent finding that resveratrol, a natural compound found in certain foods, including grapes, wine, and nuts, could affect the health and survival of mammals exemplifies the promise of research on the nature of aging and the mechanisms controlling longevity. An important activity in this area is the Intervention Testing Program (ITP) at NIH, which supports the testing of compounds with the potential to extend the lifespan and delay disease and dysfunction in a mouse model. A number of interventions, including foods, diets, drugs, and hormones, are tested through this program, which began in 2003. Under this program, intervention testing is conducted in two phases. The first stage, which typically lasts 2 to 2 ½ years, is primarily a lifespan study with a few other parameters measured. Interventions that appear to increase lifespan, based on Phase I results, move on to Phase II, which involves a broader spectrum of assays.

In determining which interventions to test, the ITP solicits proposals from the extramural research community for compounds, supplements, and diets that have potential to extend lifespan and promote healthy aging. The proposals are reviewed and prioritized based on scientific merit, feasibility and preliminary data from studies in a variety of model systems ranging from invertebrates to humans. The ITP often conducts short-term studies to evaluate bioavailability, efficacy (activity), and toxicity of compounds before investing in the large-scale study.

Rationale

A better understanding of the nature of aging and the mechanisms controlling longevity in animal models could enable the development of interventions to extend not only the length but also the quality of life for humans. If safe and effective interventions are found, benefits to the public health would include reduced health care costs for the elderly as well as the individual benefits of maintaining one's independence. This research may also benefit our quest for disease prevention, especially for age-related diseases such as cancer, diabetes, cardiovascular diseases, and Alzheimer's disease.

TARGET CONTEXT AND CONDITIONS

Implementation of this goal will occur through the Interventions Testing Program (described above). In this program, NIH-supported researchers will:

- Continue to solicit Phase I proposals
- Develop Phase II protocols
- Begin Phase II studies on candidate compounds from earlier cohorts, if Phase I data support this
- Conduct a final analysis when all the mice have died

As of 2007, 14 interventions were undergoing Phase I testing, and early results are available for the first compounds that were tested. The original 2008 target was to initiate at least three new compounds in Phase I testing. However, because the ITP was on bridge funding in 2008 while the competitive renewals were revised and resubmitted, there were not sufficient funds to initiate any new testing, only to continue the testing that was in progress. However, NIH did identify three new interventions with the potential of extending lifespan in a mouse model; primary (Phase I) testing of those interventions will begin in 2009. Also in 2009, Phase II studies on the most promising compound from Phase I will be designed and pilot studies completed. In 2010, Phase II testing will begin on this compound, and investigators will measure the effects of the Phase II compound on physical parameters that could affect lifespan.

The three compounds on which Phase I testing will begin in 2009 are acarbose, methylene blue, and 17-α-estradiol. Acarbose is used in diabetes therapy, and may confer some of the same benefits as caloric restriction (known to extend life in model systems) by preventing use of specific forms of carbohydrates. Methylene blue, used to treat malaria, has antioxidant activity and has been show to delay cellular senescence in cell cultures. 17 α-estradiol is chemically related to 17 b-estradiol, a hormone with documented neuroprotective effects. Compared to17 b-estradiol, however, the ability of 17 α-estradiol to bind to estrogen receptors in the body is greatly reduced, limiting undesirable side effects while still providing significant neuroprotection.

Long Term Objective: (SRO-8.9) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-8.9 By 2014, identify 12 pathogen and/or host factors critical for understanding the molecular and cellular basis of pathogenesis of Category A-C biodefense pathogens and/or pathogens causing emerging infectious diseases. (Outcome)	*2011*	Identify two pathogen and/or host factors. *(Baseline):* Infrastructure and capacity established to identify pathogen and/or host factors	N/A

BACKGROUND

By the mid 20th century, some scientists thought that medicine had conquered infectious diseases. With the advent of antibiotics and modern vaccines, as well as improved sanitation and hygiene, many diseases that formerly posed an urgent threat to public health were brought under control or largely eliminated. However, throughout history, infectious diseases continue to emerge and re-emerge.

A terrorist attack on the United States using biological agents, once thought to be a remote possibility, occurred in the fall of 2001 when B. anthracis spores were sent through the United States mail. The potential list of microbial pathogens that threaten civilian populations is larger than that of classical biological warfare threats. Pressures such as: rapidly changing human demographics; rapid global travel; changes in land use patterns; ecological, environmental and technological changes; and even public health practices such as widespread antibiotic use are contributing to the emergence of new diseases.

From time to time, with the right combination of selective pressures, a formerly innocuous human or animal microbe can evolve into a pathogen that can cause a major outbreak of human disease. Changes in societal and environmental factors can also lead to re-emergence of diseases that were previously under control. Recent examples of newly emerging/emerged infectious diseases include the recent outbreak of H1N1 influenza around the globe and the current epidemic of avian influenza in Southeast Asia. Some examples of re-emerging infectious diseases that are of significant public health concern are tuberculosis, malaria and polio.

Rationale

The capability to detect and counter bioterrorism and emerging infectious diseases depends to a substantial degree on the state of the relevant medical science, and the degree to which basic research provides the essential underpinning. Basic research is critical to efforts to develop interventions against bioterrorism and emerging infectious diseases as it lays the groundwork by generating new and innovative concepts based on studies of pathogen biology and host response.

A pathogen is a biological organism such as a virus, bacteria or fungus, commonly called a germ, which may cause disease or illness in its host. Host factors are the traits of a species or group which affect susceptibility to disease. Numerous medical advances have been made to safeguard against diseases caused by pathogens, through basic research and the development and use of vaccines, drug treatments, and improved diagnostics. Understanding a pathogen's potency and modes of transmission, as well as the host's traits, is critical to improving disease prevention, diagnosis and treatment. As diseases emerge and re-emerge, researchers can help identify how best to prevent or to minimize the spread of disease.

The urgent need for new vaccines, diagnostics, and treatments for Category A-C Pathogens led to the decision to use of the centers mechanism for this program. The multidisciplinary nature of the Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Program (RCE) facilitates a unique leveraging

and sharing of intellectual capacity leading to the significant advances in pathogen research described in this measure. The RCEs have an extremely successful track record of conducting basic research. In addition to being an ideal environment for intellectual collaboration, the RCEs are well positioned to rapidly translate basic discoveries into new interventions.

TARGET CONTEXT AND CONDITIONS

The overall goal of the Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Program (RCE) is to establish and maintain strong infrastructure and multifaceted research and development activities. These activities will provide scientific information and translational research capacity to facilitate the development of the next generation of therapeutics, diagnostics and vaccines against the Category A-C Priority Pathogens and emerging infectious disease (EID) agents.

Scientists conducting basic research seek to better understand infectious agents and the response of host organisms by studying the cellular and molecular biology of pathogen and host, physiologic processes, and genome sequences and structures. Their findings elucidate pathogen entry mechanisms, survival strategies, and immune evasion techniques; evolutionary adaptations; activation of the host immune system; and cellular and whole organism responses to infection. Basic research is fundamental for the development of concepts for new vaccines, drugs, and diagnostics.

Long Term Objective: (SRO-9.1) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-9.1 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). (Outcome)	*2010*	Complete goal by demonstrating 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 (eg., heart disease, cancer, Parkinson's disease, or diabetes) *(Baseline):* Several studies are underway to measure the impact of treatment for depression on functional outcomes.	N/A
	2009	Demonstrate the effect of treatment for depression on an individual's improved functional capacity as it relates to social role function, work function and employment. *(Baseline):* To be determined in FY08 based upon results from initiated project.	Researchers demonstrated that treatment for depression, especially combination psychotherapy and medicine, affects functional capacity in family and peer relationships, school attendance, and employment settings. (Target Met)
	2008	Identify at least two methodologies for examining interactions between depression and other comorbid physical disorders. *(Baseline):* (FY07) New methodologies may be applied to address interactions of depression with co-morbid physical disorders.	Researchers identified at least four methodologies for examining interactions between depression and other co-morbid disorders including imagining techniques, observational studies, and animal models. (Target Met)
	2007	Determine the relative efficacy of combined treatment strategies or sequential treatment algorithms in treating chronic depression. *(Baseline):* (FY05) Studies are underway to test the efficacy of differing treatment combinations or sequences for depressed patients.	Significant progress has been made in determining the relative efficacy of combined treatments strategies and sequential treatment algorithms of chronic or recurrent depression. (Target Met)

Measure	FY	Target	Result
	2006	Identify at least one effective strategy for treating depression in the elderly in a variety of settings. *(Baseline):* (FY05) A number of interventions to treat depression in the elderly are currently being developed and tested.	Several new effective strategies for treating depression in the elderly have been identified. (Target Met)

Data Source and Validation
Treatment for Adolescents with Depression Study (TADS) Team et al. 2009. The Treatment for Adolescents with Depression Study (TADS): Outcomes over one year of naturalistic follow-up. Am J Psychiatry. 2009 Oct: 166(10):1141-9.Epub 2009 Sep 1. http://www ncbi nlm nih.gov/pubmed/19723787 Nierenberg A. Lessons from STEP-BD for the treatment of bipolar depression Depress Anxiety. 2009; 26(2):106-9. http://www ncbi nlm nih.gov/pubmed/19177467 Menza M et al. The impact of treatment of depression on quality of life, disability, and relapse in patients with Parkingson's disease. Mov Disord, 2009 Jul 15:24(9):1325-32. http://www ncbi nlm nih.gov/pubmed/ 19412944 Foster CE et al. Remission of maternal depression: relations to family functioning and youth internalizing and externalizing symptoms. J Clin Child Adolesc Psychol. 2008 Oct;37(4):714-24. http://www ncbi nlm nih.gov/pubmed/ 18991123 Braden JB, Zhang L, Zimmerman, FJ, and Sullivan MD. Employment Outcomes Among Individuals with Mental Health Disorders and Comorbid Chronic Pain. Psychiatr Serv. 2008 August; 59(8): 878–885. http://www ncbi nlm nih.gov/pubmed/ 18678685

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. Researchers have shown that combination depression treatment, antidepressant medication and psychotherapy, positively affects functional capacity in quality of life, family and peer relationships, school attendance, and employment settings. Significant progress has been made in demonstrating the effect of treatment of depression on an individual's improved functional capacity as it relates to social role function, work function, and employment.

Several studies have examined the impact of depression treatment approaches on improved social and work-related functional capacity; these treatment approaches could include psychotherapy, pharmacotherapy, or combined treatment. For example, the Treatment for Adolescents with Depression Study (TADS) investigated the short- and long- term effect of an antidepressant medication (fluoxetine) and psychotherapy (cognitive behavioral therapy- CBT) alone and in combination for treating depression in adolescents. According to TADS findings, combination treatment (antidepressant medication and CBT) is most effective in improving functioning and quality of life. The study results suggest that for most teens with depression, long-term, evidence-based treatments are sustainable and effective in terms of functional outcomes such as, self-care, peer relationships, and school attendance

A multisite study called the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) examined the effect of psychosocial therapy and pharmacotherapy on improving symptoms and functional outcomes in individuals experiencing the depression phase of bipolar disorder, such as the impact on their relationships, work/role functioning, and satisfaction with daily activities. Results indicate that if patients

taking medications to treat bipolar disorder also receive intensive psychotherapy, they are more likely to get well faster, stay well longer, and have better overall functioning, relationship functioning, and life satisfaction.

NIH researchers studied the impact of treatment of depression on quality of life, disability, and relapse in patients with Parkinson's disease (PD). This trial provides the first controlled data on the impact of treatment of depression on PD. Results indicate that treatment of depression in PD leads to important, sustained improvements in quality of life and disability.

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)-Child study, NIH researchers examined the effects of treatment of maternal depression on family functioning and youth symptoms among mother-child dyads. Mothers and children were followed up 3 months after the mother's treatment for depression. The findings suggest that the relationship between remission of maternal depression and children's psychosocial outcomes was mediated by changes in family function and parenting. With the successful treatment of maternal depression, the mothers' ability to parent improved, as did overall family functioning, resulting in less internalizing disorders among their children.

The negative impact of depression on the workplace has been widely observed in studies examining, absenteeism and depressed employees' reduced productivity during days at work, but little experimental evidence exists for the effects of chronic pain on work disability. Previous studies have documented improvement in employment outcomes with enhanced treatment of common mental disorders such as depression. NIH researchers examined the effects of common mental health disorders and chronic pain conditions on employment and work outcomes, such as work status within past 12 months, ability to work limited due to health (physical, emotional, drug/alcohol disorder), and numbers of days missed or arrived late/left early due to health. This study used data from a national US household telephone survey and assessed common mental disorders by using the short-form version of the World Health Organization's Composite International Diagnostic Interview. Chronic pain conditions and labor market outcomes were identified by self-report. The researchers then assessed work impairment based on the presence of a mental health disorder and/or chronic pain condition. The results suggest that mental health disorders and chronic pain are associated with work disability when accompanied by chronic pain, especially in women. Depression treatment improves mental health and reduces the effects of pain on work among those with chronic pain.

BACKGROUND

Prevalence/Incidence

Mediated through the brain, mood disorders disrupt every facet of a person's life: emotions, thought processes, behavior, social relationships and physical health. Major depressive disorder (MDD) is the leading cause of disability in the US for ages 15-44. MDD is a serious, prevalent and costly chronic disease which affects approximately 14.8 million American adults (6.7 percent of US population age 18 and older) annually. Current data indicate that the point prevalence of depression among people with medical illnesses in primary care settings is significant (10%-20%), and that the more severe the medical condition, the more likely a person will experience clinical depression (e.g., as high as 40% in patients with advanced heart failure or Parkinson's disease). Medically ill patients with comorbid depression are significantly more impaired, and have higher mortality, than otherwise similar patients without depression. For example, untreated depression increases the risk of dying from heart disease by as much as six-fold. Major depression is also associated with significantly higher medical costs in all facets of medical care. For instance, among individuals with diabetes, total medical expenditures are as much as 4.5 times greater for those who are depressed, even after controlling for demographics and severity of medical illness. These effects are partly due to inherent health effects of depression, such as sleep and appetite dysregulation, and through other physiologic disturbances, such as platelet aggregation, that are just beginning to be understood. In addition, medically ill patients with comorbid depression have lower adherence to recommended treatments, such as pharmacotherapy; and to self-care regimens, such as improved diet, exercise, and smoking cessation.

Rationale

The premise of this goal is that targeted research focused on early detection, prevention and treatment of depressive disorders will have a significant impact on the overall reduction of years lost to disabilities (YLDs) 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. The quality of care available to persons with treatment-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; and (3) strategies are developed for protecting individuals from relapse and recurrence of depression. Secondly, 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. Despite the increased risk of depression in the presence of a number of other medical illnesses, depression is not sufficiently recognized or adequately 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.

Although several models of care are currently available and have proven effective in delivering adequate depression treatments, patterns for delivery of care, treatment, uptake and maintenance remain poor. Only an estimated 20 percent of patients obtain adequate treatment. Previous studies indicate that rates of underutilization are higher for racial and ethnic minorities, elderly persons, youth, and young and middle-age males. Detailed analyses across these studies found that service use is influenced by years in the United States, nativity, language, age at migration, generational status, as well as gender, age, marital status, education, income, insurance coverage, and clinical severity. Improved recognition, treatments of depression and healthcare utilization among these subgroups will help to reduce disparities in chronic depression, functional health status and co-morbid physical illnesses.

TARGET CONTEXT AND CONDITIONS

The NIH is undertaking multiple strategies in order to develop the knowledge base to guide efforts at reducing the years lost to disability as a result of depression. The first of these strategies is to investigate further the mechanisms underlying depression that may serve as important targets for intervention, such as interactions between genes and environmental stressors that may lead to depression, or the role that vascular changes in aging play in the development of depression. A second strategy involves further refinement of existing treatments for depression, such as by determining individual characteristics associated with differential treatment response so as to better be able to personalize treatment options, or by investigating the potentially increased efficacy of combined or sequential treatments. In addition, more research is being conducted to examine treatment strategies tailored for specific populations, such as racial and ethnic minorities and the elderly. NIH is also investing in the development of better tools to measure the impact of depression, not only in terms of years lost to disability, but also its influence on social functioning in general, such as workforce roles, social roles, etc. These measurement tools will allow researchers to better gauge the effectiveness of new and improved treatments for depression in alleviating disability. Finally, improved interventions based on a better understanding of the mechanisms underlying depression will sharpen efforts to reduce or prevent negative interactions between depression and other comorbid physical disorders. More research is needed to unravel the relationship between depression and, for example, Parkinson's disease or cancer, including better methods for examining these complex interactions. Improvements in the detection, prevention, and treatment of depression are likely to positively impact the course of these and other physical diseases as well.

Long Term Objective: (SRO-9.2) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-9.2 By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities. (Efficiency) (Outcome)	*2011*	Complete the testing of a tailored educational intervention to increase stroke awareness and need for urgent action in a diverse community. *(Baseline):* Development of two different educational intervention strategies is underway	N/A
	2010	Develop a pilot stroke prevention program for the Alaska Native population *(Baseline):* The Alaska Native Stroke Registry has collected epidemiological data on risk factors from one center	N/A
	2009	Recruit and train four practitioners to serve as community-based case managers in a secondary stroke prevention trial targeting African Americans and Hispanics. *(Baseline):* (FY07) Cooperative agreement awarded to begin stroke prevention trial.	Recruited and trained 10 community-based stroke navigators. (Target Met)
	2008	Establish a database of stroke patients and collect data for the purposes of identifying new stroke risk factors and developing effective stroke prevention strategies. *(Baseline):* (FY06) WHC lacks patient data needed to identify stroke risk factors, evaluate stroke prevention programs	Established a database of stroke patients; began populating database. (Target Met)
	2007	Initiate at least two collaborative, community-based prevention projects at the Stroke Prevention and Intervention Research Program (SPIRP). *(Baseline):* (FY05) Cooperative agreement awarded establishing SPIRP infrastructure, but stroke prevention projects have not yet begun	The target was not met due the complexities of developing the necessary infrastructure. (Target Not Met)

Measure	FY	Target	Result
	2006	Establish the infrastructure for a pilot Alaska Native Stroke registry that will facilitate identifying risk factors and strategies to improve stroke prevention and quality of stroke care provided to Alaska Natives. *(Baseline):* (FY04) Several registries for Alaska Natives exist, including for cancer and diabetes, but none for stroke	Established the infrastructure for the Alaskan Native Stroke Registry, began enrolling patients. (Target Met)

Data Source and Validation
Chelsea M. Kidwell, U54NS057405. Stroke Disparities Program. Progress report. Randolph S. Marshall, P50NS049060, New York Columbia Collaborative SPOTRIAS. Progress Report Brian A. Trimble, U01NS048069, Alaska Native Stroke Registry. Progress Report Progress Reports for the studies can be obtained from the NINDS Office of Science Policy and Planning

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. The project "Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment in the District of Columbia" (PROTECT DC), part of the NIH-funded Stroke Disparities Program (SDP), is a randomized Phase II clinical trial designed to determine whether hospital-based initiation of secondary stroke prevention strategies and community-based case management via stroke navigators is better than current care alone in improving stroke risk factors in a primarily urban African American community in Washington, DC. To date, PROTECT DC has recruited and trained a total of 10 stroke navigators, 2 of which work primarily as stroke navigators and 8 which work as stroke navigators but also participate on the project in other capacities.

Stroke navigators are lay individuals trained to provide information about community health-related services and healthy behaviors, and can offer social and medical support after the patient leaves the hospital. The navigator model has been shown to be successful in cancer, asthma, and other diseases. In stroke, the navigator intervention has been shown to be successful in a primarily white population. For the most part, navigators have health care or social worker backgrounds and are residents of or have close ties to the community being served by the trial. Stroke navigators in the PROTECT DC project received approximately 240 hours of training and written material education on topics such as stroke, cardiovascular risk factor management, management of stroke and its sequelae, community services and insurance, health behavior change, data collection, research principles and ethics, privacy, and cultural appropriateness. In 2009, supplemental funding via the American Recovery and Reinvestment Act (ARRA) was provided to PROTECT DC to develop standardized video training materials for stroke navigators. The interactive videos are expected to standardize information delivery, to complement current written materials, and are anticipated to decrease the number of didactic training and testing sessions needed, thus accelerating navigator training. The new materials are also anticipated to serve as the basis for a nationally implementable stroke navigator training program.

Advances or Other Highlights

The SDP has made other recent advances towards future research efforts. Under the project "Acute Stroke Program of Interventions Addressing Racial and Ethnic Disparities" (ASPIRE) investigators are continuing to explore whether a tailored community education paired with emergency medical services transport to primary

stroke centers increases treatment of stroke with tissue plasminogen activator (tPA), a drug which breaks down clots. The research group has undertaken 9 focus groups (87 participants) and 253 surveys and interviews with community members to identify public knowledge, attitudes, and perceptions regarding stroke and stroke treatment. Results so far have shown that many participants prefer to confer with family members or wait to see if symptoms worsen before going to the hospital. The information collected from these interactions has been used to develop educational materials for the intervention. The group is also collecting baseline data on tPA utilization in the absence of the intervention. To date, almost 1,000 stroke cases have been documented, 786 in African Americans and 211 in whites.

The Alaska Native Stroke Registry (ANSR) research group has also made steps to move towards the development of a stroke prevention intervention. The registry has so far identified more than 400 stroke events and the group is starting to look at how this data may be used for developing an intervention. In 2009, ANSR received ARRA support to undertake a door-to-door survey to determine the completeness of case ascertainment in individuals already entered into the registry. This will permit validation of current data and calculated incidence rates. In addition, the investigative team will perform a survey of randomly selected rural villages (by region) and of a random sample of urban Alaska Natives to identify stroke cases that may not have been captured in the ANSR registry, evaluate knowledge of stroke symptoms, and guide the design of a stroke prevention intervention.

Researchers are also studying the effects of an educational intervention on preventing first and recurring stroke in an urban population with a high proportion of African Americans and Caribbean Hispanics. Investigators from the Stroke Warning Information and Faster Treatment (SWIFT) study, part of the NIH-supported New York Columbia Collaborative Specialized Program of Translational Research in Acute Stroke (SPOTRIAS), have completed the development of a culturally-sensitive educational intervention and are in the process of testing its effects on knowledge retention and on time to arrive to the Emergency Department (ED) after a stroke. The investigators have already enrolled over 1,200 stroke patients and 300 stroke-free community members.

BACKGROUND

A stroke or “brain attack” occurs when the blood flow to a part of the brain is suddenly stopped by a clot or when a blood vessel in the brain bursts, spilling blood into the spaces surrounding brain cells. The lack of oxygen and nutrients from the blood or the sudden bleeding into or around the brain can cause brain cells to die. After a stroke, the abilities controlled by the affected area of the brain may be lost. Hypertension, high cholesterol, diabetes, tobacco use, obesity, and a sedentary lifestyle have been identified as significant risk factors for stroke. In addition, a previous stroke greatly increases the likelihood of a second stroke. Common signs of a stroke include sudden numbness or weakness, especially on one side of the body; sudden confusion or trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble with walking, dizziness, or loss of balance or coordination; or sudden severe headache with no known cause. Every minute counts when someone is having a stroke. Calling 9-1-1 and getting to the hospital in time can save lives by ensuring prompt treatment with clot-busting drugs or other medical attention. NIH supports the development and validation of interventions to promote stroke prevention and preparedness in diverse communities and populations.

Prevalence/Incidence

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. Mortality from stroke among African Americans is nearly twice that of Caucasian Americans, and among Native Americans and Alaska Natives, has increased significantly during the 1990s. 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. 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.

Rationale

There is a wide range of hypothesized causes of the excess stroke mortality in the southeastern United States 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. For example, hypertension, one of the most important risk factors for stroke, is disproportionately prevalent and less effectively controlled in African Americans. A recent report based on a national probability sample of over 600,000 persons identified hypertension as the single initiating cause of death independent of socioeconomic status that contributed the most to the racial disparity between African Americans and Caucasians in potential life-years lost. Patterns of accessing the existing health care system for acute stroke also vary among racial/ethnic groups; for example, some data suggest that minorities are less likely to use the emergency medical system when experiencing a stroke and to receive the standard tPA (a clot-dissolving agent) intervention if they do. The reasons for these racial/ethnic variations in stroke-related risk factors and utilization of health care are not fully understood and will require further study. Ultimately, a combination of prevention (both primary and secondary) and intervention strategies may be needed to reduce or eliminate racial/ethnic disparities in stroke.

The DHHS Research Coordination Council (RCC) has identified the research theme Understanding Health Disparities—Closing the Gaps as a priority. In addition, eliminating health disparities is one of the two stated goals of Healthy People 2010, the disease prevention agenda for the Nation.

TARGET CONTEXT AND CONDITIONS

Reducing racial and ethnic disparities in stroke will require a reduction in stroke incidence as well as improvements in stroke outcome in minority communities. Effective prevention programs can reduce stroke incidence, while effective interventions can save lives and prevent the development of motor and cognitive problems following a stroke. NIH is investing in research on stroke intervention, stroke prevention, and combination strategies in minority communities. To more accurately represent the range of NIH efforts, NIH will expand current research efforts to include stroke intervention and provide ample time for results gathering. Several promising pilot studies are underway to test the feasibility of new intervention and prevention strategies. NIH is committed to provide follow up support with full-scale studies to validate the effectiveness of strategies in reducing stroke incidence and improving outcomes in minority communities.

NIH has established a program to create Nursing Partnership Centers to reduce health disparities. These centers established collaborations between research-intensive schools of nursing and minority-serving university schools of nursing to address health disparities, including stroke. The Centers 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.

NIH has established an acute stroke research and care center at a private community hospital, where more than 75 percent of stroke patients are African American or Hispanic. The hospital has begun building a database to gather epidemiological data on its stroke population. The hospital will use these data to identify new risk factors and measure rates of previously reported risk factors. Information on risk factors is necessary to identify

populations to be targeted by stroke prevention programs. The data will also serve as a baseline against which to measure the effectiveness of future stroke prevention programs. The hospital is also initiating a phase II clinical trial to determine whether an in-hospital education program coupled with community-based case management (via "stroke navigators") can reduce the likelihood of a secondary stroke, as compared to standard clinical practice. One of the first steps in this project is to recruit and educate practitioners to serve as "stroke navigators." In a parallel intervention study, the hospital will test a strategy to increase the number of minority stroke patients who receive tPA.

NIH has established an Alaska Native Stroke Registry at an Indian Health Service supported health care system for Alaska Natives 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 populate the pilot stroke registry, targeting Yupik Eskimos living in the Yukon-Kuskokwim Delta and Bristol Bay regions, to establish registry infrastructure and data gathering methods. If successful, the registry will be expanded statewide to all regions and include all Alaska Native subgroups. Registry data will be used to identify strategies to reduce risk factors for stroke and develop statewide prevention and intervention programs. Building on a thirty-year experience with chronic disease registries at the Alaska Native Medical Center, this Registry is providing critical data on the disparity in stroke-related mortality in Alaskan Natives compared with other populations. Specifically, the goals of this project include: (1) describing the epidemiology of stroke among Alaska Natives; (2) monitoring the quality of stroke care provided; (3) guiding the design of prevention/intervention programs; and (4) evaluating the effectiveness of those programs.

NIH also is sponsoring several clinical trials on stroke interventions appropriate for minority populations. The Field Administration of Stroke Therapy trial, a multicenter, randomized, phase III clinical trial, will determine if very early administration of the neuroprotective agent magnesium sulfate improves functional outcomes, including the prevention of the development of motor and cognitive problems. The research team will administer the magnesium within two hours of a stroke, in the ambulance if necessary, and the team plans to enroll 45% Hispanic and 15% African Americans into the study. Another phase III clinical trial will explore two different therapeutic strategies for preventing small subcortical strokes, which are the most common stroke subtype affecting Hispanic Americans. Trial investigators plan to enroll 20% of the participants from this ethnic group. In a third study, NIH-funded investigators are exploring the efficacy of blood transfusions in preventing recurrences of stroke in children with sickle cell anemia who have had silent cerebral infarcts. This form of stroke is a common contributor to severe neurological disease in children with sickle cell anemia, which predominantly affects African Americans.

NIH researchers at the Stroke Disparities Program (SDP) are developing an integrated program of collaborative research in the Washington, DC area to overcome current gaps in stroke knowledge in an underserved population. The three key areas of stroke disparities under study include utilization of the intravenous (IV) clot-busting drug tissue plasminogen activator (tPA), secondary stroke prevention, and an observational study of cerebral microbleeds -- small brain bleeds that may serve as useful imaging markers of impending larger brain bleeds -- in primary intracerebral hemorrhage (ICH).

Long Term Objective: (SRO-9.3) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-9.3 By 2011, characterize the progression of normal, healthy brain development in a nationally representative sample of children in the United States by creating a database of MRI and clinical/behavioral data and analytical software. (Efficiency) (Outcome)	*2011*	Complete the creation of a database that contains MRI and clinical/behavioral data and analytical software to characterize the progression of normal, healthy brain development in a nationally representative sample of children in the United States. *(Baseline):* Added completely processed diffusion tensor imaging and magnetic resonance spectroscopy data to the data available from the database.	N/A
	2010	Continue to maintain database of information collected from approximately 500 children that includes repeated anatomic magnetic resonance imaging scans and clinical data via BIRN. Disseminate with the database, complete with processed diffusion tensor imaging and magnetic resonance spectroscopy data. *(Baseline):* (FY09) The data has been developed for inclusion in the BIRN.	N/A
	2009	Disseminate the database of information collected from approximately 500 children that includes anatomic magnetic resonance imaging scans, clinical data, and preliminary data collected from diffusion tensor imaging and from magnetic resonance spectroscopy via the Biomedical Informatics Research Network (BIRN) to enable researchers outside the project to collaborate and share information gained from subsequent analyses. *(Baseline):* (FY08) Disseminated scans and clinical data through limited web-based access.	Data that includes anatomic magnetic resonance imaging scans, and clinical information were collected from over 500 children. The data has been developed for inclusion in the Biomedical Informatics Research Network. (Target Met)

Measure	FY	Target	Result
	2008	Prepare and disseminate all three stages of anatomical neuroimaging scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community. *(Baseline):* (FY07) Preliminary analyses of changes of brain growth in children over time completed.	Prepared and disseminated three stages of anatomical neuroimaging scans and other data, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community. (Target Met)
	2007	Complete preliminary analyses of changes of brain growth in children over time and share findings with research community. *(Baseline):* (FY06) First and second of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.	Preliminary analyses of changes of brain growth in children over time have been shared with the research community through two publications. (Target Met)
	2006	Complete the second of three stages of neuroimaging scans and data collection of approximately 500 children across the United States. *(Baseline):* (FY05) The first of three stages of scans, demographic, medical, cognitive, and behavioral data were collected from 500 children and disseminated to research community.	A total of 514 children have been enrolled in the study. Ninety-five percent of the children between the ages of 4.5 to 20 years old who completed the first stage of data collection have completed the second stage of neuroimaging scans, demographic, medical, cognitive, and behavioral data collection. (Target Met)

Data Source and Validation
NIH MRI Study of Normal Brain Development (http://www.bic.mni mcgill.ca/nihpd/info/index.html)

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target has been Met with the development of data for inclusion in the Biomedical Informatics Research Network (BIRN) infrastructure. The BIRN is a national initiative to advance biomedical research through data sharing and online collaboration. Funded by the NIH, BIRN provides data-sharing infrastructure, software tools, strategies and advisory services.

The database of information was collected from over 500 children and includes anatomic magnetic resonance imaging scans and clinical data. The data is available for electronic access to the research community via the NIH MRI Study of Normal Brain Development website. Additional diffusion tensor imaging and magnetic resonance spectroscopy data have been successfully collected from approximately 400 and 150 children, respectively.

BACKGROUND

Before the development of magnetic resonance imaging (MRI), relatively little was known about healthy brain development in humans. MRI has made it possible to safely study normal brain development in all age groups, including healthy infants and young children. Different MRI technologies are available, including anatomic MRI to measure structural brain development, Magnetic Resonance Spectroscopy (MRS) to examine neurochemical brain development, and Diffusion Tensor Imaging (DTI) to characterize white matter fiber tracts that form the pathways connecting different brain regions.

In the 1990s, the first findings on structural brain development showed age-related changes in gray and white matter volumes and in the development of critical inner brain structures. Since then, several small studies and limited longitudinal studies have allowed researchers to identify some developmental changes in the brain. Researchers have also found some relationships between certain regions of the brain and specific cognitive abilities in children. These findings have yielded insights into brain development; however, their role in clinical and behavioral development is unclear. The limitations of the earlier studies make it difficult to identify subtle differences between normal and abnormal brain development and to apply the findings to the general pediatric population. Many studies examined children of different ages all at one time and/or were based on small sample sizes. Furthermore, little information is available on children younger than age six, when brain growth and development is the most rapid.

Understanding healthy brain development is essential in finding the neural correlates of a myriad of childhood disorders related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases, which can persist into adulthood. To define the healthy ranges and trajectories in brain growth and development in children as they mature, longitudinal studies of representative samples of healthy children using state-of-the-art MRI technologies are needed. Such a study is extremely challenging given the difficulties in acquiring anatomic, MRS, and DTI brain images in young children. Despite these major challenges, NIH is leading an ambitious large-scale effort, the first of its kind, to develop a database and analytical tools to characterize normal, healthy brain development and its relationship to cognitive and behavioral development.

The NIH Clinical Exemption Committee approved the study protocol and consent forms. In addition, each data collection site received Institutional IRB Committee approval to scan and to collect clinical and behavioral data from children and adolescents. There are no known adverse effects of undergoing an MRI scan, including during pregnancy. Following prudent clinical practice, pregnant women will remain outside of the scanning suite.

Rationale

At this time, no single standardized and comprehensive source of information exists on MRI measurement of normal brain development over time in children and adolescents in the United States. This project will create the nation's first such research database using state-of-the-art technologies by bringing together the expertise of basic and clinical scientists. These standardized data are critical because they will provide a basis for determining deviations in brain development associated with a variety of brain diseases, disorders, and conditions. In addition, the database will include comprehensive longitudinal neurobehavioral assessments including medical and family history, demographic, behavioral, neurocognitive, and school achievement measures. Moreover, the database will provide researchers with an effective means for developing standardized comparison groups when examining brain disorders, psychopathology, or brain-based disabilities, which will, in turn, facilitate clinical and translational studies in the future.

The project was designed with 20 percent compounded attrition across the data collection phases. This ensures that a sufficient number of children remain enrolled in the study to detect growth and changes in key brain structures in a representative sample of children in the United States as they develop over time.

TARGET CONTEXT AND CONDITIONS

NIH has brought together a diverse array of researchers to design and support a large-scale longitudinal study that uses state-of-the-art brain imaging technologies and that collects clinical and behavioral data, which will be used to develop analytical software tools.

This effort is highly ambitious in the number of children enrolled (approximately 500) at a wide range of ages (7 days to 18 years). In addition, researchers will combine data collected from complex technologies--magnetic resonance imaging, diffusion tensor imaging, and magnetic resonance spectroscopy--scanning the same children over a period of approximately 6 years. This will require retaining every family's participation in the project and collecting extensive demographic, medical, cognitive, and behavioral data at every visit.

Obtaining brain images from healthy children is a challenge in itself. The scans will be conducted in healthy, unsedated children who will be required to remain motionless for varying lengths of time. To conduct the study, researchers had to develop new and adapt existing techniques to scan children of different ages, the most difficult being toddlers. Approaches include studying children during their sleeping periods and training children to lie motionless in brain imaging scanners.

As the data are collected, researchers are creating normal pediatric growth curves for the whole brain and for specific regions of interest, and are establishing the characteristics of healthy white matter fiber tract development. In addition, analytical software and image processing tools are being developed to automatically generate the volume and area of specific brain regions and of white matter fiber tracts. The neuroanatomical and clinical/behavioral data are integrated and housed in the Pediatric MRI Data Repository. The database is available to biomedical and biobehavioral researchers outside of the project through a web-based portal to encourage further data analyses such as studies of brain-behavior relationships and comparisons to children with a variety of disorders and diseases. This effort may also serve as a model for new NIH neuroinformatics initiatives that can link to the anatomic MRI database.

Long Term Objective: (SRO-9.4) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-9.4 By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life. (Outcome)	*2011*	Enroll children who tested positive for CMV infection in the follow-up study to monitor hearing function. *(Baseline):* (FY10) The FY 2010 target was MET. NIH-supported scientists successfully determined the percentage of infants born with CMV infection.	N/A
	2010	Begin analyses to determine the percentage of enrolled children that have congenital CMV infection. *(Baseline):* (FY09) More than 11,000 children enrolled at 7 hearing screening sites.	N/A
	2009	Initiate patient enrollment at 7 hearing screening sites to enroll approximately 10,000 children. *(Baseline):* (FY08) Obtained OMB approval for collection of information from the public.	More than 11,000 children were screened and enrolled for follow up CMV studies at participating medical centers. (Target Met)
	2008	Obtain OMB approval for collection of information from the public. *(Baseline):* (FY07) Manual of Procedures (MOP) delivered to all hearing screening sites.	The study was granted a clinical exemption, which allows for the collection of information from the public without the need for submission to the Office of Management and Budget (OMB). (Target Met)
	2007	Compile Manual Of Procedures (MOP) and distribute to all hearing screening sites. *(Baseline):* (FY06) Clinical protocols and other needed study documents are available.	NIH-supported scientists successfully developed the Manual of Procedures (MOP) for the CHIMES Study and delivered it to each of the screening sites. (Target Met)
	2006	Design and develop clinical protocols and other needed study documents. *(Baseline):* (FY05) Previous studies have strongly suggested that congenital CMV infection is a leading cause of sensorineural hearing loss in children.	NIH-supported scientists designed and developed needed clinical protocols and other needed study documents, such as patient brochures for the CMV & Hearing Multicenter Screening (CHIMES) Study. (Target Met)

Data Source and Validation
Seven (7) patient enrollment centers for the NIDCD-sponsored CHIMES Study: Central Coordinating Unit University of Alabama at Birmingham, Birmingham, AL - Suresh Boppana, Karen Fowler, William Britt, Mirjam Kempf, David Kimberlin, Whitney Lin, Shannon Ross, Masako Shimamura Clinical Sites University of Mississippi Medical Center, Jackson, MS - April Palmer, Glenn Graves Saint Peters University Medical Center, New Brunswick, NJ – Robert Tolan, Kristina Feja Carolinas Medical Center, Charlotte, NC - Amina Ahmed, David Rupar Cincinnati Children's Medical Center, Cincinnati, OH - David Bernstein, Daniel Choo, John Greinwald, Kurt Schibler Pittsburgh Children's Hospital, Pittsburgh, PA – Marian Michaels, Diane Sabo Southwestern University Medical Center, Dallas, TX – Pablo Sanchez, Gregory Jackson, Kristina Owen, Angela Shoup, Elizabeth Stehel "Semi-annual Progress Report Jan-June2009", item V. Enrollment Numbers & Projections (January 2009 – June 2009) my be obtained from the NIDCD Science and Policy Planning Branch.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

Clinical & Audiology Activities

The FY 2009 target was Met. The focus of the past six months has been to continue to screen infants born at the participating medical centers for CMV and to enroll the children who tested positive in the follow-up arm of the study were enrolled in order to monitor hearing function. The study procedures, including newborn screening, enrollment and follow-up activities, audiology protocols and the other procedures have been continuously monitored for necessary modifications. All sites have maintained local IRB renewals for newborn screening and the follow-up components of the study.

BACKGROUND

Congenital cytomegalovirus (CMV) is the most common viral infection passed from a mother to her unborn child. Approximately one percent of newborns, or about 40,000 infants each year, are born infected with CMV. Children born with CMV infection who have symptoms of infection, such as hearing loss, seizures, visual impairment, and cerebral palsy, are usually identified at birth and receive appropriate medical care. Although few population based studies of the etiology of hearing loss in infants have been performed, when such studies have included assays for congenital CMV infection, they have strongly suggested that congenital CMV infection is a leading cause of sensorineural hearing loss in children. In addition, even though a majority of infants born in the United States are already screened for hearing loss, most infants are not tested for CMV unless they already show signs of the disease. Further, newborn hearing screening cannot detect or predict hearing loss that will occur later in childhood.

Prevalence/Incidence

The majority of CMV-infected children—roughly 90 percent—have no symptoms at birth. These children have what is called a "silent" infection, which often goes unnoticed. In addition, CMV is a leading cause of progressive hearing loss in children in the United States. Approximately 10% to 15% of children with congenital CMV infection have some degree of hearing loss that has delayed onset and worsens during childhood. While the causes of childhood hearing loss remain largely unknown, estimates indicate that as much as 20% to 30% of childhood hearing loss is caused by CMV infection.

Rationale

Due to the compelling but limited data on congenital CMV infection and hearing loss in infants, in March 2002, the NIH convened a workshop with a panel of experts on congenital CMV infection and newborn

hearing and metabolic screening. The panel made several recommendations regarding future research priorities in the area of congenital CMV infection and hearing loss. Based on the workshop recommendations, in 2005, the NIH supported research for the CMV and Hearing Multicenter Screening (CHIMES) Study, on the role of congenital CMV in the development of hearing loss in children. Identifying asymptomatic children and following their progress to determine if hearing loss develops is a major focus of this research. The CHIMES study is one of the largest studies of its kind with approximately 100,000 children to be screened at birth for CMV infection. Study participants that test positive for CMV will undergo follow-up diagnostic hearing testing to determine the onset, severity, and progression of hearing loss. The scientists will analyze the data to better understand the relationship between CMV infection and hearing loss and to determine the extent to which CMV screening together with hearing testing can improve the detection and prediction of permanent hearing loss in children.

TARGET CONTEXT AND CONDITIONS

The NIH has developed a strategy to implement neonatal screening for CMV infection to permit the identification of infants who will develop CMV-induced hearing loss. Initially, in 2006, NIH researchers developed clinical protocols and other needed study documents, such as patient information brochures. NIH-supported researchers compiled the Manual of Procedures (MOP) and delivered the MOP to all hearing screening sites in 2007. Finally, patient enrollment was initiated at all hearing screening sites in 2009.

Based on the outcome of patient enrollment, the research will proceed to the pilot phase of the CHIMES study. If the pilot phase is successfully accomplished, the NIH will move forward with efforts to improve the health of individuals with hearing loss.

Long Term Objective: (SRO-9.5) Advance scientific and biomedical research in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.

Measure	FY	Target	Result
SRO-9.5 By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia. (Outcome)	*2011*	Continue recruitment to 914 subjects. *(Baseline):* TBD number of subjects enrolled in FY2010.	N/A
	2010	Continue recruitment to 476 subjects. *Previous wording: Achieve cumulative enrollment of 1776 subjects.* *(Baseline):* (FY09) Achieve cumulative enrollment of 38 subjects.	N/A
	2009	Achieve cumulative enrollment of 444 subjects. *(Baseline):* (FY08) TBD number of subjects enrolled in FY08.	Only 38 subjects were enrolled Enrollment has been much more difficult than expected because many potential subjects were excluded due to blood oxygen levels outside of the acceptable range or current oxygen use and patient unwillingness to be randomized. The target enrollment has been reduced to 1134. (Target Not Met)
	2008	Obtain approvals for initiation of trial from the Data Safety and Monitoring Board (DSMB) and all local Institutional Review Boards (IRBs). Begin enrolling patients at 14 sites and reach enrollment of 470 subjects. *(Baseline):* (FY07) Trial protocol and model informed consent documents developed.	The original study protocol was approved by the DSMB and IRBs. 38 patients were enrolled, which did not meet the target of 470. (Target Not Met)

Data Source and Validation
Further information on the outcome of the study can be obtained from Clinical Trials.gov http://clinicaltrials.gov/ct2/show/NCT00692198?term=nct00692198&rank=1

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Not Met. By the end of 2009, the Long-Term Oxygen Treatment Trial (LOTT) enrolled 38 subjects. Enrollment has been much more difficult than expected because many potential subjects

were excluded due to 1) blood oxygen levels outside the acceptable range or 2) current oxygen use and unwillingness to be randomized.

BACKGROUND

Chronic obstructive pulmonary disease, COPD, is a progressive disorder of the lungs characterized by a gradual loss of lung function and airflow limitation that is not fully reversible. The term COPD includes chronic bronchitis, chronic obstructive bronchitis, emphysema, or combinations of these conditions. Symptoms range from constant coughing, excess sputum production, and wheezing, to severe shortness of breath. Although no cure exists for COPD, symptoms can be managed and damage to the lungs can be slowed.

Several NIH-sponsored research programs have increased understanding of COPD and fostered new treatments. For example, the Nocturnal Oxygen Therapy Trial showed that some patients with advanced COPD live longer if given long-term oxygen therapy. The Lung Health Study showed that a smoking cessation intervention can improve long-term survival of COPD patients. The National Emphysema Treatment Trial (NETT) showed that lung-volume-reduction surgery can improve the quality and/or length of life in certain groups of patients with severe COPD. The NIH continues to conduct clinical research to improve COPD treatment. Most recently, the NIH launched a new trial to assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia (low blood oxygen level).

Prevalence/Incidence

COPD, a lung disease that over time makes it hard to breathe, is the fourth leading cause of death in the United States. Approximately 12 million adults in the U.S. are diagnosed with COPD, and more than 120,000 die from it each year. An additional 12 million adults in the U.S. may have undiagnosed COPD. In decades past, COPD was predominantly a disease of older men. Now, the disease affects men and women equally, with a slightly greater number of women now dying of COPD each year than men.

Disease Burden

COPD costs the U.S. economy an estimated $32.7 billion per year in healthcare expenditures and indirect costs of morbidity and mortality.

Rationale

Little is known about the safety or effectiveness of long-term oxygen therapy in patients who have COPD but only moderate hypoxemia. Although oxygen therapy is known to be beneficial for COPD patients who have severe hypoxemia when resting, its value for patients with less serious disease is not known and there is some concern that it may actually be harmful in such patients. Nevertheless, many physicians routinely prescribe oxygen for COPD patients with less than severe hypoxemia, who may actually represent the majority of the 1 million patients in the United States who receive long-term oxygen therapy and of the $2 billion in annual costs to the Centers for Medicare and Medicaid Services (CMS) for its provision.

In May 2004, the NIH and the CMS, recognizing major gaps in knowledge regarding the mechanisms of oxygen benefits, optimal indications for its prescription, and its effects on patient outcomes other than survival, convened a working group of scientific experts entitled “Long-Term Oxygen Treatment in COPD” to review the state of science related to oxygen therapy and to make recommendations regarding future research. The working group identified several areas for further research. The recommendations included a clinical trial to determine the efficacy of long-term oxygen therapy in patients with COPD and moderate resting hypoxemia.

TARGET CONTEXT AND CONDITIONS

In November 2006, the NIH and the CMS launched the Long-Term Oxygen Treatment Trial (LOTT), the largest ever randomized clinical trial of the effectiveness and safety of long-term, home oxygen therapy for COPD. The NIH administers and oversees the study, and the CMS provides support for items and medical services that are generally available through the CMS to beneficiaries enrolled in the trial. The objectives of the

trial are to assess the efficacy of around-the-clock, supplemental oxygen therapy for patients with chronic obstructive pulmonary disease (COPD) and moderately severe hypoxemia, provide a scientific basis for decisions regarding the clinical use of long-term oxygen treatment, and improve clinical management of COPD. The results also will help the CMS conclude if coverage for home oxygen treatment should be extended to patients with moderate disease. Currently, the CMS limits coverage of home oxygen therapy to beneficiaries with very low blood oxygen levels at rest or during exercise or sleep.

Although the 2008 target was extended to 2009, investigators revised the study protocol in response to enrollment challenges. The Steering Committee for the trial proposed modifications to the study that will involve more inclusive enrollment criteria and a reduction in the target sample size from 3108 to 1134. The trial endpoint is now a composite outcome: time from randomization to the first occurrence of either hospitalization from any cause or death from any cause. The expansion of the endpoint to a composite outcome allowed for a reduction in the sample size to one third of the original, when only mortality was the endpoint. On recommendation of the DSMB, the NIH has approved the protocol modifications, and implementation of the revised protocol by the study sites is now pending IRB approvals.

The LOTT, researchers at 14 clinical centers across the United States plan to study approximately 1134 patients with COPD. The trial is expected to progress in three phases. During the first phase LOTT investigators developed the trial protocols, modeled informed consent documents, and other necessary trial materials. The trial Steering Committee developed procedures and tools for training of staff, randomization of subjects, data management, and quality assurance/quality control of study activities and data, which includes required review by the Institutional Review Boards. The second phase will include training of staff, subject screening and recruitment, interventions, and follow-up with data collection and monitoring.

Patient recruitment for the trial began in 2008. Participants are randomized to receive or not to receive supplemental oxygen for approximately 3 years. All participants will be periodically monitored; those who are not randomized to receive oxygen initially will be prescribed oxygen if their blood oxygen levels significantly worsen during the trial. The final phase of the trial will include data analysis and reporting.

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.

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. 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 public health and advancing the research enterprise.

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.

Long Term Objective: (CTR-1) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CTR-1 By 2014, 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). (Efficiency) (Outcome)	*2011*	Conduct a SIDS risk-reduction training workshop at the Southeastern Region Alpha Kappa Alpha, Inc. Conference for 2,000 African American community leaders, community health workers, and child care providers from a tri-state area (Mississippi, Tennessee, Alabama) where SIDS rates disproportionately affect African Americans. *(Baseline):* There are no known efforts to systematically distribute "Back to Sleep" materials through an African American sorority regional conference.	N/A
	2010	Develop and present two communication programs at national conferences for health professionals who can further disseminate the Back to Sleep message among African American parents, caregivers, and health care providers. *(Baseline):* (FY08) There are segments of the African American population that have not heard the SIDS risk reduction message.	N/A
	2009	Conduct a continuing education program for approximately 500 pharmacists in the DC metro area. *(Baseline):* (FY08) There are no known continuing education programs on the SIDS risk-reduction message in the DC metro area.	A continuing education (CE) program on SIDS risk-reduction for over 500 pharmacists was conducted at the "Infant Mortality Continuing Education for D.C. Pharmacists Program". A CE program was also conducted for over 300 pharmacists from the D.C. metro area at the NIH sponsored "Pharmacotherapy Frontiers Program". (Target Exceeded)

Measure	FY	Target	Result
	2008	Distribute approximately 43,000 special “Back to Sleep” campaign materials targeting African American communities in collaboration with the Arkansas Department of Health. *(Baseline):* (FY07) There are no known efforts to systematically distribute “Back to Sleep” materials at a statewide campaign level in Arkansas.	NIH distributed over 47,000 special “Back to Sleep” campaign materials targeting African American communities in collaboration with the Arkansas Department of Health for their statewide 'Back to Sleep' campaign. (Target Exceeded)
	2007	Extend the continuing education module for nurses in appropriate community-based clinical settings in African American communities in the Mississippi Delta region. *(Baseline):* (FY05) There are no known efforts to systematically educate nurses on a community level about SIDS risk reduction.	NIH extended the continuing education module to approximately 50 nurses in the Mississippi Delta Region. (Target Met)
	2006	Promote a continuing education module with at least six national nursing organizations serving African American communities to extend the Back to Sleep campaign messages. *(Baseline):* (FY03) There are no known efforts to systematically educate the nursing community on a national level about SIDS risk reduction.	The Nurses Continuing Education Program was presented at eight national and four regional nurses conferences. Approximately 5,250 nurses participated in the training. (Target Exceeded)

Data Source and Validation
To obtain copies of CE Program Evaluations, please contact the *Back to Sleep* Campaign Project Office at 301-435-3459.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and Exceeded. The “Pharmacist Continuing Education Program: Reducing the Risk of Sudden Infant Death Syndrome” was conducted at the Infant Mortality Continuing Education for D.C. Pharmacists Program for over 500 Washington, DC area pharmacists. The training was extremely well received and a curriculum was developed based off of the "Nurses' Continuing Education Program on SIDS Risk Reduction". The session included an interactive dialogue between the training coordinators and the pharmacists for the purpose of developing a program in which pharmacists will be provided with the tools and skills to address issues related to SIDS risk-reduction and safe sleep with clients.

Evaluations indicated that pharmacists agreed that the information was relevant and appropriate for clients based on the demographics served. Participants noted that the information was relevant on an overall level. The group was able to validate the idea that a continuing education module targeting pharmacists would be a new

and unique way to reach underserved populations, minority groups and the general population in a variety of community and health care settings. Subsequent pharmacist discussion groups reinforced and validated the need for a curriculum and the ability of pharmacists to perpetuate the Safe Sleep and SIDS Risk-Reduction Messages particularly in African American communities where the health disparity exists.

The NIH conducted a partners' meeting with representatives from national pharmacist organizations, which indicated that a variety of venues would be appropriate to target Pharmacist Continuing Education efforts. A combination of electronic, online modules as well as in-person seminars will be appropriate for dissemination of the module. Local, regional, and national conferences will be selected in collaboration with the pharmacist partners, and NIH.

Advances or Other Highlights

The "Nurses' Continuing Education Program on SIDS Risk Reduction", which was created in collaboration with national nursing and health organizations across the country, continues as an education resource. As of 2009, over 8,000 nurses have completed the nursing modules and received CE credit. This includes nurses who have completed the learner-led as well as the individual-led curriculum. NIH is partnering with the community to complete the development of the online nurses' CE module. This will provide increased accessiblity of the CE program to nurses across the country.

Many activities continue to emerge for the African American outreach initiative as a result of the focused effort put forth by partners to reduce the risk of SIDS in states with the highest SIDS rates such as Mississippi and Arkansas. These projects have included health fairs throughout the state of Mississippi, trainings in churches and community health forums, the Mississippi statewide October SIDS Awareness month and partnerships with the Mississippi SIDS Alliance and Mississippi Department of Health. SIDS risk-reduction materials have been provided for packets that were distributed to local health units across the state of Arkansas for two consecutive years. A special presentation was given for the Arkansas Department of Health's Public Health Grand Rounds for health professionals. Strategic outreach continues to occur to ensure states and community partners are disseminating the SIDS risk-reduction message to areas most at need.

Efficiency

Originally, the CE program was only going to be conducted at the "Infant Mortality Continuing Education for D.C. Pharmacists Program" for 500 D.C. pharmacists. However, due to the high need for information dissemination and additional requests from pharmacists, a CE program was given for another 300 D.C. area pharmacists to better get the SIDS risk-reduction message out to the communities. The CE program was given at the NIH's Clinical Center at the annual "Pharmacotherapy Frontiers Program". This was an excellent opportunity to expand the reach to pharmacists who did not attend the "Infant Mortality Continuing Education for D.C. Pharmacists Program".

BACKGROUND

Sudden Infant Death Syndrome (SIDS) is a syndrome of unknown cause and is defined as the sudden death of an infant under one year of age, which remains unexplained even after a thorough case investigation, autopsy and review of the clinical history. SIDS is the leading cause of post neonatal mortality in the U.S. According the National Center for Health Statistics, the 2002 SIDS rate is 0.57/1,000 live births. 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 under 1 year of age. Stomach sleeping is a major risk factor for SIDS. The campaign promotes placing babies on their backs to sleep to reduce the risk of SIDS. The NIH, as a leading supporter, is collaborating with the following campaign sponsors: AAP, Maternal and Child Health Bureau of HRSA, First Candle/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 to sleep on their stomachs more often than white infants. The SIDS rate for African American infants is two times greater than that of white infants.

The NIH and other campaign sponsors hosted a meeting of experts to identify strategies for reaching African American communities with the Back to Sleep campaign messages. Representatives from various organizations including the Alpha Kappa Alpha Sorority, Inc. (AKA), Women in the National Association for the Advancement of Colored People (WIN), National Coalition of 100 Black Women (NCBW), National Medical Association, and the Congress of National Black Churches, Inc. and others proposed outreach and education strategies aimed at eliminating the racial disparity in SIDS rates. As a result, the NIH and partner organizations developed the Resource Kit for Reducing the Risk of SIDS in African American Communities, which is designed to help organizations initiate SIDS risk reduction programs in their local communities. It contains materials such as facts sheets and brochures to encourage people to lead discussion groups on ways to reduce the risk of SIDS in various community settings.

The Partnerships for Reducing the Risk of SIDS in African American Communities was a project with the AKA, NCBW, and WIN. The leaders of these three organizations committed to hosting three summits featuring the NIH SIDS risk reduction information and materials. In 2003, summits were held in: Tuskegee, Alabama; Los Angeles, California; and Detroit, Michigan.

The goal for the summit meetings was to encourage regional leaders 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. A "train-the-trainer" approach was used so that participants could transfer the knowledge to their local settings. Culturally appropriate materials were developed for African American communities. After the regional summits were completed, informal interviews were conducted to determine subsequent outreach strategies that developed as a result of their participation.

TARGET CONTEXT AND CONDITIONS

Comprehensive strategies are being developed to satisfy the overall goal of SIDS reduction in African American communities. First, NIH launched communication efforts to disseminate the AAP safe sleep guidelines in Mississippi. The project has multiple components including training public health workers on the conveying SIDS risk reduction messages, developing partnerships with state and local stakeholders, and providing mini-grants to community and faith-based organizations to assist in their outreach efforts. Second, a continuing education curriculum was developed for nurses on the safe sleep guidelines and effective ways to convey the risk reduction message. This curriculum is being implemented at regional and national conferences.

Arkansas has SIDS rates that are higher than the national average. The NIH partnered with the Arkansas Department of Health (ADH) to conduct an intensified statewide SIDS risk-reduction outreach to African American communities. Working with ADH's Office of Minority Health and Health Disparities, information was distributed statewide through the Arkansas Hospital Association (AHA) to the 45 Arkansas Hospital Association members who have obstetrical and/or maternity services. Local Hometown Health Coalitions and ADH Local Health Units across Arkansas also participated.

The continuing education program on SIDS risk-reduction for pharmacists has been developed and disseminated to DC area pharmacists via local workshops who serve African American women of childbearing age and their families. The successful pharmacist CE program will continue future development in collaboration with the D.C. Pharmacy Association, national pharmacy organizations, and the U.S. Public Health Service commissioned officer and civil service pharmacists from the Department of Health and Human Services agencies/offices.

NIH will develop abstracts on the development and the delivery of the national Back to Sleep program and mechanisms that can be employed to spread the infant safe sleep message. The abstracts will be submitted to professional meetings attended by nurses, pharmacists, physicians and/or community health workers. Examples of organizations' annual meetings that will be targeted are the National Association of Boards of Pharmacy and the Centers for Disease Control and Prevention (CDC). Presentations to these audiences will allow for further dissemination of the SIDS risk reduction message to unreached African American populations.

NIH sponsored SIDS risk reduction outreach activities stimulate other activities in communities and can be associated with a reduction in SIDS due to increased awareness and behavior change. The National Infant Sleep Position (NISP) Study examines the increase in back sleeping of infants, which leads to a lower rate of SIDS. SIDS outreach activities educate communities about the importance of back sleeping. It can be inferred that one of the major reasons for the reduction in SIDS is because of the relationship between the Back to Sleep campaign activities and the increase in back sleeping among infants. As a result, the campaign's reach can be used as a proxy to measure the success of the outreach activities having an impact on the disparity in SIDS.

In order to understand and eliminate the disparity in SIDS mortality and the resultant contribution to infant mortality, it is imperative to fully understand the barriers to diffusion of the Back to Sleep message into vulnerable minority or low socioeconomic status populations. The NIH announced a Request for Applications (RFA) to examine trends in infant care practices, and environmental and cultural influences on the diffusion of the public health recommendations in a nationally representative sample of minority and non-minority mothers. NIH sponsored research began in 2008. Without a better understanding of what influences infant care practices among all population groups, the delayed diffusion of effective SIDS prevention strategies will serve to exacerbate disparities, rather than eliminate them.

Long Term Objective: (CTR-6) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CTR-6 By 2010, improve the efficiency and reduce the unit cost of producing authoritative serials cataloging records used to improve access to the biomedical literature in libraries worldwide. (Outcome)	*2010*	Reduce cataloging time by 7 minutes per title and realize an additional savings of 0.10 FTE. *(Baseline):* (FY09) 95 minutes per title	N/A
	2009	Reduce cataloging time by 8 minutes per title and realize an additional savings of 0.10 FTE. *(Baseline):* (FY08) 103 minutes per title	The time to catalog an item has been reduced by 8 minutes, from 103 minutes to 95 minutes, and a savings 0.10 FTE has been realized. (Target Met)
	2008	Reduce cataloging time by 7 minutes per title and realize a savings of 0.10 FTE. *(Baseline):* (FY07) 110 minutes per title	The time to catalog an item has been reduced by 7 minutes from 110 minutes to 103 minutes and a savings of 0.10 FTE has been realized. (Target Met)

Data Source and Validation
The internal NLM first quarter FY10 report for the Technical Services Division, Division of Library Operations, NLM will document that the cataloging serials time standards have been revised to reflect the reality that serials cataloging time has decreased due to the various efficiencies that have been introduced. The NLM contract person for access to the quarterly report and for further information is Diane Boehr, Head, Cataloging Section, Technical Services Division, Division of Library Operations, NLM, phone 301-435-7059, email boehrd@mail nlm nih.gov .

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. The number of minutes to catalog an item has been reduced by 8 minutes, from 103 minutes to 95 minutes. This has saved 0.10 FTE time to catalog records. The time reduction in serials cataloging is the outcome of several new procedures. Catalogers no longer need to supply translations of Chinese, Japanese and Korean titles. Title abbreviations are now created from the data used by the ISSN (International Standard Serial Number) Centre, rather than looking up each word in the title to find the appropriate abbreviation. Serials cataloging guidelines have been revised to simplify the decision making process and eliminate redundancies in transcription. Added efficiency has been gained as a result of the prior year's experience using the new procedures.

BACKGROUND

Journal literature is one of the primary means of communicating scientific research and discovery; thus, it is critical to have accurate and authoritative records in the NIH online catalog for serials. Getting these records created in the timeliest fashion, with all the data essential for access and retrieval, allows these records to be used promptly by researchers throughout NIH, other libraries worldwide, and all of the automated systems that depend on this data, most notably the PubMed indexing system. Therefore NIH recognizes the importance of standardizing and streamlining the cataloging process wherever possible.

Rationale

Pilot testing of the new cataloging guidelines in a dozen libraries have demonstrated a potential time and cost savings of up to 20% from current procedures. This will permit decreasing the average serial cataloging time and unit cost by 20%, for an annual savings of .3 FTE (GS-12 level), based on annual production of 1700 titles, and allow the reassignment of staff to new initiatives based on this savings.

TARGET CONTEXT AND CONDITIONS

The efficiency and reduction in unit cost of cataloging records will be achieved through several strategies. Cataloging procedures will be streamlined by implementing revised guidelines for serials cataloging that simplify the training and decision making process, focus on controlled access points for subjects, names and titles, and eliminate redundancies in transcription. The revised guidelines utilize title abbreviation data from the ISSN International Centre, and edit only for format, rather than content. The revised guidelines eliminate cataloger-supplied translations of Chinese, Japanese and Korean titles, and instead provide access to the vernacular data.

Long Term Objective: (CTR-7) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CTR-7 By 2010, establish the feasibility of sharing information from already-conducted scientific studies of warfarin (coumadin^{R}) anti-coagulation, through the knowledge base PharmGKB. (Outcome)	*2010*	Establishing the feasibility of sharing from already-conducted scientific studies of warfarin (Coumadin) anti-coagulation, through knowledge base PharmGKB. *(Baseline):* (FY09) Begin meta-analysis using the standardized data from PharmGKB to determine an algorithm for warfarin dosing based upon genotype.	N/A
	2009	Begin meta-analysis using the standardized data from PharmGKB to determine an algorithm for warfarin dosing based upon genotype. *(Baseline):* (FY08) Collect data from the 13 participating groups and begin standardizing datasets.	Data from the participating groups was collected from PharmGKB and the datasets were standardized to prepare the meta-analysis. (Target Met)
	2008	Begin standardizing datasets in PharmGKB to prepare for the FY09 meta-analysis. *(Baseline):* (FY07) 13 participating groups of PharmGKB have agreed on the critical column headings for depositing data (e.g., genotypes, INR phenotypes, BMI, etc.).	The participating groups began standardizing datasets in PharmGKB to prepare for the FY09 meta-analysis. (Target Met)

Data Source and Validation
The International Warfarin Pharmacogentics Consortium: Estimation of the Warfarin Dose with Clinical and Pharmacogentic Data. The New England Journal Of Medicine.Volume 360, Number 8, February 19, 2009 Pages 753-764. http://www.pharmgkb.org/views/loadConsortia.action, http://content.nejm.org/cgi/content/short/360/8/753

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. The participating groups were able to standardize datasets in PharmGKB and prepare the meta-analysis. A standardized template defined by PharmGKB was used by all participants. The pooled data held significant findings. The consortium was better than "feasible" - it was highly successful. The results were published in the NEJM in 2009 (see citation and abstract) with an accompanying editorial from the FDA entitled "Pharmacogenetics — Tailoring Treatment for the Outliers". One important finding was that the use of a pharmacogenetic algorithm for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than those derived from a clinical algorithm or a fixed-dose approach.

BACKGROUND

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) was developed to help researchers understand how individual genetic variation contributes to differences in drug reactions. It is a publicly available repository for genetic and clinical data from pharmacogenomics research studies. Over the next three years, up to 13 international groups have agreed to share existing data sets via PharmGKB. The risk is in whether these groups will be able to effectively share data and harmonize between their non-standardized methods for conducting the studies.

Studies of warfarin (Coumadin®) were selected for this goal because the drug is widely used and individual response is highly variable. Warfarin is an anticoagulant used to prevent blood clots from forming or enlarging. Initiating warfarin therapy involves a great deal of cost and coordination because optimal dosing levels vary among individuals. Clinicians monitor patients using warfarin with frequent blood testing in order to maximize the therapeutic benefit without causing dangerous side effects.

The groups plan to use PharmGKB data to perform a meta-analysis that will yield a possible algorithm for warfarin dosing based upon genotype. If successful, this will establish a procedure for data-sharing and maximize its extractable value, with the pay-off of incorporating the pharmacogenetic information gained into establishing the starting dose for warfarin therapy (testable in a replication data set and/or a de novo clinical trial). This work will potentially lead to better patient management and ultimately reduced health care costs.

Rationale

Through growing knowledge of individual genetic differences and response to environment, NIH is increasingly able to implement individually targeted or personalized treatment. One cost-effective approach to the development of individualized treatments is to make optimal use of existing information prior to commissioning new, expensive, randomized clinical trials. Warfarin therapy is one area of treatment in which NIH is poised to test the utility of this approach. An established dosing algorithm could inform the design of clinical trials. For example, a trial could test the hypothesis that use of genotyping information to set the initial dose and protocol for warfarin therapy has clinical utility and is an improvement over current practice. The GPRA goal would be proof-of-principle of a useful process for effectively sharing basic pharmacogenetic results and preparing to translate those results into clinical practice (for anticoagulation). If successful, this paradigm could be extended to personalize other medical treatments.

TARGET CONTEXT AND CONDITIONS

In FY 2008, NIH ensured that all relevant information to individual dosing of warfarin has been contributed to the PharmGKB by the 13 participating groups. Work will begin on analyzing differences among the various treatment and research protocols and standardizing the datasets. In FY 2009, NIH grantees will begin a meta-analysis using standardized data. By FY 2010, the meta-analysis will suggest whether a dosing algorithm based on these existing datasets can be used to establish initial dosing levels in clinical trials. If successful, these targets will establish the feasibility of sharing data from scientific studies to develop personalized treatments for testing in clinical trials.

Long Term Objective: (CTR-8) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CTR-8 By 2012, increase communication efforts and enhance centralized outreach strategies regarding extramural research funding policy, compliance and administration as demonstrated by the type and frequency of communications and related activities. (Outcome)	*2011*	Offer one NIH Regional Seminar on grants writing, submission and administration that is accessible for remote viewing by applicants and grantees around the world. *(Baseline):* NIH Regional Seminars are offered only as in-person events.	N/A
	2010	Measure the breadth and number of centrally maintained multi-media outlets to expand usage to describe the grants process, and utilize at least one new technology to reach audience. *(Baseline):* As of FY'08, the NIH Office of Extramural Research provides two instructional videos on parts of the grants process.	N/A
	2009	Provide a single source of information on grants policy and process to integrate and synchronize related communications efforts across NIH. *(Baseline):* Leadership for carrying grant-related message distributed across NIH Institutes and Centers.	Developed and maintained robust public Web sites and staff intranet sites on key issues such as NIH's Recovery Act grant policies/opportunities and changes resulting from NIH's Enhancing Peer Review initiative. (Target Met)
	2008	Realign staff centrally to support the execution of a comprehensive communications strategy. *(Baseline):* Multiple groups focused on grant-related, extramural communications.	Final staff realignment completed in July 2008. (Target Met)
	2007	Complete redesign of NIH's main grants Web sites and improve Web content. *(Baseline):* Web site design and content prior to redesign and update effort.	NIH launched a complete redesign of its main grants website in August of 2007, involving changes to over 600 Web pages and dozens of pages of completely new content explaining the NIH grants process. (Target Met)

Data Source and Validation
2009 NIH Recovery Act Grant Information: http://grants nih.gov/recovery/ Enhancing Peer review at NIH http://enhancing-peer-review.nih.gov/index html NIH Human Resource and Office of Management Assessment records. Contact: Acting Director, Division of Communications and Outreach @ Phone: 301-435-0937

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to provide a single source of information on grants policy and process to integrate and synchronize related communications efforts across NIH was MET.

Over the past few years, the NIH Office of Extramural Research (OER) has developed numerous centralized resources on grants policy and processes for use by the grantee community and NIH staff at each of the NIH Institutes. The OER "About Grants" site, launched at the end of FY07, provides a comprehensive view of the grants process keeping NIH Institutes and Centers from having to each develop and maintain this information separately on their individual Web sites. The public OER Grants Web site had over 12 million user sessions in FY09.

In FY 2009, OER established a new public Web site for NIH's Recovery Act grants information. This site serves as a central resource for NIH's Recovery Act funding opportunities, funding policies, processes, and communications resources. The companion intranet site for NIH staff served the important role of ensuring that staff were informed and had a central location to find guidance specific to NIH's Recovery Act implementation. In this way NIH helped thousands of extramural staff members to communicate with a consistent message to the applicant community, and award and administer grants communicating consistently with our applicant community.

In FY 2009 OER also used the same strategy for communicating changes resulting from the trans-NIH Enhancing Peer Review Initiative, which fundamentally altered the structure and length of NIH grant applications and how NIH grants are scored in peer review process. To ensure consistency of information provided on this topic, a central NIH site was developed for the public, to include history, policy, timelines, guidance, communication and training information and FAQs with a companion intranet for information and guidance for NIH staff.

BACKGROUND

The NIH has a history of maintaining a collaborative relationship with the extramural research community and has a strong reputation for providing timely and clear research-funding related communications. It is vital to maintain two-way communications between NIH and the extramural community, thereby ensuring that NIH policies and requirements are effectively developed, implemented, and communicated.

The NIH plans to implement a broad communications strategy for centralized grant-related communications, including such activities as organizational consolidation of extramural research communications activities, restructuring and developing new Web site content, exploring emerging technologies, integrating and synchronizing communications efforts across NIH, and conducting ongoing evaluation of NIH grants-related communications. These efforts will allow NIH to achieve efficiencies of scale, ensure currency of information, broaden its reach into the community and ensure a consistent message.

Rationale

The magnitude of recent and upcoming changes to grants policy and process has a profound effect on grants administration and the facilitation of research within the applicant community. Clear and effective

communication with the research community becomes increasingly important as NIH makes policy changes to facilitate increasingly complex and interdisciplinary science, align with federal-wide application and reporting standards, and streamline and improve the review process.

The NIH must adapt to a changing communications environment. The broad usage of the Internet, Web sites, podcasts, video availability, and other electronic media create expectations of information being immediately available and in a variety of formats. These technologies provide new opportunities to reach larger, specialized and previously underserved audiences.

Policy changes, coupled with changes in how people communicate, necessitate the development of an NIH extramural research communications office. This office would generate new efficiencies, use new technologies, and maintain effective two-way communication with the extramural community.

TARGET CONTEXT AND CONDITIONS

A working group of staff, stakeholders and consultants was formed in 2006 to analyze the usability and content of the existing grants Web site. In FY2007, a redesign of the main NIH grants Web site was launched for the extramural community. The updated Web site implements the recommendations of the working group and provides new content, improved search capabilities, and easier navigation. The updated Web site is an integral component of the overall communication strategy. The Web site is the central location for grants-related information and is referenced from many other types of communications and websites across NIH.

The consolidation of communications activities within the extramural research program began in FY07 by reorganizing staff into a central office while maintaining existing roles and responsibilities. In FY08, the new office realigned staff, roles and responsibilities to realize efficiencies of scale and improve message consistency. This group is responsible for development and execution of a comprehensive communications strategy that involves numerous activities such as development of an automated system for creating funding opportunity announcements, exploring emerging technologies, coordinating outreach activities and events, and developing outreach materials. The consolidated office and its activities, including the improved Web site content, will set the foundation to centralize and create a single trusted source of information related to research-funding related process and policy.

In an effort to reach a large and diverse audience, NIH will take advantage of emerging technologies that can be used to explain the NIH grants process. This could include webcasts, streaming video, Web 2.0 technologies, podcasts, interactive training and on-line dialog. At least one new technology will be utilized by 2010.

As budgets at grantee institutions decrease, it becomes increasingly difficult for junior faculty members and grants support teams to travel to conferences, even those held by NIH. Offering an NIH Regional Seminar on grants writing, submission, and administration that is accessible for remote viewing by applicants and grantees around the world provides interactive access to information that inexperienced personnel often require to help their institution to successfully win and manage NIH grants. A customer satisfaction survey of the 2011 seminar will be conducted to determine whether the remote viewing participants were adequately served. The results will enable an estimate (at a minimum) of the volume of additional participants who were served by remote feed to determine whether this outreach modality expands our outreach capability.

Long Term Objective: (CTR-9) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CTR-9 By 2012, increase awareness of the NIH SBIR and STTR funding opportunities available for women-owned and socially and economically disadvantaged small business concerns (SBCs). (Outcome)	*2011*	Utilize new on-line technologies to provide at least one virtual forum that targets women-owned and socially and economically disadvantaged small business researchers that enables them to learn about funding opportunities and resources available through the SBIR and STTR programs. *(Baseline):* 0 on-line events past several years	N/A
	2010	Conduct or participate in at least two outreach activities (i.e., local, regional or national conferences) that specifically target women-owned or socially and economically disadvantaged small businesses to communicate SBIR and STTR opportunities and how to apply for them. *(Baseline):* 1 event over past several years	N/A

BACKGROUND

The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs are Congressionally-mandated programs that require NIH to set-aside 2.5% and 0.3% respectively of its extramural budget for domestic small business concerns to engage in Research/Research and Development (R/R&D) that has the potential for commercialization.

These programs include the following objectives: (1) using small businesses to stimulate technological innovation, (2) strengthening the role of small business in meeting Federal R/R&D needs, (3) increasing private sector commercialization of innovations developed through Federal R&D, and (4) fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned business concerns in the SBIR and STTR programs.

Rationale

In its 2009 study, the National Research Council of the National Academies of Sciences recommends that the NIH extend its outreach to younger women and minorities and encourage and solicit women and underrepresented minorities working at small firms to apply as Principal Investigators or Co-Investigators for SBIR awards. The NRC recognizes in this recommendation that while the number of women, and to a lesser extent, minorities graduating with advanced scientific and engineering degrees has risen over the past decade, many of them may not yet have arrived at the stage in their careers ready to effectively compete in the SBIR program. Further, in order to meet the statutory objective for encouraging the inclusion of women-owned SBCs and socially and economically disadvantaged SBCs in the SBIR and STTR programs, agencies must conduct outreach efforts that target this specific population of small business researchers. Clear and effective communication with this community is increasingly important for NIH to facilitate access to information and resources available through the SBIR and STTR programs and to keep this community apprised of new

programmatic enhancements. In this vein, enhanced targeted outreach to diverse small business groups will directly allow the NIH to meet this statutory program goal more effectively.

The NIH SBIR/STTR Office will explore and develop new outreach activities to strengthen effective communication with the woman-owned and socially and economically disadvantaged small business research community.

TARGET CONTEXT AND CONDITIONS

It is routine practice for the NIH SBIR/STTR staff to reach out to the small business research community by presenting at SBIR/STTR national, state, and regional conferences around the country. Currently, evidence shows that woman-owned and socially and economically disadvantaged small businesses continue to be underserved. Although specific reasons are unknown, several factors including costs, geographic location and other socio-economic variable may pose direct barriers to accessing resources and businesses opportunities.

Improvements in reaching this underserved population can be made that are not cost prohibitive. These would include presenting at conferences specifically targeting this group, and using on-line technologies and other advancements in electronic communications. Reaching out to these researchers through partnerships with various regional organizations and groups dedicated to facilitating access to essential information may further assist with the transfer of knowledge without a cost burden. NIH is hopeful that these approaches will reach this population of researchers and thus increase their interest and participation in the NIH SBIR/STTR program.

Long Term Objective: (CTR-10) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CTR-10 By 2014, expand the scope of the Hazardous Substances Data Bank to include 14 nanomaterials. (Outcome)	*2011*	Modify the current Hazardous Substances Data Bank structure to accommodate the data records specification for the identified range of nanomaterials *(Baseline):* The HSDB is not currently capable of storing data on nanomaterials.	N/A

BACKGROUND

The Hazardous Substances Data Bank (HSDB) is a toxicology data file produced by the National Institutes of Health, and available through the Toxicology Data Network (TOXNET®) at http://toxnet.nlm.nih.gov/ . HSDB focuses on the toxicology of more than 5000 potentially hazardous chemicals, and includes information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, and related areas. Each record is a comprehensive review of published information, ranging from thirty to one hundred pages in length, addressing the following factors:

Human Health Effects	Chemical/Physical Properties
Emergency Medical Treatment	Chemical Safety & Handling
Animal Toxicity Studies	Manufacturing/User Information
Metabolism/ Pharmacokinetics	Laboratory Methods
Pharmacology	Special References
Environmental Fate & Exposure	Synonyms and Identifiers
Environmental Standards & Regulations	

All data are referenced and derived from a core set of books, government documents, technical reports and selected primary journal literature. HSDB records are peer-reviewed by a Scientific Review Panel (SRP), a committee of experts in the major subject areas within the data bank's scope.

Nanotechnology is an emerging field with great potential in materials science and medicine. Nanomaterials are complex, as are their interactions with biological organisms and the environment. While microscopically sized, they come in all sizes, shapes and compositions. Carbon nanotubes, for example, are molecules shaped like cylinders that have unique properties potentially useful in electronics, optics and various other materials. They are manufactured and synthesized in many different ways, and produce different results when tested to assess their safety. Dendrimers are a type of nanostructure that can be precisely designed and manufactured for a wide variety of applications, including treatment of cancer and other diseases. Nanoscale silver is used in anti-bacterial wound dressings. A nanoscale dry power can neutralize gas and liquid toxins in chemical spills and elsewhere. Sunscreens containing nanoscale titanium dioxide or zinc oxide reflect UV light to prevent sunburns.

Rationale

Along with the promise of nanotechnology is the need to explore potential environmental and health implications, and there is a recognized need to accelerate the collection of definitive data on nanomaterial hazards. Scientists have found indications that certain nanoscale materials need to be handled with caution, and the National Institute of Occupational Health and Safety has recommended the need for appropriate precautionary measures for handling new materials to avoid worker exposure to nanoscale materials. Within

the National Nanotechnology Initiative (www.nano.gov), The Nanotechnology Environmental and Health Implications Working Group is devoted to addressing environmental, health and safety issues related to nanotechnology.

Though research on the safety of nanomaterials is still at an early stage, as the research progresses, there is the need to capture and disseminate the results through authoritative databases. Augmenting the HSDB to accommodate nanochemical materials is an important initiative for maintaining comprehensive coverage of potentially hazardous materials through this information resource.

TARGET CONTEXT AND CONDITIONS

Accommodating this new type of chemical material in an existing database represents a significant effort and has a certain degree of risk. The first step is identifying and retaining appropriate experts to serve on the Scientific Review Panel, as expert review is a requirement for inclusion of any record into the HSDB and expert guidance is required to ensure that we undertake appropriate database re-design steps to represent the information about nanomaterials. The next step is identifying the range of nanomaterials that will be appropriate for inclusion in the HSDB, as well as selecting those materials for which sufficient research on safety has been conducted. The number of eligible materials is currently estimated at about fourteen, but is expected to increase as the field of nanotechnology expands. Next, creating the database infrastructure component requires database re-design, new programming, and changes in the interface. The type of information to include in the database record will be significantly different from the existing database and will there require a significant database restructuring that will also affect all the existing records. Further, the database depends on outside expert scientific reviewers who meet three times a year to consider new records as well as review a rolling set of existing records for currency. Each HSDB record requires a comprehensive review of literature and evidence and data from multiple sources, so that each new record represents a significant effort analogous to the writing a comprehensive review article, typically approximately 2-3 months.

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.

Research 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. 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.) The following training and career development opportunities are offered:

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.

Postdoctoral Training. At the postdoctoral level, NIH supports an extension and expansion of the apprenticeship approach. For individuals continuing their formal education in the biomedical 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.

Career Development. Career development awards provide support for acquiring specialized new skills to trained investigators (postdoctoral researchers) just commencing independent research careers or well established researchers looking to expand into new areas.

Mechanisms of Support. Extramurally, NIH offers a flexible and varied series of high-quality training opportunities 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://grants2.nih.gov/training/extramural.htm. Intramurally, 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/.

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.

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, new information technologies (IT) 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. 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 supports HHS at the departmental level. For example, the eRA is playing a major role in supporting the HHS 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) makes better use of IT investments to increase efficiency, reduce the paperwork burden, and improve government response time. The Draft HHS Enterprise Information Technology Strategic Plan (FY 2006 – FY 2010) outlines strategic goals and strategic objectives that will advance the best and most effective HHS IT resources and will drive progress for public health and human services. All the NIH enterprise systems dovetail with the Draft HHS Enterprise IT Strategic Plan.

Long Term Objective: (CBRR-1.1) 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.

Measure	FY	Target	Result
CBRR-1.1 By 2012, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds the relevant comparison groups within 10 years of graduation. (Output)	*2011*	N ≥ 12% *(Baseline):* 10%	N/A
	2010	N ≥ 12% *(Baseline):* 10%	N/A
	2009	N ≥ 12% *(Baseline):* 10%	Award rate to comparison group reached 13% and exceeded the target by at least 1%. (Target Met)
	2008	N ≥ 12% *(Baseline):* 10%	Award rate to comparison group reached 14% and exceeded the target by at least 2%. (Target Met)
	2007	N ≥ 12% *(Baseline):* 10%	Award rate to comparison group reached 12%. (Target Met)
	2006	N ≥ 12% *(Baseline):* 10%	Award rate to comparison group reached 13% and exceeded the target by at least 1%. (Target Met)

Data Source and Validation
Analyses of career outcomes for predoctoral and postdoctoral NRSA participants, compared to individuals that did not receive NRSA support," using the Doctorate Records File and the NIH IMPAC II database. Contact: Research Training Coordinator Office of Extramural Programs @ 301- 435-2686

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to retain NRSA predoctoral trainees and fellows in research relative to comparison groups of Ph.D.s was Met. In contrast to other doctoral students at the same institution over the same time period (Comparison Group A) and doctoral students at institutions not receiving NRSA support (Comparison Group B), NRSA trainees and fellows from 1988 through 1998 were more than 3 times as likely to remain active in biomedical research, as indicated by the greater percentage applying for and receiving NIH research project grant support within 10 years of completing their Ph.D.s.

To determine the outcome of this target, predoctoral researchers trained under NIH NRSA funding are compared to those not trained under NIH NRSA funding. In FY 2009, NIH predoctoral trainees and fellows were 13% more likely to remain active in biomedical research than non-NIH trainees and fellows; this exceeded the annual target of 12%. The results demonstrate that former trainees and fellows funded by NIH are more likely to remain in research careers and are better able to compete for funding ten years past their degree. Data for this analysis were obtained from the NIH IMPAC II system and the national Survey of Earned Doctorates.

Group	Percent Applying for NIH Research Awards	Percent Receiving NIH Research Awards
Former NRSA Trainees and Fellows	31.1% (6,176/19,875)	18.4% (3,656/19,875)
Comparison Group A	10.5% (7,723/73,763)	5.2% (3,835/73,763)
Comparison Group B	5.0% (1,085/21,705)	1.9% (406/21,705)

The Extramural Research Training and Research Career Development Program was assessed in FY 2008 and found to be effective. The assessment cited strong program management and successful progress toward the measure as significant attributes of the program. As a result of continuing efforts since then, the program has maintained progress towards the achievement of its annual objectives.

Advances or Other Highlights

NIH issued 65 new or updated research education, research training, and career development funding opportunity announcements in FY 2009. In addition, to foster the retention of newly trained investigators in research, NIH's Loan Repayment Program made awards of up to $35,000 to more than 1,600 individuals in FY 2009. By reducing the burden of educational debt, these loan repayment awards allow recipients – many of whom are clinical investigators – to concentrate on launching their research careers.

BACKGROUND

A critical part of the NIH mission is the education and training of the next generation of biomedical, behavioral, and clinical scientists. The overall goal of the NIH research 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. Although other Federal agencies and private philanthropies support research training, none provide the focus, breadth, or depth required to ensure capacity for research personnel across the biomedical, behavioral, and clinical sciences.

Training for a career in research generally requires an investment of 8 to 12 years of pre- and postdoctoral education, during which time science is advancing, new diseases are emerging, and existing diseases are becoming better understood, diagnosed, and prevented. To be successful, trainees must have an aptitude for research, be highly committed as well as agile in their ability to address emerging research questions, and also possess the organizational skills and acumen required to manage complex research projects.

Rationale

Success of NIH predoctoral research training programs can be measured, in part, by the number of trainees and fellows that go on to apply for and receive subsequent NIH support; subsequent support is an indicator of retention success in the research arena, and reflects the impact of NIH-funded training on the ability of trainees and fellows to be competitive and sustain a research career with independent funding.

TARGET CONTEXT AND CONDITIONS

A number of activities are conducted to support the achievement of this measure. These include updating and developing new research education and training initiatives to meet the evolving needs of science and public health; engaging the National Research Council of the National Academies to periodically perform evaluative studies of the Ruth L. Kirschstein National Research Service Award (NRSA) program; informing the scientific research community of new, updated, and ongoing training and career development opportunities through presentations at national, regional, and local meetings and other outreach activities; and communicating with other Federal agencies that support similar research training goals.

In particular, NIH seeks to retain predoctoral trainees and fellows in the scientific workforce by aiding their transition to independent research careers through strategies such as:

- Opportunities for postdoctoral training and fellowships; and
- Loan repayment programs for newly-trained scientists committed to research careers.

Through these and other related activities, NIH strives to ensure the appropriate retention of NRSA pre-doctoral trainees and fellows in research careers. To assess its performance, NIH routinely monitors degree completion of former NRSA pre-doctoral trainees and fellows and their subsequent involvement in research, using data from the national Survey of Earned Doctorates and the NIH IMPAC II administrative database.

Long Term Objective: (CBRR-1.2) 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.

Measure	FY	Target	Result
CBRR-1.2 By 2012, ensure that the proportion of post-doctoral fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups within 10 years of fellowship completion. (Output)	*2011*	N ≥ 12% *(Baseline):* 12%	N/A
	2010	N ≥ 12% *(Baseline):* 12%	N/A
	2009	N ≥ 12% *(Baseline):* 12%	Award rate to comparison group reached 14% and exceeded the target by at least 2%. (Target Met)
	2008	N ≥ 12% *(Baseline):* 12%	Award rate to comparison group reached 13% and exceeded the target by at least 1%. (Target Met)
	2007	N ≥ 12% *(Baseline):* 12%	Award rate to comparison group reached 13% and exceeded the target by at least 1%. (Target Met)
	2006	N ≥ 12% *(Baseline):* 12%	Award rate to comparison group reached 13% and exceeded the target by at least 1%. (Target Met)

Data Source and Validation
"Analyses of career outcomes for postdoctoral NRSA participants, compared to individuals that did not receive NRSA support," using the NIH IMPAC II database. Contact: Research Training Coordinator Office of Extramural Programs 301- 435-2686

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to ensure the retention of postdoctoral fellows receiving research training through the NRSA program relative to comparison groups was Met. In contrast to postdoctoral fellows that applied for, but did not receive NRSA research fellowship support during the same time period, NRSA postdoctoral fellows from 1988 through 1998 were more than 1½ times as likely to remain active in biomedical research, as indicated by the greater percentage applying for and receiving NIH research project support within 10 years of completing their training.

To determine the outcome of this target, postdoctoral researchers trained under NIH NRSA funding are compared to those not trained under NIH NRSA funding. In FY 2009, NIH postdoctoral fellows were 13.9% more likely to remain active in biomedical research than non-NIH fellows; this exceeded the annual target of 12%. The results demonstrate former postdoctoral fellows funded by NIH are more likely to remain in research careers and are better able to compete for funding ten years past their training. Data for this analysis were obtained from the NIH IMPAC II system.

Group	Percent Applying for NIH Research Awards	Percent Receiving NIH Research Awards
Former NRSA Fellows	46.1% (4,529/9,814)	30.9% (3,035/9,814)
Other Postdoctoral Fellows	28.7% (3,251/11,341)	17.0% (1,932/11,341)

The Extramural Research Training and Research Career Development Program was assessed in FY 2008 and found to be effective. The assessment cited strong program management and successful progress toward the measure as significant attributes of the program. As a result of continuing efforts since then, the program has maintained progress towards the achievement of its annual objectives.

Advances or Other Highlights

NIH issued 65 new or updated research education, training, and career development funding opportunity announcements in FY 2009. Over the course of the year, NIH also continued its efforts to support new investigators through awards designed to foster their career transition and reward innovation. In FY 2009, NIH made more than 200 career transition awards to newly independent scientists and more than 50 New Innovator (DP2: http://commonfund.nih.gov/newinnovator/) awards.

BACKGROUND

A critical part of the NIH mission is the education and training of the next generation of biomedical, behavioral, and clinical scientists. The overall goal of the NIH research 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. Although other Federal agencies and private philanthropies support research training, none provide the focus, breadth, or depth required to ensure capacity for research personnel across the biomedical, behavioral, and clinical sciences.

Following a 5-6 year investment in graduate school, a new graduate still has several years of postdoctoral research training and career development before becoming a fully-established independent investigator. During this time, postdoctoral fellows continue the important work of honing their research, communication, and management skills.

Rationale

Success of NIH postdoctoral training programs can be measured, in part, by the number of fellows that go on to apply for and receive subsequent NIH support; subsequent support is an indicator of retention success in the research arena, and reflects the impact of NIH-funded training on the ability of fellows to be competitive and sustain a research career with independent funding.

TARGET CONTEXT AND CONDITIONS

NIH awards Ruth L. Kirschstein National Research Service Award (NRSA) Individual Postdoctoral Fellowships as one of its primary means of supporting postdoctoral research training. To help ensure that these highly-trained investigators are retained in research following the completion of their fellowships, NIH aids their transition to independent research careers through strategies such as:

- Encouraging training in laboratory and project management for postdoctoral trainees
- Providing career development awards that explicitly target the transition process, such as the K22
- Career Transition Award and K99/R00 Pathway to Independence Award

Through these and other related activities, NIH strives to ensure the appropriate retention of NRSA postdoctoral fellows in research careers, as indicated by applying for and receiving subsequent NIH support.

Long Term Objective: (CBRR-2) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CBRR-2 Promote data sharing and provide information in real time through the NIH Business System (NBS) by developing, integrating, deploying and maintaining business modules. (By FY 2014, the NBS will be in an ongoing status) (Output)	*2011*	(Development [Dev]) Initiate development of planned business modules to build capacity and functionality of the NIH Business System. * Planned - Service and Supply Activities Fund Module [Int.2012] * Planned - Oracle 12i Upgrade [Int.2011]	N/A
	2011	(Integration [Int]) Complete integration activities for full functionality and usability of priority modules for successful development efforts within 3 years of initiated development. * Planned - Oracle 12i Upgrade [Dev.2011/Dep.2012]	N/A
	2011	(Deployment [Dep]) Conduct priority deployment activities to enable user accessibility and skill development within 2 years from the onset of integration. * Planned - NIH Grants Interface Module (ERA) [Int.2010/Mat.2011]	N/A
	2011	(Maintenance [Mat]) Maintain deployed business modules. * Planned - GovTrip with Phase II Travel Module [Dep.2010] * Planned - NIH Grants Interface Module (ERA) [Dep.2011]	N/A
	2010	(Development [Dev]) Initiate development of planned business modules to build capacity and functionality of the NIH Business System. * Planned - NIH Grants Interface Module (ERA) [Int.2010] * Planned - Oracle 12i Upgrade [Int.2011]	N/A

Measure	FY	Target	Result
	2010	(Integration [Int]) Complete integration activities for full functionality and usability of priority modules for successful development efforts within 3 years of initiated development. * * Planned -NIH Grants Interface Module (ERA)[Dev2010/Dep.2011]	N/A
	2010	(Deployment [Dep]) Conduct priority deployment activities to enable user accessibility and skill development within 2 years from the onset of integration. * Planned – GovTrip Phase II Travel Module [Int.2009/Mat.2011]	N/A
	2010	(Maintenance [Mat]) Maintain deployed business modules. * Planned - GovTrip and Phase II (Pilot) Travel Module [Dep.2010]	N/A
	2009	(Development [Dev]) Initiate development of planned business modules to build capacity and functionality of the NIH Business System. * GovTrip Phase II Travel Module [Int.2009] * Oracle 10g, 11.5.10 Upgrade [int.2009] * Prism 6.2 Upgrade [Int.2009] * E-invoicing [Int.2009]	Initiated Deployment of GovTrip Phase II Travel Module, Oracle 10g, 11.5.10 Upgrade, Prism 6.2 Upgrade, and E-invoicing. (Target Met)
	2009	(Integration [Int]) Complete integration activities for full functionality and usability of priority modules for successful development efforts within 3 years of initiated development. * GovTrip Phase II Travel Module [Dev.2009/Dep.2010] * Oracle 10g, 11.5.10 Upgrade [Dev.2009/Dep.2009] * Prism 6.2 Upgrade [Dev.2009/Dep.2009] * E-invoicing [Dev.2009/Dep2009]	Completed integration activities for GovTrip Phase II Travel Module, Oracle 10g, 11.5.10 Upgrade, Prism 6.2 Upgrade, and E-invoicing. (Target Met)

Measure	FY	Target	Result
	2009	(Deployment [Dep]) Conduct priority deployment activities to enable user accessibility and skill development within 2 years from the onset of integration. * GovTrip Phase II Travel Module (Pilot) [Mat.2011] * Oracle 10g, 11.5.10 Upgrade [Mat.2009] * Prism 6.2 Upgrade [Mat 2009] * E-invoicing [Mat.2009]	Deployed GovTrip Phase II Travel Module, Oracle 10g, 11.5.10 Upgrade, Prism 6.2 Upgrade, and E-invoicing. (Target Met)
	2009	(Maintenance [Mat]) Maintain deployed business modules. * Property & Contracts / Acquisition / Accounts Payable & Receivable / Supply / Travel (Gelco) [Dep.2007] * GovTrip [Dep.2008] * E-invoicing [Dep.2009]	Maintained deployed business module Property & Contracts / Acquisition / Accounts Payable & Receivable / Supply / Travel (Gelco), GovTrip, and E-invoicing. (Target Met)
	2008	(Target 3) Report critical elements of General Ledger and Travel Module performance. * Key performance indicators for Tracks 1,2,3 and 4 *(Baseline):* (FY04) NBS performance with General Ledger and Travel Modules deployed	Critical elements of General Ledger and Travel Module performance (Tracks 1,2,3 & 4) were reported to include the number of NBS Help Desk tickets, percent of total NBS tickets closed, number of purchase orders approved, number of days to close the books and captured percent of server uptime statistics. (Target Met)
	2008	(Target 5) Commencement of NBS/UFMS migration activities. *(Baseline):* (FY06) NBS without the UFMS migration	Commencement of NBS/UFMS migration activities have been initiated in relation to functionality. (Target Met)
	2008	(Target 6) Continue to provide NBS post deployment support for property and contracts/acquisition/accounts payable and receivable/supply modules. *(Baseline):* (FY06) No NBS post deployment support currently exist	Provided NBS post deployment support for property and contracts/acquisition/accounts payable and receivable/supply modules. (Target Met)

Data Source and Validation
Contact: NBS Management Center @ 301-451-1913 Supporting File locations: http://sps.nbs nih.gov/default.aspx...

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

DEVELOPMENT

The FY 2009 Development target was Met.

GovTrip Phase II Travel Module

Phase II of the GovTrip effort leveraged all interfaces and functionality from Phase I development. In addition, there were development efforts for interfaces and functional coding for all Phase II functionality including that were undertaken through June 2009 that included:
GovTrip-NBS Data Integration, HR Organizational Interface, Constructed Trip, Advisory Committee Travel, IMPAC II Interface, Copy Function, Sponsored Travel, Long Term Travel, Patient Travel, Adjust Advances applied on Vouchers and Split Disbursement.

Oracle 10g Database Upgrade

Activities around the NBS Oracle 10g Database upgrade began in October 2008. The upgrade began with initial analysis of all database patches that had to be applied along with analysis of the upgrade for the other Oracle technology stack components. Once the analysis was complete, the patches/upgrades were applied in the NBS Patch environment, timed, and issues documented. The initial patched environment was tested by the NBS Infrastructure and Development teams to ensure that there were no major issues. Subsequently, the NBS Development environment was patched/upgraded and released to the NBS Functional Teams for more detailed testing.

11.5.10 Upgrade and PRISM 6.2 Upgrade

In an effort to leverage "Commercial-Off-The-Shelf" (COTS) functionality, an in depth impact analysis was conducted by the Upgrade Team to research all areas where existing Reports, Interfaces, Customizations, and Extensions ("RICE") may be impacted as a result of the deploying the upgrades. The analysis and planning activities conducted from November 2008 to December 2008 helped drive the scope of the development activity. The scheduled development tasks started December 2008 and completed February 2009. An additional development window targeted to meet our code freeze date was expanded to accommodate defects uncovered as a result of the integration and user acceptance testing effort.

E-invoicing

NIH met its intended goal of the procurement and implementation of an electronic invoicing tool for the NIH Business System for a small, specifically selected pilot vendor community. The Commercial-Off-The –Shelf (COTS) product was procured from a vendor in October 2008. According to direction from the Office of Management and Budget, Federal Agencies are, wherever possible, to purchase, not build software applications. Development of this COTS application has been limited to installation, configuration, and extensions to allow for Federal and NIH specific requirements. The product configuration and implementation was divided into two phases --internal and external. The internal phase provided the NIH internal system users (over 4,000 users) with a comprehensive view of vendor invoices, payments, orders/awards, and receipt of goods transactions. The external view was designed for NIH external vendors and suppliers as a tool for the creation and submission of electronic invoices.

INTEGRATION

The FY 2009 Integration target was Met.

GovTrip Phase II Travel Module

Full Unit Testing of all GovTrip application functionality was conducted, as well as full Integration Testing for all NIH travel scenarios and business processes to ensure interfaces to Oracle functioned as designed. Identified issues were logged and resolved. Additional rounds of testing were conducted through July 2009 as necessary before deploying to NIH community.

Oracle 10g Database Upgrade

The NBS Functional Teams conducted thorough integration testing of all the NBS applications including Prism (Acquisitions), Sunflower (Property), and Gelco (Travel) to ensure that all functionality was still intact and that all interfaces to Oracle were functioning properly. Issues encountered were remediated and re-tested. A second round of testing was completed before the upgrade was approved for deployment in the production environment.

11.5.10 Upgrade and PRISM 6.2 Upgrade

The Integration Testing and User Acceptance Testing (UAT) cycles heavily involved NBS, Office of Financial management (OFM), Institutes/Centers (ICs), and third party communities. Integration Testing covered a large percentage of the NIH community's integrated business scenarios. These activities were successfully conducted from February 23, 2008 through March 31, 2009. The scope of UAT covered a subset of the end-to-end business scenarios used during Integration Testing, as well as, scenarios associated with unresolved defects carried over from Integration Testing. 37 users from the NIH IC and OFM business areas contributed to the User Acceptance Testing effort, held from April 13, 2008 to April 24, 2008.

In preparation for deployment, the change management team along with project leadership documented a workforce impact assessment and communications plan, which informed the NIH community on high-level systemic changes and key project milestone dates, as a result of deploying the upgrades. In addition to relaying project communications, an extensive effort was focused on reviewing the repository of existing NBS and PRISM navigational aids, and modifying them as appropriate, to visually be in line with the changes resulting from the Upgrades. Business owners from the Budget & Finance, and Acquisitions and Logistics areas were also briefed on the workforce impacts resulting from the Upgrades, community participation for UAT, results from test cycles, and expected downtime cutover dates.

E-invoicing

Because the NIH Oracle iSupplier application was deployed as a Commercial -Off-The- Shelf product, the COTS product was already fully integrated into the existing NBS financial software suite of applications, no additional code integration was required. Full range of system development life cycle testing was conducted to ensure Federal extensions to the product meet Federal mandates and end user requirements.

System and user acceptance testing for NIH electronic invoicing Internal View was completed in April 2009.

System and user acceptance testing for NIH electronic invoicing External View was completed in September 2009.

Extensive navigation aids and end user desk top procedures (for NIH and for NIH external vendors) were composed, vetted, and distributed for use by all users. All user guides and Frequently Asked Questions have been posted and are kept current on NIH Business Systems internal websites. External Pilot Vendors are provided navigation and user guides upon provisioning into the pilot program.

DEPLOYMENT

The FY 2009 Deployment target was Met.

GovTrip Phase II Travel Module

In July 2009, the GovTrip Phase II Travel Module deployed to Production. Conducted full GovTrip hands-on training and deployed to all targeted Institutes and Centers with Just-In-Time training as they rolled into Production. Additionally, deployed eVoucher and eProfile capabilities for all NIH travelers and provided CBT self-training module to all NIH Executive Level Approvers.

Oracle 10g Database Upgrade
On April 21, 2009, the Oracle 10g upgrade along with upgraded Oracle technology stack components were deployed in production. The goals of the Oracle 10 g upgrade were to stay current with technology ensure continued support from Oracle due to impending de-support, improve performance of the NBS applications, and to set the groundwork for the Oracle application and Prism upgrades. These goals were all fulfilled and the NBS Oracle and Prism applications were upgraded approximately three months later.

11.5.10 Upgrade and PRISM 6.2 Upgrade
Cutover for the upgrades implementation started the evening of May 21, 2009, and completed late in the evening on May 27, 2009. Routine status meetings were conducted twice daily and real time status reports were provided in advance for cutover resources to be aware of the upcoming implementation tasks. NBS and PRISM environments were made available first thing in the morning on May 28, 2009.

E-invoicing
In March 2009 full deployment to NIH Internal System Users for consolidated view of all NIH invoices, awards/orders, receiving items, and Treasury payments was deployed for over 4,000 internal NIH Business System Users. Approximately six months later, the external view for pilot external vendors was deployed. Six months was granted as lead time for the NIH Internal Community to prepare for the implementation and roll out of the external vendor electronic invoicing pilot program. The NIH Electronic Invoicing External View completed system and user acceptance testing in September 2009. Implementation to NIH External Pilot Suppliers began on October 1, 2009 for four pilot vendors.

MAINTENANCE
The FY 2009 Maintenance target was Met.
FY2009 maintenance of deployed business modules has been met with full user support which includes: NBS Management Center direct support for users via electronic and telephone responses to user request for assistance on functionality; provisioning review and processing; support from subject matter experts; supplemental training materials to NIH users; mass electronic communication efforts regarding system functionality and availability; and targeted user group information sessions and forums.

Post-deployment system support has been transitioned to the NBS Operations and Maintenance (O&M). A sustainable NBS training environment and strategy is in place to keep NIHTC instructors and users abreast of system changes and reinforce desired user behavior.

Advances or Other Highlights
The NBS Management Center (NMC) supports the deployed NBS modules (Budget/Finance, Travel, Acquisitions, Property, and Supply) by employing standard escalation protocols for assisting users who are experiencing difficulty. In FY 2009 the NBS saw a 5% reduction in the number of user call assistance tickets from FY 2008. This can be attributed to continued system stability, user comfort with the system, and NBS education outreach efforts that include emails and supplementary training materials. Topics were derived from trend analysis from monitoring NBS user call assistance tickets as well as direct user feedback. In addition, the NBS Program maintains close coordination with the NIH Training Center to ensure proper education of future users.

The NBS Program Management Office is following Program Practices to provide consistent guidance to NBS Program staff to support a matrix organizational structure for project management. Practices include areas such as status reporting, risk and issue management, action item monitoring, software configuration and control management, and human resources. The NBS governance structure is operational and fosters full engagement of the NIH Business Owners and their respective stakeholder groups. The model includes internal and external components to support software configuration and control management and decision-making.

BACKGROUND

The core mission of the National Institutes of Health (NIH) is to conduct and support biomedical research. After an extensive review of its administrative processes and current information technology support, the NIH began implementing an enterprise resource planning system known as the NIH Business System (NBS). The NBS Project will replace the NIH administrative and financial core operations systems, including the general ledger, finance, budget, procurement, supply, travel, and property management systems. The NBS will enable administrative/scientific support that is cost effective, provide more accurate and timely information, and facilitate the scientific mission of the NIH. The NBS will ultimately improve internal controls, require accountability, and reduce the amount of time required by NIH scientists to complete administrative tasks (for example, related to travel requests or acquisition), thereby freeing these valuable resources in direct support of NIH's core research mission.

Rationale

Deployment of the NBS should position the NIH to meet the Chief Financial Officers (CFO) Act and Government Management Reform Act (GMRA) requirements and Office of Management and Budget's (OMB) timeframes. The successful implementation of the NBS general ledger module for FY 2004 reduced the need for previously constructed adjustments required to prepare financial statements. This was a critical step for the 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 the 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 is a major element of the Department of Health and Human Services (DHHS) Unified Financial Management System (UFMS). The NIH staff actively participates on DHHS UFMS teams to meet common goals, address Department-wide challenges, and ensure that the NBS can provide NIH financial data necessary to DHHS to support the NIH/HHS Consolidated Financial Statement.

TARGET CONTEXT AND CONDITIONS

The NBS Implementation is a phased approach, as recommended by Financial Systems Integration Office (FSIO), previously the Joint Financial Management Improvement Program [JFMIP], to incorporate individual modules as they are completed or additional modules as mandated. Modules of the NBS will serve similar functions to the legacy Administrative Database System (ADB). Targeted functional areas of ADB include travel, finance, acquisitions (warehouse supply, contracts, simplified), property, grants, service and supply, and fellowship payment. Due to inevitable conditions priorities may shift in order to meet emergent needs, governing body requirements, and/or leadership directions. Consequently, the completion process from development to maintenance of each module as planned may be disrupted as priorities shifts.

Since the initial deployment of NBS travel (GELCO), DHHS' goal of deploying one e-Travel system throughout the Department has been mandated. Predeployment activities associated with Phase 1 of a graduated deployment for the DHHS directive to implement GovTrip travel were completed in FY 2008. GovTrip Phase II which addresses NIH mission-critical travel requirements was delayed due to the eTS vendor's ability to deliver acceptable software that fulfills NIH's defined business requirements. Although a Phase II Pilot will be deployed in July 2009, the full deployment of the remaining NIH Phase II Institutes/Centers (ICs) will not be completed until January 2010 due to the vendor software delivery delays.

Funding shifts and prioritization of new administration initiatives could impact FY2010 planning; however, FY2010 initiatives include several enhancements related to corrective action plans resolving audit deficiencies for Access and Preventive Transaction Controls and software configuration management, and integration of

NIH Grants are target for development in FY2010 and implementation in early FY2011. Additionally, the availability of American Recovery and Reinvestment Act (ARRA) funds may permit other development efforts to proceed in FY2010, including Oracle Projects (Interagency and Reimbursable Agreements), and planning to upgrade NIH's existing base software systems support the NBS transition to Oracle 12.FSIO. The eRA/NBS integration activities have been accelerated from FY2011 to FY2010 due to the availability of ARRA funding for NIH CIO designated enterprise wide IT systems. eRA and NBS were provide ARRA funding which permits integration activities to begin in FY2010 with implementation in 1st quarter FY2011. Development efforts for a mandated initiative related to IRS Section 3402-(t) has been delayed until FY2012 per the ARRA legislation. The development of the NBS Service and Supply Fund solution has been delayed to correspond to the commencement of development activities for implementing Oracle Projects which is scheduled to occur in FY2011. Service and Supply fund functionality is expected to be subsumed by the provided Oracle Projects standard functionality. Upgrades to the base software systems supporting the NBS will be a necessary undertaking in the coming years. These upgrades move through a similar development to maintenance support process as independent software initiatives. Several of these software support implementations, along with the development of e-business online functions such as e-invoicing are occurring in FY 2009. FY2011 initiatives include configuration and implementation of NBS Funds Control, conversion and implementation of of the Common Government Account Classification structure in the NBS, and completion of transition to comply with DHHS Consolidated Reporting Project and Treasury GTAS initiatives.

Since FY 2005, the NBS implementation and deployment activities the functional, technical and change management teams have undertaken include the ongoing design, configuration, and testing of the baseline systems and integrated system phases along with follow-on deployment of individual modules when finalized and accepted. The phases include segments: Development, Integration, Deployment, and Maintenance (described below). At any given time, the NBS implementation teams may be dealing with one or all of the segments dependent on the number of modules moving toward production. In addition, any project going through the phases may be impacted by emergent priorities.

Development: Initial efforts to develop business modules or major software upgrades to process and record business transactions on behalf of the NIH business operations are initiated via Enterprise Resource Planning (ERP) directives. Requirements gathering, design, configuration, testing of the baseline system module, preliminary identification of organizational impacts and role applications based at the user level are included in the development phase. Framework (e.g., layout, design, and table shells), requirements traceability matrices and to-be process designs are developed for planned functionality and specific solutions are developed to answer and conclude open process issues.

Integration: The design, configuration, and testing of an integrated system module (user acceptance testing) including system role analysis and workflow management as well as analysis and development of technical training materials and user documentation for each function to be deployed. Typically, modules or major software upgrades with successful development will enter integration no later than 3 years from the onset of development. Execution of pilot testing programs and user acceptance testing (UAT), development of training and communication plans that support workforce transitions, development of training materials and execution of end user meetings introducing new modules or major software upgrades as well as data collection and test conversions of master data would be accomplished during this phase.

Deployment: Identification and training of users in specific role contexts; authorization of users to access the new system module functionality. Business functionality is turned on for users. Support of deployment by employing standard escalation protocols for assisting users who are experiencing difficulty is executed at this stage. Typically, modules/major software upgrades with successful integration will enter deployment no later than 2 years from the onset of integration.

Maintenance: Full user support including direct support via electronic and telephone responses to request for

assistance on functionality; mass support efforts via communication forums to user staff; onsite support with subject matter experts; supplemental training offerings; mass electronic communication efforts regarding system functionality; targeted user group information sessions and forums; support hotline telecommunication meetings; development of key performance indicators to recognize and address trends; and provision of supplemented targeted contract support, when necessary. Transition of ongoing training initiatives to appropriate entities. Initiation of regular reporting to required parties. Development/support of agency wide sharing initiatives.

Baselines
Development - Identification/initiation of development efforts for target initiatives
Integration - Initiation of integration testing for modules that have moved out of the development phase
Deployment - Initiation of deployment for modules that have moved out of the integration phase
Maintenance - Commencement of support for business modules

Long Term Objective: (CBRR-4) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CBRR-4 By 2013, provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic Research Administration (eRA) system. (Efficiency) (Output)	*2011*	Continue conversion of business processes: 90% of business processes being done electronically by FY 2011. (FY12) 93% electronic business processing *(Baseline):* (FY10) TBD% of business processes being done electronically.	N/A
	2010	Continue conversion of business processes: 87% of business processes being done electronically by FY 2010. (*Previous Target*): 85% electronic business processing *(Baseline):* (FY09) 87% of business processes being done electronically.	N/A
	2009	Continue conversion of business processes: 83% of business processes being done electronically by FY 2009. (*Previous Target):* 80% electronic business processing *(Baseline):* (FY08) 83% of business processes being done electronically.	Approximately 87% of all business process transactions, from grant submission at the front end to grant closeout at the back end, are now being carried out electronically. (Target Exceeded)
	2009	(FY03 Extended Target 2) Begin pilot-testing of progress reporting for multi-project mechanisms. *(Baseline):* (FY99) 14 simple competing grant applications received	Collaboration Initiated with Grants.Gov to facilitate electronic processing of multi-component projects. (Target Not Met but Improved)
	2008	(Target 7) Continue conversion of Business Processes: 75% of convertible business processes done electronically by FY 2008. *(Baseline):* (FY07) 55% of business processes being done electronically	Approximately 75% of the transactions in the business processes are now being done electronically. The proportion of competing grant applications received electronically increased to 83% during the past fiscal year. (Target Met)

Measure	FY	Target	Result
	2007	(Target 8) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. (FY07) 100% code conversion *(Baseline):* (FY03) Migration plan developed. Current architecture is client-server mix with web	100% code conversion completed (Target achieved in 2006). (Target Met)
	2007	(Target 7) Continue conversion of Business Processes: 55% of business processes done electronically by FY2007. *(Baseline):* (FY06) 40% of business processes being done electronically	Approximately 55% of the transactions in the business processes are now being done electronically. (Target Met)
	2006	Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006. -- (FY06) 100% of eligible HHS OPDIV's *(Baseline):* Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIVs, AHRQ and CDC/ NIOSH	100% of the eligible HHS OPDIVs (AHRQ, CDC, FDA, and SAMHSA) are using eRA for administration of research grants. (Target Met)
	2006	By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. -- (FY06) 75% code conversion *(Baseline):* (FY03) Migration plan developed. Current architecture is client-server mix with web	The target was met and exceeded. 100% of the code was converted before the end of FY06, and all of the Web-based applications were deployed by the end of FY06 (Target Exceeded)
	2006	(Target 7) Continue conversion of Business Processes: 40% of business processes done electronically by FY2006. *(Baseline):* (FY05) 33% of business processes being done electronically	Approximately 40% of the transactions in the business processes are now being done electronically. (Target Met)

Data Source and Validation
The primary data source used to evaluate performance is the eRA database transactional records. Contact: Office of Research Information Systems, Office of Extramural Research, NIH @ 301-594-9747

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY09 target of 83% of grant administration business processes being conducted electronically was Met and Exceeded. The proportion of competing grant applications received electronically (i.e., from grant submission at the front end through receipt & referral, peer review, award, execution, to grant closeout at the back end) increased to 87% during the past fiscal year. Other core processes, including Referral, Peer Review, Award, and Close-Out, are supported electronically at rates of 87% or more. A significant number of paper-based processes were automated during the past fiscal year, as noted in the summary of accomplishments provided in the Target Context and Conditions section, below.

The FY03 extended target plan to begin pilot-testing of progress reporting for multi-project mechanism has not been Met, but have Improved. Progress towards this target continues to be constrained by the inability of Grants.gov to accept NIH's multi-component mechanisms (Centers, Program Projects, Training Grants, etc.) in electronic format. These activities represent a subtantial proportion of the applications NIH receives (approximately 7% in FY 2009), and they are stored in IMPAC II as scanned images upon receipt by NIH as paper applications. The unstructured format of these scanned documents limits the extent to which NIH can automate downstream business processes to support multi-component activities. Electronic business processes that involve the NIH Commons user-interface, used by NIH grant applicants and grantees to submit documents to NIH such as electronic progress reports, are particularly affected by the delays in implementation of electronic submission for multi-component grant applications. Conversion of multi-component progress reports to an electronic submission process will be tabled, because it would not reflect the best stewardship of the IMPACII database to implement multi-component progress reporting in advance of electronic submission for multi-component grant applications.

NIH has recently entered into a collaboration with Grants.Gov to facilitate progress toward the implementation of electronic submission of multi-component applications and remains hopeful that progress can be achieved in this realm in the near future.

Advances or Other Highlights

In addition to advances that had been planned to support conversion to electronic processes, numerous unscheduled developments were necessitated by the rapid changes to the grants business processes that were needed to accommodate the Recovery Act programs. Separate reporting requirements for Recovery Act programs imposed the need for separate financial status reporting and closeout documents for administrative supplements and competitive revisions. In addition to accommodating new reporting requirements imposed on the grantees by Recovery Act programs, new system developments were needed to meet the Recovery Act reporting requirements of NIH, such as the Tracking Accountability in Government Grants System (TAGGS) reporting data exports, and reporting processes performed by the Research, Condition, and Disease Categorization (RCDC) system. Limits on the numbers of applications and reviewers that could be assigned to peer review meetings were raised to accommodate the large numbers of applications reviewed for the NIH Challenge Grant program. These new developments for the Recovery Act will support ongoing electronic reporting, monitoring and new grants programs.

The Extramural Research Program was assessed in FY 2006. The assessment cited a successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

Efficiency

Efficiencies were achieved as a result of the large number of applications received in electronic format in response to the Recovery Act programs.

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. In 2004, DHHS designated eRA as a Center of Excellence for all DHHS research grant processing. In response NIH has undertaken the responsibility of integrating the electronic grants systems of the Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Substance Abuse and Mental Health Administration (SAMHSA), and the Health Resources and Services Administration (HRSA).

eRA developed the eRA eXchange, a business-to-business system, by which it can electronically receive grant applications from Grants.gov, the federal government's e-Grants storefront initiative. It is also being used for other grants-related activities with commercial service providers and research institutions who establish system-to-system capabilities with NIH. The eXchange uses eXtensible Markup Language (XML) and PDF attachments. 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 Grants.gov, and ultimately to achieve the ability to execute end-to-end electronic processing between NIH and the external community using shared electronic resources.

Rationale

A significant goal for eRA is completing the move of internal work flows from paper-based business processes to electronic processes. The electronic submission and receipt of grant applications through Grants.gov is an intense effort and has already succeeded with the vast majority of the grant applications received by NIH. When completed, this undertaking will permit a revitalized focus on the administration of grants from application through grant closeout. This will include substantial improvements to Receipt and Referral processes, peer review facilitation, and project oversight. The availability of applications on-line eliminates the need for multiple copies of applications for each reviewer. Financial and progress reporting can now largely be done electronically. In fact, most aspects of the grant administration process have now been automated, resulting in improved process efficiencies and lower managerial and administrative costs.

TARGET CONTEXT AND CONDITIONS

Electronic reporting was 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. After ensuring acceptable performance of the progress reporting system once all FDP institutions had been invited to use it, its availability was expanded to all grantee institutions and a formal announcement was publicized on the NIH Commons during the third quarter of FY 2004. The ability for a grantee institution to submit progress reports through the Commons is now in the hands of the institution's business official.

In terms of developing XML capability, NIH started building pilot software to accept competing grant applications from the grant community in FY 2003. This pilot software focused initially on competing applications for simple research mechanisms. The initial version of this pilot software was completed successfully in FY 2004 and was further refined and improved over the course of several subsequent receipt cycles. These competing grant application pilots have produced several positive results for the NIH. Most notably, these efforts have resulted in a robust and extensible technical infrastructure for receiving and

handling XML transactions. In FY2006, this capability was expanded to enable NIH to accept grant applications via Grants.gov system-to-system interface. NIH continues to expand upon the types of grant applications it receives through Grants.gov via the exchange.

Migration of existing client/server applications was completed by implementing an eRA J2EE Migration Plan. This plan staged the transition of proprietary client/server applications to a standard, multi-tier, component-based technology. The J2EE architecture complements the XML technology, transforming eRA into a non-proprietary, secure enterprise system.

The overall implementation strategy for the integration of electronic grant processing for HHS Operating Divisions (OPDIVs) involved identifying OPDIV integration requirements and, where there were gaps, determining whether OPDIV business processes needed to be changed or whether eRA business processes/system modifications were necessary. To this end, a 'fit/gap' analysis of OPDIV requirements was finalized in FY05. An eRA-led working group, with participation from the integrating OPDIVs, met bi-weekly and finalized a list of issues that required changes to existing business processes or system modifications. Coding and testing of OPDIV grant processing was ongoing in FY05, and FDA, SAMHSA, and CDC (non-research) began processing grants through eRA by the end of FY05. Full grant processing for the OPDIVs by eRA was achieved during FY06, and the migration of legacy data was completed in FY07.

The transition from a paper-based business process to fully electronic processing has been part of the eRA vision for several years. The conversion of paper applications to electronic format has been fully implemented, and the system is capable of accepting electronic applications and doing 'Internet Assisted Review.' Other conversion activities are currently underway, and other processes will be converted as time, budget resources and other priorities allow. It will likely be several years before all of the conversion is completed.

Major accomplishments in FY09 include automation of the following business processes: grants-related budget formulation and execution reporting (electronic Tracking & Analysis); financial conflict of information (FCOI) reporting; submission of appointment forms and termination notices via the Electronic Trainee Activities System (xTrain); Federal Funding Accountability & Transparency Act reporting; American Recovery & Reinvestment Act reporting; grant receipt & referral (including integration with the Center for Scientific Review's Automated Workflow Referral System); display of multiple principal investigators (Multi-PI); processing of multiple active applications; enhancements to NIH's Peer Review processes; tracking of early-stage and new investigators; addition of electronic applications for various mechanisms, including fellowship grants; enhancements to Electronic Grant Folder functionality to include access to reviewer comments, multiple file display (blossoming), and access to 'historic' documents. Remaining conversion targets include the following: grant mechanisms yet to be made available in electronic format through Grants.gov; end-to-end processing of external training grants and fellowships; referral workflow; data quality functions; and loan repayment processes.

Even though NIH is targeting increased conversion to electronic processing of documents, it may not be cost-effective or desirable to expect a 100% conversion of the elements that comprise end-to-end grants processing. eRA continues to map electronic processes to existing business models. As these continue to evolve, eRA systems will be adapted to support them. Additionally, as eRA is asked to support the grants management automation of other agencies, additional flexibility may be necessary. These unknowns make it difficult to commit to a specific schedule for total completion of paperless processing. NIH expects the capability for paperless processing to expand during the next several years, and this progress will be reported.

Long Term Objective: (CBRR-6.1) Build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.

Measure	FY	Target	Result
CBRR-6.1 By 2011, construct or renovate 153 biomedical research facilities in order to build the capacity to conduct the proposed research. (Output)	*2011*	Complete 1 facility *(Baseline):* Number of projects completed: (FY10) TBD	N/A
	2010	Complete 12 facilities *(Baseline):* Number of projects completed: (FY09) TBD	N/A
	2009	Complete 25 facilities *(Baseline):* Number of projects completed: (FY08) 115	All 25 construction grants were completed either early or on time. (Target Met)
	2008	Complete 30 facilities *(Baseline):* Number of projects completed: (FY07) 89	26 of the 30 construction grants were completed either early or on time. Two sites are part of larger institution construction projects and can not be completed and authorized for occupancy until the entire institutional construction project is completed. Two sites experienced delays and requested and was granted an extension from NIH. (Target Not Met)
	2007	Complete 48 facilities *(Baseline):* Number of projects completed: (FY06) 43	46 of the 48 construction grants were completed either early or on time. Two sites are part of larger institutional construction projects and can not be completed and authorized for occupancy until the entire institutional construction project is completed. (Target Not Met)
	2006	Complete 44 facilities *(Baseline):* Number of projects proposed to be completed annually: (FY05) 0	43 of the 44 construction grants were completed either early or on time. One site was unable to begin construction due to unforeseen circumstances, and NIH is seeking a legal opinion regarding final disposition of the funds. (Target Met)

Data Source and Validation
The completion dates are located in the NCRR Construction Grants Management System. For more information, please contact the NCRR Office of Science Policy at 301-435-0864.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 Target to complete 25 construction or renovation of biomedical research infrastructures in order to build the capacity to conduct the proposed research was Met. All 25 construction grants were completed either early or on time. The newly completed buildings will support basic and/or clinical biomedical and behavioral research, and may also support research training.

The Extramural Construction Program was assessed in FY 2008. The assessment cited a successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

The National Institutes of Health's (NIH) extramural construction grant program supports construction and renovation projects that facilitate and enhance the conduct of PHS-supported biomedical and behavioral research. The extramural construction grant program supports the costs of designing, constructing and/or renovating non-Federal basic and clinical research facilities to meet the biomedical and behavioral research, research training, or research support needs of an institution or a research area at an institution.

The principal objective of the program is to facilitate and enhance the conduct of PHS-supported biomedical and behavioral research by supporting the costs of designing and constructing non-federal basic and clinical research facilities to meet the biomedical or behavioral research, research training, or research support needs of an institution or a research area at an institution.

Rationale

The Research Facilities Improvement Program (RFIP) makes awards to construct and renovate research facilities and thereby builds capacity to conduct biomedical and behavioral research. The RFIP needs to takes certain factors into account when making award decisions in order to ensure that the RFIP helps to meet the mission and provide support for construction and renovation of biomedical and behavioral research facilities that is the most beneficial to the research community. These factors include: ensuring that the facilities constructed or renovated are geographically disbursed, promoting interdisciplinary collaborations; facilitates the institution's ability to conduct, expand, improve or maintain biomedical or behavioral research and the ability of the facility to meet an unmet health need.

TARGET CONTEXT AND CONDITIONS

NIH not only ensures research infrastructure is available but makes sure that the infrastructure is safe and sound. Therefore, throughout the construction process, NIH staff provides additional oversight related to environmental impact issues, design specifications, and financial management of construction projects. At the completion of the building or renovation, NIH may conduct a site visit to ensure the building was built properly with all of the latest codes met. NIH staff works closely with institutions that have had difficulty completing the project on time. In some cases, delays are unavoidable therefore the completion of the construction may also be delayed. However, NIH staff monitors these grants to ensure that delays are kept to a minimum and provide expedited review of construction designs as needed.

The objective of this measure is to build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.

Long Term Objective: (CBRR-6.2) Build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.

Measure	FY	Target	Result
CBRR-6.2 By 2012, complete 15 biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases. (Output)	*2011*	Complete 0 biocontainment facilities. (FY12) Complete 1 facility *(Baseline):* Number of biocontainment facilities completed: (FY10) TBD	N/A
	2010	Complete 1 facility *(Baseline):* Number of biocontainment facilities completed: (FY09) TBD	N/A
	2009	Complete 7 facilities *(Baseline):* Number of biocontainment facilities completed: (FY08) 7	NIH completed construction of seven (7) extramural biocontainment facilities. All 7 of the biocontainment facilities were met either early or on-time. (Target Met)
	2008	Complete 4 facilities *(Baseline):* Number of biocontainment facilities completed: (FY07) 2	NIH completed construction of five extramural biocontainment facilities. (Target Exceeded)
	2007	Complete 2 facilities *(Baseline):* Number of biocontainment facilities completed: (FY06) 0	NIH completed 2 biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases. (Target Met)

Data Source and Validation
The completion dates are located in the NIAID BUZZSAW database. For more information, please contact the NIAID Office of Strategic Planning and Evaluation Branch @ 301-443-9941.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH completed construction of seven extramural biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases. All seven of the biocontainment facilities were completed either early or on-time. The facilities are part of the following universities: Boston University, University of Pittsburgh, University of Louisville, and Tufts University.

The Extramural Construction Program was assessed in FY 2008. The assessment cited a successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program.

As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

Improving our nation's defenses against bioterrorism is a key part of the U.S. Government's homeland security effort. The Department of Health and Human Services supports activities to improve local and state public health systems, to expand existing biosurveillance efforts, and to fund and conduct research on medical countermeasures against potential bioterror agents.

The principal objective of NIAID's program is to support the construction of National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs) at research institutions across the country. The NBLs will serve as a national and regional resource for research on biodefense and emerging infectious disease agents that require biosafety Level 2, 3 or 4 (BSL-2/3/4) biocontainment, while the RBLs will serve as a regional resource for research requiring BSL-2/3 biocontainment. The NBLs and RBLs will complement and support the research activities of NIAID's Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, and will be made available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

Rationale

NIAID's Extramural Biocontainment Facilities Construction Program's purpose is to build biocontainment facilities to support translational, product development-related and clinical research in biodefense and emerging infectious diseases, including research on Category A-C Priority agents and newly emerging infectious diseases,. Under the program, awards have been made to support construction of 15 facilities, including 2 BSL-3/4 National Biocontainment Laboratories (NBLs) and 13 BSL-3 Regional Biocontainment Laboratories (RBLs). These facilities will provide high-level biocontainment for more advanced stages of biodefense and emerging infectious disease research that were anticipated as a part of the expansion of NIAID's research in these areas following September 11, 2001. These more advanced stages of research play a critical role in supporting NIAID's role in the biodefense effort to conduct research and develop biomedical countermeasures to potential agents of bioterrorism in order to protect the Nation's public health. The facilities will provide centralized research space access for NIH-funded researchers across the country who are conducting biodefense and emerging infectious disease research. The facilities will also be available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

TARGET CONTEXT AND CONDITIONS

The objective of this measure is to build capacity to conduct research on biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases, by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.

NIH not only ensures research infrastructure is available but makes sure that the infrastructure is safe and sound. Therefore, throughout the construction process, NIH staff provides additional oversight related to environmental impact issues, design specifications, and financial management of construction projects. At the completion of the building or renovation, NIH may conduct a site visit to ensure the building was built properly with all of the latest codes met. NIH staff works closely with institutions that have had difficulty completing the project on time. In some cases, delays are unavoidable therefore the completion of the construction may also be delayed. However, NIH staff monitors these grants to ensure that delays are kept to a minimum and provide expedited review of construction designs as needed.

The Hawaii facility is not expected to be completed before 2012. Environmental and budgetary issues have delayed the onset of construction. This resulted in a 2011 target level of zero.

Long Term Objective: (CBRR-7) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CBRR-7 By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research. (Output)	*2010*	Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research. *(Baseline):* (FY10) 100% of expiring grants eligible for renewal	N/A
	2009	Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research. *(Baseline):* (FY09) 421 expiring grants eligible for renewal	100% of the 421 expiring grants eligible for renewal or recompetition were reviewed. (Target Met)
	2008	Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research. *(Baseline):* (FY08) 707 expiring grants eligible for renewal	100% of the 707 expiring grants eligible for renewal or recompetition were reviewed. (Target Met)
	2007	Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research. *(Baseline):* (FY07) 728 expiring grants eligible for renewal	100% of the 728 expiring grants eligible for renewal or recompetition were reviewed. (Target Met)
	2006	Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research. *(Baseline):* (FY06) 723 expiring grants eligible for renewal	100% of the 723 expiring grants eligible for renewal or recompetition were reviewed. (Target Met)

Data Source and Validation
ARIS is an internal management database. For more information, please contact the OAR, Office of Program Planning, Evaluation and Analysis at 301- 496-0357.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. The OAR utilized the enhanced ARIS, a database that allows tracking of all AIDS research expenditures coded to the research objectives articulated in the annual Trans-NIH Plan for HIV-Related Research (http://www.oar.nih.gov/strategicplan/), to efficiently conduct a trans-NIH portfolio analysis of 100 percent of the 421 grants eligible for renewal or recompetition. This portfolio analysis was conducted in concert with the ICs and a panel of outside experts.

Approximately 14 percent of the grants assessed were determined to be currently of a lower priority for funding with AIDS-designated dollars than when they were originally funded. These grants, if successfully recompeted, may no longer be funded with AIDS-designated dollars, thus allowing funds to be redirected to higher priority research projects. For example, during the portfolio analysis, a number of grants related to the basic pathogenesis of opportunistic infections were identified as low priority. Several years ago when these grants were awarded, they were aligned with high priority research objectives. However, in the past years, with the success of NIH research and the development of multi-drug antiretroviral regimens, some of these infections are no longer common among HIV-infected individuals. Similarly, some of the low priority grants were in the area of basic research on AIDS-related malignancies, some of which are no longer common in HIV-infected individuals utilizing antiretroviral therapy. In FY 2009, the highest priorities for AIDS research were prevention of acquisition and transmission of HIV, and prevention and treatment of HIV-associated co-morbidities, co-mortalities, and co-infections.

It is important to reiterate that the determination of "low priority for AIDS funding" is not related to the scientific or technical merit of the projects, but only to the focus area relevance within the current AIDS research agenda, as it relates to the changing demographics of the epidemic, scientific advances, and new opportunities. Should the investigator choose to submit a renewal application that is determined to be highly meritorious in the peer review process, the IC may choose to fund the project with money not designated for AIDS research.

BACKGROUND

The NIH represents the largest and most significant public investment in AIDS research in the world. The response to the pandemic requires a unique and complex multi-institute, multi-disciplinary, global research program. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every Institute and Center (IC). The AIDS-related research portfolio includes research relating to HIV infection, co-infections, opportunistic infections, malignancies, and metabolic, cardiovascular and other clinical complications. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds. The Office of AIDS Research (OAR), located within the Office of the Director, coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program.

OAR develops the annual Trans-NIH Plan for HIV-Related Research, in collaboration with the ICs, and with non-government experts from academia, foundations, industry, and community representatives. The Plan and the processes instituted to ensure its implementation allow NIH to pursue a united research front against the global AIDS epidemic. The Plan is used to: 1) frame the development of the NIH AIDS research budget; 2) determine the use of NIH AIDS-designated dollars; 3) define those research areas for which AIDS-designated funds may be allocated; and 4) track and monitor AIDS research expenditures. OAR has supported the AIDS

Research Information System (ARIS), a 15-year old mainframe system to track and monitor AIDS research expenditures.

Rationale

In FY 2006, a critical new element was added to the annual planning and budget development process -- a multi-tiered comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds. This review: 1) established a new model to ensure that AIDS research dollars support the highest priority science; 2) allows OAR to direct the transfer of funds to better manage the AIDS research portfolio; 3) ensures that resources are focused on the highest scientific priorities, taking into account the ever-changing domestic and international AIDS epidemic, as well as the evolving scientific opportunities; and 4) assists in developing the trans-NIH AIDS research budget from the commitment base. The trans-NIH AIDS research budget, developed by OAR, is explicitly tied to the objectives of the strategic plan.

TARGET CONTEXT AND CONDITIONS

The process was designed to review AIDS funded projects with the goal of ensuring that the projects supported with AIDS-designated dollars are devoted to the highest priority areas of AIDS research. The review is intended to identify dollars that can be redirected to higher priority AIDS research projects. Within each scientific coordinating committee (Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science Research) a grant-by-grant review is initiated of all NIH extramural projects supported with AIDS-designated dollars, concentrating on those grants eligible for recompetition in the fiscal year of the strategic plan. Working with relevant IC program staff, grants are identified that are now of lower priority than when they were originally funded. This does not mean that these grants should not have been funded or were not of high priority at the time. However, as the science has evolved, and the priorities of the epidemic have shifted, these areas no longer represent the highest priorities. For example, many grants were awarded to address basic research on then-common opportunistic infections. Over the past few years, with the advent of combination antiretroviral therapy, these infections are no longer common among HIV-infected individuals, and thus now deemed of lower priority for AIDS-designated funding.

Then a small group of eminent non-government scientists is convened to provide expert advice, review each scientific area and all of the grants now deemed of lower priority, and to provide recommendations for redirecting funds to catalyze future initiatives and multi-disciplinary endeavors. The IC is notified when a grant is identified as now too low a priority for future support with AIDS-designated dollars. Each IC has an opportunity to reinvest those dollars in higher priority AIDS programs in their portfolio. For those ICs who cannot identify higher priority projects, those dollars are shifted to other ICs with higher AIDS research priorities needing additional support. The IC may renew the highly-meritorious grants that fall into the low priority category with non-AIDS dollars.

This process has been implemented as a part of the annual trans-NIH strategic planning and budget processes, to enhance NIH's ability to ensure that resources are focused on the highest scientific priorities, taking into account the evolving scientific opportunities to address the domestic and international AIDS epidemic.

Long Term Objective: (CBRR-8) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CBRR-8 By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management. (Output)	*2011*	Ensure that 75% of trainee appointment forms are processed electronically *(Baseline):* (FY10) TBD 0% processed electronically	N/A
	2010	Enhance system usability, capacity, and functionality, and promote use. (*Previous Target*): Ensure that 50% of trainee appointment forms are processed electronically. *(Baseline):* (FY09) 10.9% processed electronically	N/A
	2009	Ensure that 25% of trainee appointment forms are processed electronically. *(Baseline):* (FY08) 5.4% processed electronically.	10.9% of trainee appointment forms were submitted electronically. (Target Not Met but Improved)
	2008	Ensure that 5% of trainee appointment forms are processed electronically. *(Baseline):* (FY07) 0% processed electronically	5.4% of trainee appointment forms were submitted electronically. (Target Met)

Data Source and Validation
xTrain performance results were calculated using reports from NIH's internal IMPAC II information management system. For more information, contact: Research Training Coordinator , Office of Extramural Programs at 301- 435-2686

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to process 25 percent of research training appointments electronically was Not Met, but improved. Over the course of the past year, more than 65 universities used the system, and submitted 535 NRSA research training appointments electronically. Ultimately, electronic research training appointments represented 10.9% percent of the 4,385 FY 2009 research training appointments processed.

As with every new IT system development, xTrain users during the first years of the system's availability experienced a few minor issues and bugs. In order to prepare for an NIH policy change that will require appointment forms to be submitted via xTrain beginning in January 2011, NIH will increase outreach and training in the coming year, while simultaneously working to improve system functionality.

The Extramural Research Training and Research Career Development Program was assessed in FY 2008. The assessment cited a successful program management and appropriate achievement of progress toward the

measure as a strong attribute of the program. As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

The National Institutes of Health (NIH) is dedicated to improving the health of Americans by conducting and funding biomedical research that will help prevent, detect, treat, and reduce the burden of disease and disability. To achieve these goals, NIH supports the preparation of investigators through research training and career development programs, and monitors the size and distribution of the research workforce to ensure that scientists are available in adequate numbers and with appropriate training to address the Nation's biomedical, behavioral, and clinical research needs.

For participants in the NIH's largest research training program – the Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants – training-related information is captured and reported to the NIH annually on paper forms. For participating students and postdoctorates, NIH Institute and Center staff manually enter data from paper appointment and termination forms into the agency's IMPAC II information management system. Capturing data on NRSA trainees this way is a time-consuming process that is susceptible to data entry errors, but is essential for program management and evaluation.

Rationale

As part of its commitment to electronic research administration, NIH has developed a system that will allow NRSA-related data to be directly entered at research training sites and transmitted to the NIH electronically. By 2012, NIH aims to transform the existing, cumbersome NRSA paper process into a streamlined, end-to-end electronic flow of data that will not only increase the efficiency of program administration for NIH and its university partners but also enhance data integrity for program monitoring and assessment.

Through this new system, known as xTrain, research training grant directors can electronically appoint students and postdoctorates to NRSA training grants and report to NIH when their training is complete. Ultimately, xTrain will replace the paper forms that have been used since the beginning of the NRSA program in 1974 and will help NIH Institutes and Centers identify program gaps in a timelier fashion and manage their research training portfolios more effectively.

The annual targets for this goal are designed to allow for its gradual adoption by universities and other research training sites and provide NIH an opportunity to fine-tune the system, as necessary, in response to feedback from its users.

TARGET CONTEXT AND CONDITIONS

After piloting the xTrain system with the 100-plus institutions participating in the Federal Demonstration Partnership through much of FY 2009, NIH opened the system to all institutions registered in the eRA Commons in June of 2009. By the end of FY 2009, over 65 universities had submitted research training appointments through xTrain more than triple the number doing so in FY 2008. Yet despite the substantial growth in institutions using xTrain, the number of appointments submitted electronically fell short of projections in 2009. As a result, NIH expects to announce plans to begin requiring institutions to use xTrain to submit appointments to selected training grants in January 2011. The FY 2010 target has therefore been adjusted to focus 2010 activities to address issues with system usability, functionality, capacity, user training, and outreach. NIH anticipates that it will be back on track to meet the FY 2011 target for processing training appointment forms electronically.

NIH typically phases in new electronic research administration practices and procedures, and the xTrain system will follow the same approach until FY 2012, after which paper appointment and termination forms will no longer be accepted. To facilitate the implementation of xTrain, the system's development is incorporated into the performance plans of the Deputy Director for Extramural Research and the NIH Research Training

Coordinator. Achievement of this goal depends on the continuing commitment and involvement of a sizeable team of staff, including systems analysts and developers, technical writers, grants management specialists, and policy experts.

Long Term Objective: (CBRR-9) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CBRR-9 By 2011, achieve average annual cost savings of managing construction grants by expanding the use of electronic project management tools that enhance oversight and 20 year usage monitoring. (Output)	*2011*	Maintain the process to achieve average annual cost of managing construction grants *(Baseline):* Proposed annual costs: (FY11) $36,813 per grant	N/A
	2010	Achieve average annual cost of managing construction grants *(Baseline):* Proposed annual costs: (FY10) $36,703 per grant	N/A
	2009	Achieve average annual cost of managing construction grants *(Baseline):* Proposed annual costs: (FY09) $36,530 per grant	Achieved an average annual cost of $36,530 per grant. (Target Met)
	2008	Achieve average annual cost of managing construction grants *(Baseline):* Proposed annual costs: (FY08) $36,419 per grant	Achieved average annual cost of $36,419 per grant. (Target Met)
	2007	Achieve average annual cost of managing construction grants *(Baseline):* Proposed annual costs: (FY07) $35,837 per grant	Achieved average annual cost of $35,837 per grant. (Target Met)
	2006	Achieve average annual cost of managing construction grants *(Baseline):* Proposed annual costs: (FY06) $35,643 per grant	Achieved average annual cost of $35,643 per grant. (Target Met)

Data Source and Validation
Data used to calculate cost saving are maintained in either an internal database or total number of labor hours. For more information, please contact the: NCRR Office of Science Policy at 301-435-0864 or the NIAID Office of Strategic Planning and Evaluation at 301-443-9941.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. NIH achieved an average annual cost of $35,530 per grant through the use of electronic project management tools. The Extramural Construction Program was assessed in FY 2008. The assessment cited a successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

The NIH Extramural construction grant program supports construction and renovation projects that facilitate and enhance the conduct of PHS-supported biomedical and behavioral research. Under legislative law, NIH must monitor the scientific use of funded facilities for 20 years post construction completion. Grantees accepting NIH support for construction must agree to use the facility to conduct biomedical and/or behavioral research for the entire 20 years. Although the focus of the research can change, biomedical research must continue to occur throughout the agreed upon years.

By 2012, all extramural construction projects will be completed. Approximately, 200 plus facilities including 15 biocontainment labs will be monitored through a variety of cost efficient strategies. Due to the sensitive nature of the biocontainment facilities, these labs are monitored annually with onsite inspections to ensure safety compliance as well as to confirm scientific research.

NIH's extramural construction program supports the construction of two groups of biocontainment laboratory facilities for biodefense and emerging infectious disease research. The National Biocontainment Laboratories (NBLs) will serve as a national and regional resource for research on biodefense and emerging infectious disease agents that require biosafety Level 2, 3 or 4 (BSL-2/3/4) biocontainment, while the Regional Biocontainment Laboratories (RBLs) will serve as a regional resource for research requiring BSL-2/3 biocontainment. The NBLs and RBLs will complement and support NIH's biodefense and emerging infectious diseases research program, and will be made available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

NIH uses two electronic tools to make the management of its extramural construction program more efficient: Buzzsaw, an internet based project collaboration tool that provides a platform to organize, manage and share information among designated project participants and Webex, an internet based virtual conferencing tool that provides a method for participants to share, view, edit and modify complex electronic files (such as blueprints) and information remotely.

NIH supports research that spans the entire continuum of biomedical research, from basic discovery to patient-oriented research as defined in Section 479 of the Public Health Service Act. The extramural Research Facilities Improvement Program (RFIP), which began in 1994, helps NIH achieve its cross-cutting mission to increase the Nation's capacity to conduct biomedical and behavioral research by building and enhancing a strong research infrastructure as defined in Section 481A of the Public Health Service Act. The NIH construction program provides laboratory scientists and clinical researchers with biomedical facilities and fixed equipment they need to understand, detect, treat, and prevent a wide range of diseases that would be otherwise unavailable or inadequate to conduct the research necessary to advance human health. These grants enable institutions to construct or renovate facilities that contain basic and clinical research laboratory space, improve research imaging capabilities, augment informatics capabilities, and support animal research. Since its inception, this program has supported 340 construction projects in 45 states and Puerto Rico, demonstrating broad and comprehensive geographic distribution to build the Nation's capacity as a whole to conduct biomedical research.

In order to enhance the management of its large and diverse extramural construction program, NIH has developed the Construction Grants Management System (CGMS) database to perform critical data management functions, including tracking when necessary documentation is required.

Rationale

Since the administration of construction grants involves management of complex information and interactions of many partners, electronic management tools offer critically needed data management capability to program managers. Use of electronic tools for the management of extramural construction programs during the pre-construction, construction and post-construction/compliance monitoring stages the projects saves the

government time, money and materials.

The following describes the pre-award, award and post-award requirements that are unique to the NIH extramural construction program and demonstrates the need for a sophisticated electronic system to accurately track and monitor pre-construction, construction and post-award compliance related data and allow for enhanced interaction between project partners.

The additional pre-award requirements, beyond those found in NIH's intramural construction program, are associated with the availability of matching funds, the applicant's compliance with additional public policy requirements and ensuring sufficient title to site. Unless otherwise waived, the NIH must ensure that the applicant has sufficient funds available to meet the matching requirement in order to ensure sufficient funds are available to complete the project. In addition, the applicant must also comply with additional public policy requirements and be able to ensure they have sufficient title to site to ensure an undisturbed use of grant-supported space throughout the usage obligation that is associated with the award.

After award, the awardee must obtain NIH approval of all plans and specifications at each stage of design to ensure the grant-supported space is designed in accordance with NIH Design Policy and Guidelines and Good Laboratory Standards. The proper design of the facility will ensure the safety of NIH grant-supported researchers who will occupy the completed facility. During the design phase, complex documents must be viewed and shared between government managers and the grantees. In addition, at the time construction begins the awardee is also required to file a Notice of Federal Interest (Notice) in the local land records in the jurisdiction in which the property is located. Filing of this Notice results in a lien on the property to ensure that the property will not be: used for any purpose inconsistent with that authorized by the grant program statute, mortgaged or otherwise used as collateral, or sold or transferred to another party without written permission of the NIH. The Notice ensures the Federal interest in the property will not be subordinated to those of non-Federal parties unless a deviation is approved.

Lastly, after construction is complete, the grantee must ensure that the property is protected from physical destruction and that they are using the grant-supported space for its intended purpose throughout the usage obligation. Therefore, immediately upon completion of the construction project, a grantee is required to provide a certification that the property is adequately insured against physical destruction or provide a certification that the grantee is self-insured against the risks involved. This requirement safeguards the government's investment in case of natural disaster or other eventuality. In addition, the authorization and/or appropriation language for construction grant programs requires construction grant recipients to use the grant-supported space for the research purposes for which the space was built for a 20 year period after completion of construction. In order to ensure the grantee's compliance with the usage obligation and to protect the NIH's interest in grant-supported property, NIH monitors this usage in a variety of ways, including periodic facility use certifications or reports, site visits, or other appropriate means for the duration of the required usage period.

To better monitor all phases of the construction projects, track the large number of documents associated with each project and facilitate communication among the grantees and NIH staff, NIH uses the Buzzsaw and Webex electronic tools mentioned above, and NIH has developed the Construction Grants Management System (CGMS) database to track and notify NIH staff when necessary documentation is required.

TARGET CONTEXT AND CONDITIONS

NIH efficiently manages its extramural construction program with use of two electronic tools: Buzzsaw, an internet based project collaboration tool and Webex, an internet based virtual conferencing tool. These electronic tools decrease the amount of travel needed in order for NIH staff to manage grants. These tools also save on costly shipping charges by allowing groups to view, review and mark up documents such as blueprints remotely, limiting the need to ship documents.

NIH uses the Construction Grants Management System (CGMS) to better monitor grantees compliance with the requirements of the extramural construction awards. The CGMS was created as a tool for grants management staff and program staff to enhance their governance of public funds. To increase its efficiency and accuracy, the CGMS automatically downloads relevant data from the NIH IMPAC system. The CGMS also automatically determines which construction phase (pre-award, award-design, award-construction and post-award) a project is in based on reported or outstanding data thus, improving the monitoring efficiency of the program. Alerts and notifications are automatically sent via email to appropriate NIH staff informing them that self-certifications and other program documentation are due.

Long Term Objective: (CBRR-10) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CBRR-10 By 2013, make freely available to researchers the results of 300 high-throughput biological assays screened against a library of 300,000 unique compounds, and the detailed information on the molecular probes that are developed through that screening process. (Outcome)	*2011*	Increase depositions of bioassays in PubChem to a rate of five (5) per month. *(Baseline):* PubChem bioassay depositions are at rate of three (3) per month.	N/A
	2010	Establish 35 new assays in the Molecular Libraries Program (MLP) Portfolio *(Baseline):* (FY09) 100 assays exist currently in the Molecular Libraries Program (MLP)Portfolio.	N/A
	2009	Establish repository of 300,000 compounds *(Baseline):* (FY07) Repository of 145,000 compounds currently exists	The Molecular Libraries Small Molecule Repository (MLSMR) contains 341,830 unique compounds, (Target Exceeded)

Data Source and Validation
NIH Roadmap Molecular Libraries Small Molecule Repository: http://mli nih.gov/mli/compound-repository/ N Singh, R Guha, MAGiulianotti, C Pinilla, RA Houghten, JL Medina-Franco, Chemoinformatic analysis of combinatorial libraries, drugs, natural products, and Molecular Libraries Small Molecule Repository, J. Chem. Inf. Model. 49, 1010–1024, 2009 http://pubs.acs.org/doi/pdf/10.1021/ci800426u

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met and Exceeded. The Molecular Libraries Small Molecule Repository (MLSMR) added almost 200,000 compounds, for a total of 341,830 unique compounds, exceeding the target of 300,000 compounds.

The MLSMR is designed to acquire, manage, store and distribute the compounds that are screened by the centers funded through the Molecular Libraries Program (MLP). To build the collection, it purchases compounds from companies and receives novel compounds from the laboratories of investigators funded through both initiatives within the MLP and other NIH programs. The shared collection allows annotation of one "library" of compounds, with the goal of enhancing the utility of the data collected by the centers. The compounds undergo quality control at the repository and are distributed to the centers for screening. Screening centers are expected to deposit novel compounds to the library, increasing the diversity of the collection.

Compounds in the MLSMR collection are grouped into five categories with the percent of compounds in each.

1. Non-commercial compounds (NC), mainly from academic labs (4.5%)
2. Natural products (NP) and derivatives from known and documented natural sources (0.5%)
3. Specialty sets (SS), comprising known bioactives such as drugs, toxins, metabolites, and others (1.0%)
4. Targeted libraries (TL) containing specified categories of compounds (3.0%)
5. Diversity compounds (DC), that is, a diverse set that complements the first three categories and

provides a broad coverage of biological space (91.0%)

Efficiency

Compound acquisition for the MLSMR exceeded the target due to a lower than anticipated quality control failure rate. Compound selected for inclusion in the MLSMR must meet the high quality standards set for the collection. In the past, only approximately 77% of compounds met or exceeded these standards. As the MLSMR has established relationships with compound suppliers, both commercial and academic, compounds submitted to the collection have been of a higher quality, with approximately 85% meeting or exceeding standards. The higher rate of acceptance has allowed the MLSMR to grow more rapidly, and the larger collection increases the probability of identifying hits in high throughput screens performed within the Molecular Libraries Probe Production Network.

BACKGROUND

Many of the critical biochemical processes that regulate health and disease are mediated by proteins. While the functions of some of these proteins are well understood, the majority remain obscure. Two powerful methods for determining the function of a protein are 1) to increase or inhibit its function and 2) to detect its presence under controlled circumstances. Both of these methods rely on small molecules (probes) that bind selectively to the protein of interest. Access to a broad spectrum of small molecules that bind to proteins of interest could accelerate the understanding of the biochemical processes that cause disease.

A tremendous opportunity to expand the number of probes available to public sector biomedical laboratories has become possible due to three major advances in biomedical research. First, the human genome project revealed there may be up to a million human proteins. Second, the use of robotics and other advanced technology now allows the testing of thousands of chemicals in a single laboratory. Third, powerful computer-based information retrieval systems allow the storage and sharing of complex information. These three areas of research have converged to provide an opportunity to expand the number of probes available to decipher protein function.

Rationale

To date, most information about potentially useful small molecules has been generated by the private sector in the search for new drugs. As a result, this information is proprietary and access to these molecules and their associated data is restricted. Moreover, the private sector focuses its attention on proteins known to be causal to common diseases. Therefore, it has limited interest in many other critical proteins whose functions are yet to be defined and/or are important in rare and orphan diseases. Thus, it has little incentive to develop small molecules that bind to these proteins, limiting the knowledge base of chemical compounds that could be useful for deciphering protein function. As a result, many important proteins remain enigmatic due to the lack of small molecule probes.

The NIH Roadmap is a set of initiatives designed to rapidly advance biomedical research through new approaches to science that are transforming. As part of the NIH Roadmap theme, Pathways to Discovery, the Molecular Libraries Program (MLP) was intended to revolutionize biomedical research by making a multitude of new probes available to the public sector researchers.

TARGET CONTEXT AND CONDITIONS

This innovative program is expected to provide a scientific resource that will accelerate the discovery of protein functions that control critical processes such as development, aging and disease. The MLP is expected to have a very high impact by facilitating the understanding of basic biological mechanisms, identifying new biological targets for evaluation in disease models, and shortening the timeline for ligand and tool discovery. To facilitate the use of small molecules in public sector biomedical research laboratories, three hurdles have to be overcome. First, there must be an increase in the number of small molecules known to bind to proteins of

interest. Second, information about these probes must be freely available to the research community. Third, the small molecules must be stored and distributed appropriately. The MLP was designed to overcome these hurdles by generating and providing open access to information about the structure and biological activity of small molecules that bind to proteins of interest or alter cellular processes.

The major MLP initiative is the establishment of research centers charged with identifying potent new small molecules. These centers use advanced technology to screen thousands of small molecules for their ability to activate or inhibit protein activity or cellular processes of interest. All of the information derived from these screens is being deposited in a new public database, PubChem. Another critical aspect of the MLP is a new repository to gather, validate, store, and distribute a unique and diverse collection of small molecules. The goal described here is to further develop this new national network into a stable research resource for the discovery and development of novel molecular probes that will lead to new ways to explore the functions of proteins and signaling pathways important in health and disease.

The MLP funded ten screening centers in FY2008. Some of the centers are comprehensive centers that , in addition to screening compounds, modify the structures of candidate probes to discover the most potent and selective probes. The comprehensive centers are expected to rapidly screen hundreds of thousands of compounds in each of dozens of assays per year. Other centers will specialize in complex screens such as those involving cellular processes, whole organisms, and/or in modifying chemical structures to make more effective probes. Together, these centers will produce a diverse set of probes that can be used by many scientists to investigate proteins, signaling pathways, and cellular processes in their field of interest.
The number and diversity of the candidate probes will be increased by collecting compounds from many sources, both industrial and academic. Enhanced quality control measures will be put in place so that the quality of the compounds is increased.

The goal depends on the development of a sufficient number of high quality, high throughput assays against targets of importance in biomedical research.

Long Term Objective: (CBRR-11) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
CBRR-11 (RA) By 2010, determine the number of shared instrumentation grants awarded that will contribute to the success of many NIH-funded research projects. (Output)	*2010*	350 shared instrumentation grants awarded with sample shared usage. *(Baseline):* 350 RA SIG Awards	N/A
	2009	84 shared instrumentation grants awarded with sample shared usage. *(Baseline):* 84 RA SIG Awards	Eighty-four (84) shared instrumentation grant awards were made to domestic public and nonprofit institutions. (Target Met)

Data Source and Validation
All of the information on the grant awards are located in the NIH research Portfolio Online reporting Tool (RePORT) at http://RePORT nih.gov.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 Recovery Act (RA) target to award 84 shared instrumentation grants with sample shared usage was Met. Eighty-four shared instrumentation grant awards were made to domestic public and nonprofit institutions. Types of instruments supported include magnetic resonance systems, confocal microscopes, mass spectrometers, and protein x-ray crystallography systems. It is anticipated that these awards will stimulate the economy and in turn create or maintain jobs in America.

BACKGROUND

The Shared Instrumentation Grant (SIG) program provides a cost-effective funding mechanism for groups of NIH-supported investigators to obtain or update commercially available, technologically sophisticated equipment.

Instrumentation purchased with a SIG award must be shared by at least three NIH-supported scientists. This arrangement optimizes the use of federal funds. To promote sharing by a number of investigators and to foster collaborations, SIG-supported instruments are typically located in central core facilities that provide technical expertise and user education.

Rapid technological development has led to the production of a new generation of advanced instruments. As the capabilities of these high-sensitivity, high-resolution instruments increases, so does their cost. To meet the investigators needs for this advanced technology, in FY 2002, NIH began the High-End Instrumentation (HEI) grant program, which allows institutions to acquire expensive equipment. The HEI grant program complements the Shared Instrumentation Grant program.

The SIG/HEI Programs are designed to enable researchers to purchase or update expensive shared-use instrumentation not generally supported through other NIH mechanisms, such as the standard research project, program project, or center grant programs.

Rationale

The objectives of the Recovery Act Shared Instrumentation program align with the existing Shared Instrumentation program, which is to facilitate state of the art biomedical research through support for advanced instrumentation and technologies that enable better images, diagnostics, data analysis, and improved

discovery tools. Innovative biomedical research requires access to the newest and most advanced technologies and instrumentation. It is expected that these awards will stimulate the economy and in turn create or maintain jobs in America.

TARGET CONTEXT AND CONDITIONS

Eligible recipients include 1) Public/State Controlled Institution of Higher Education; 2) Private Institution of Higher Education; and 3) Nonprofit with or without 501(c)(3) IRS Status (Other than Institution of Higher Education).

Awards are made to public and non-profit domestic institutions only, including health professional schools, other academic institutions, hospitals, health departments, and research organizations.

Institutions submit grant applications which are selected using NIH's standard, competitive, peer-reviewed process – a two level review process. Briefly, the first level of review for scientific and technical merit is conducted by expert peer review study sections convened by the NIH and comprised of external reviewers. The second level of review is conducted by the NIH. The final decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to the NIH program priorities, the national geographic distribution of awards, and the priorities specified in the Recovery Act, such as energy efficiency and job creation.

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 team building, 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 employees tools needed 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.

Long Term Objective: (SMHC-4) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
SMHC-4 Ensure NIH reports tracked commercial functions and cost savings from completed commercial services studies efficiently and on time. (Ongoing) (Efficiency) (Output)	*2011*	Complete FAIR Act Inventory and Post-Competition Accountability reporting. *(Baseline):* FAIR Act Inventory and Post Competition Accountability data is reviewed and reported annually.	N/A
	2010	Complete FAIR Act Inventory and Post-Competition Accountability reporting. *(Baseline):* FAIR Act Inventory and Post Competition Accountability data is reviewed and reported annually.	N/A
	2009	Complete negotiated competitive sourcing reviews annually. *(Baseline):* Functional areas identified as appropriate for review	Due to language in the Omnibus Appropriations Bill (H.R. 1105) prohibiting any competition that could result in outsourcing, target will not be met. (Target Not Met)
	2008	(Target 1) Identify annually commercial activities for competitive sourcing comparison. *(Baseline):* Preplanning initiated for identifying functional areas	Three functional areas were identified for reviews and announced for competitions. (Target Met)
	2008	(Target 2) Complete negotiated competitive sourcing reviews annually. *(Baseline):* Functional areas identified as appropriate for review	The five studies under three functional areas identified for review were announced for competition in FY 2008. (Target Met)
	2007	(Target 1) Identify annually commercial activities for competitive sourcing comparison. *(Baseline):* Preplanning initiated for identifying functional areas	Identified two potential functional areas for review. Both were deemed appropriate for streamlined reviews with a Most Efficient Organization (MEO). (Target Met)
	2007	(Target 2) Complete negotiated competitive sourcing reviews annually. *(Baseline):* Functional areas identified as appropriate for review	Two functional areas that were identified for reviews were announced for competition. (Target Met)

Measure	FY	Target	Result
	2006	(Target 1) Identify annually commercial activities for competitive sourcing comparison. *(Baseline):* Preplanning initiated for identifying functional areas	Identified 4 potential functional areas for review, all 4 were deemed appropriate for streamlined reviews. (Target Met)
	2006	(Target 2) Complete negotiated competitive sourcing reviews annually. *(Baseline):* Functional areas identified as appropriate for review	Four functional areas identified for reviews were announced for competition. (Target Met)

Data Source and Validation
Contact: Director, Office of Competitive Sourcing Office: HHS/OS/ASAM Phone: 202-690-5803

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to complete negotiated competitive sourcing reviews annually, was Not Met. Language in the Omnibus Appropriations Bill (H.R. 1105) prohibits any competition that could result in outsourcing. HHS interprets the Bill to indicate there will be no new studies or re-competitions of previously reviewed functional areas that resulted in a Most Efficient Organization (MEO) completing their final period of performance. Therefore, NIH will have no reviews or competitions in 2009. NIH is currently working on transitional activities for MEOs that are extending or expiring after the final period of performance. These activities are being developed to minimize disruption to the NIH workforce and to provide an appropriate clost-out of the A-76 process for the functional areas that were competed. NIH continues to focus on FAIR Act Inventory reporting and post-competition accountability requirements.

BACKGROUND

The purpose of competitive sourcing or A-76, is to implement the OMB Circular A-76 (Revised May 2004). The intent of competitive sourcing is to determine the most cost effective method for procuring commercial services for the Federal Government from either public or private sector sources. Due to recent OMB language within the Omnibus Appropriations Bill, Agencies have been directed to discontinue competitive sourcing reviews until further guidance. It further states Agencies are required to continue with the FAIR Act Inventory and post-competition reporting. NIH has revised our goal to reflect the current guidance.

To assess the commercial activities performed by the federal workforce, the Federal Activities Inventory Reform (FAIR) Act of 1998 (P. L. 105-270), requires Federal agencies to prepare and submit to OMB, by June 30th of each year, inventories of commercial activities performed by all Federal employees. This inventory is a list of all Federal Employees who are assigned a specified code identifying the type of work they perform to help identify the work being performed within the government. OMB guidance also requires Agencies to identify if the work being performed is commercial in nature or inherently governmental. By annually reviewing and revising complete workforce inventories, agencies are able to consider what functions could be considered for competitive review.

In support of the HHS objectives, NIH began identifying commercial activities for competitive sourcing reviews in FY 2002. The OMB A-76 Circular provides policies and procedures for conducting public-private competitions and post competition accountability. As of 2009, NIH has performed 38 reviews, retaining 37

functions in-house. Upon implementation of the competition decision, each study must complete post-competition accountability reporting requirements. Agencies are required to submit quarterly and annual reports on completed studies to ensure performance within cost ceilings and quality standards.

NIH has used all tools at its disposal to retrain, counsel, and place affected employees within NIH, HHS, other federal agencies or alternate employers. Use of Voluntary Early Retirement Authority (VERA) and Voluntary Separation Incentive Payments (VSIP) helped to reduce the number of affected employees.

Rationale

The DHHS views competitive sourcing as a method to "achieve excellence in management services and thereby improve overall Department management," (goal number 8 in the DHHS strategic plan). Commercial Services Management is designed to provide transparency, fairness and integrity into public-private competitions, encourage competition in the management and performance of commercial activities, and empower Federal managers to make sound and justifiable business decisions. Implementation of Commercial Services Management improves the Department's efficiency, thus enabling DHHS to more effectively deliver health and human services.

TARGET CONTEXT AND CONDITIONS

NIH continues to carry out objectives as directed by OMB and the DHHS Office of Commercial Services Management. To accomplish this task, NIH submits annual FAIR Act Inventory reports and cost savings reports to Congress. Submitting these reports satisfies this commercial service requirement. Due to the Appropriations Bill language that prevents competitions, NIH is only completing the annual reports as required. The FAIR Act Inventory will continue as stated by law. The cost savings reports will continue until the completion of the final period of performance for each commercial study reviewed. This measure will be discontinued if this target continues to remain in maintenance mode.

The following is a summary of NIH MEO awards through 2008:

Year	Reviews	Awards Retained	Areas of Streamlined Review
2004	9	8	• IT Telecommunications • NIEHS Logistics • Clinical Center Materials Management • Freight Forwarding • RML Logistics • RML Visual and Medical Arts • IT Help Desk • IT Data Center
2005	11	3	• IT systems administration • Food services • Patient care unit clerk
2006	4	4	• EEO Administrative Support • Clinical Center Administrative Support • IT Network Support • IT End User Support/Technical Writers
2007	2	2	• IT Systems Development • IT Administrative Support
2008	5	5	• HR Administrative Support • HR Strategic Programs Divisions • HR Classification and Recruitment • Equal Employment Opportunity and Diversity Management Program • Facilities Services

Long Term Objective: (SMHC-5) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
SMHC-5 By 2011, improve and monitor the use of human resource services by providing real-time access to tools via the NIH portal. (Efficiency) (Output)	*2011*	Establish future Portal technology, determine move or maintenance plan, and continuously monitor satisfaction and usage of human resources content for NIH-wide distribution against the established baseline. *(Baseline):* Quality management plan established.	N/A
	2010	Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline. *(Baseline):* Quality management plan established.	N/A
	2009	Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline. *(Baseline):* Quality management plan established.	Conducted usability testing with HR and non-HR IC users. Monitored ratification by implementing changes to the information architecture and consolidated Portal from six down to two communities for ease of use. (Target Met)
	2008	Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline. *(Baseline):* Quality management plan established.	Implemented a corrective strategies plan to improve usability and the quality of HR information. Consulted with Content Managers as well as Administrative Officers and HR staff to improve the HR content on the NIH Portal. (Target Met)
	2007	Implement corrective strategies with subject matter experts and customers. *(Baseline):* (FY 06) A plan for corrective strategies to improve usability and quality of HR information has been established.	Implemented a corrective strategies plan to improve usability and the quality of HR information. Consulted with Content Managers as well as Administrative Officers and HR staff to improve the HR content on the NIH Portal. (Target Met)
	2006	(Target 3) Establish baselines for the HR critical elements to monitor over time. *(Baseline):* (FY05) HR critical elements and tools identified.	Baselines were established for the HR critical elements: freshness of human resources information; relevance of human resources information to the NIH audience; and usability of the HR tools. (Target Met)

Measure	FY	Target	Result
	2006	(Target 4) Develop plan for corrective strategies to improve usability and the quality of HR information. *(Baseline):* (FY05) HR Community established.	A Corrective Strategies Plan was developed to address improved usability and quality of HR information. (Target Met)

Data Source and Validation
HR Community Map (showing HR Communities & Pages) - http://hr.od nih.gov/HRSystems/Portal/map htm HR Portal User Guides - http://hr.od nih.gov/HRSystems/hrssuserguides.htm#portal

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline was Met.

- Meetings with Content Managers from throughout the NIH Office of Human Resources (OHR) were held quarterly to gather feedback from these Content Manager to improve the presentation and usability of the HR information presented to NIH employees.
- Feedback from the "Community Leader" portlet on the HR Community was monitored for any technical difficulties as well as for any suggested improvements to the HR Community. All technical difficulties were resolved and suggested improvements were reviewed by the Web/Portal Team.

Highlights for continuously monitoring satisfaction and usage of human resources content on the NIH Portal against the established baselines in FY09 included:

- HR Professionals Community - http://hr.od.nih.gov/hrintranet/hrprofcommunity.htm
  - Consolidated 10 OHR projects into one OHR Knowledge Directory.
  - Consolidated Portal from 6 down to 2 communities for ease of use
- Human Resources (HR) Community - http://hr.od.nih.gov/hrintranet/hrcommunity.htm
  - Revised "Who are my HR Contacts" to create more usable interfaces for both NIH and OHR staff
    - Admin/Manager Page - http://hr.od.nih.gov/hrintranet/admincommunity.htm.
  - Improved Recruitment information for managers and highlighted new HR systems including the HR Classification and Recruitment Documents System
- Interns and Fellows Community was eliminated due to non-usage but continued to support an online collaboration space through several projects.
- HR Metrics Community pages were moved within the HR Professionals community to facilitate the distribution of important internal OHR information.
- 508 Compliance. Continued the process of making all OHR information and content 508-compliant. 508 compliance means making our information available to individuals with disabilities who use screen readers or other technology to read and access our information. In FY2009, we revised and archived an additional 450 OHR documents.

BACKGROUND

The NIH Portal is the next generation intranet for the NIH community. The NIH Portal serves as a launch pad for enterprise systems and access to information that pertains to the NIH mission. The NIH Portal has been

integrated with a Single-Sign-On (SSO) solution so that NIH HR applications that are SSO-enabled can be launched from the NIH Portal. The Portal uses approximately 100 “portlets” to launch or interact with enterprise systems such as ITAS, HRIBS and the NIH Delegations database. The NIH Portal employs a document directory to organize documents, regardless of source, into a logical topic-based taxonomy. And finally, the community space on the Portal is available for different groups of employees such as the intramural research community or the travel community to collaborate and share information.

By presenting human resources information on the NIH Portal, OHR is providing HR content in a current and flexible design that can easily be repurposed for addressing specific audiences as well as being available to the NIH community for populating on users own MyPage of content relevant to individual needs. Instead of relying on static websites, OHR is providing interactive portlets, a launch pad to applications that are Single-Sign-On (SSO) enabled, and up-to-date content from reliable sources to the audience and presenting it n several formats. Making the HR Community of the NIH Portal available to the NIH community will give users one-one-stop shopping for relevant HR information, resources and systems.

Rationale

The HR community and other users of HR resources have often expressed frustration when trying to find current, relevant HR information. The Human Resources community and HR content on the NIH Portal is constantly drawing new content for a variety of sources and removing dead links and adding new content to the appropriate subject area. Additionally the portal technology will allow for the repurposing of content so that specific audiences can be addressed – NIH Employees, Administrative/Managerial community and HR Professionals. This allows those audiences to receive information tailored to each individual's needs without becoming an oppressive content management burden.

TARGET CONTEXT AND CONDITIONS

Beginning in 2002, CIT worked with NIH focus groups to develop a logical taxonomy and identify documents and applications to be accessed through the NIH Portal. OHR helped identify human resources documents and applications that should be included on the NIH Portal. Dozens of HR and HR-related applications were made accessible through the NIH Portal and over 10,000 HR documents were reviewed from over 20 websites. The relevance, currency and appropriate placement of the applications were considered in determining which ones would be accessible through the Portal. Duplicates and obsolete versions were discarded and the remaining 4,000 to 5,000 documents were categorized in the document directory.

In 2003, OHR assumed management of its own content and committed to launching all new HR systems through the NIH Portal. In 2004, the Strategic Programs Division (SPD), OHR began maintaining these documents by 'crawlers,' which automatically check target websites for new or revised information. If changes are detected, the new or revised document is automatically crawled to the Portal. The same is true for deleted documents. If a document has been deleted from its host website, the crawler will automatically remove it from the Portal. The SPD Web/Portal Team merely reviews new documents and approves them before they are published to the document directory. OHR has 112 crawlers that check designated sites nightly.

NIH achieved Target 1 which was to develop an HR Community on the NIH Portal. This has become the primary site for NIH HR information, systems and resources. The target to identify HR critical elements and tools to monitor use and quality of the HR information was also realized. In FY 2005, SPD launched the HR Community area of the NIH Portal, trained users on accessing the Portal and the Community, marketed the Community's availability, and eliminated where feasible and appropriate, access to HR systems, information and resources through means other than the Portal.

Also in FY05, SPD established the HR critical elements and identified methods to measure the elements. For example, assuming usage of the HR Community site is one of the critical elements, SPD worked with CIT to determine methods to greater quantify and define usage as distinct hits on the HR Community site. SPD can

subsequently demonstrate the increased usage (expressed as percentage of the NIH population) of the HR Community area by measuring the number of HR documents and systems available on the HR Community and the number of people accessing HR systems available only through the HR Community.

In FY06, SPD established baselines of the previously defined HR critical elements through the use of the Analytics Server which measure usage of the HR Community and HR tools and information on the NIH Portal. SPD also developed a corrective strategies plan to improve the usability and quality of HR information on the HR Community on the NIH Portal.

In FY07, new pages were added to the HR Community in 2007, for HR Professionals, Career Development and Training, Clinical Center Employees, Senior Executives Services (SES) Members, Administrators/Managers, Title 5 Compensation, Title 42 at NIH, HR Calendar, HHS Careers for HR, USAJOBS, and Alphabetical HR Search. These corrective strategies were implemented to improve usability and quality of HR information.

SPD began to monitor the success of the corrective strategies plan compared to the established baselines. The monitoring will be continued into FY10 and FY11 as SPD continues to monitor satisfaction and usage of human resources content on the NIH Portal.

The HR Portal has proven to be a useful resource for the NIH community. The data below shows the number of hits, visits, and unique users that accessed the HR Community Portal.

Human Resources Community (Audience NIH Community)

	1st Q FY09 October – December 2008	2nd Q FY09 January – March 2009	3rd Q FY09 April – June 2009	4th Q FY09 July – September 2009
Hits	25,819	26,861	24,054	22,443
Visits	19,672	20,261	18,495	16,634
Users	3,310	3,479	3,202	3,118

HR Professionals Community (Audience OHR Staff)

	1st Q FY09 October – December 2008	2nd Q FY09 January – March 2009	3rd Q FY09 April – June 2009	4th Q FY09 July – September 2009
Hits	16,934	18,253	18,015	19,140
Visits	11,587	12,157	11,895	12,120
Users	590	567	548	603

Improvements and integration activities are ongoing and maintained. In FY10, HR Systems, Analytics and Information Division (SAID), formerly SPD, will begin evaluating new portal technology platform options such as SharePoint. For FY11, HR SAID may be moving to a new portal platform because the NIH Portal is no longer being maintained by CIT at the level that is necessary for NIH-wide collaboration and information sharing.

Long Term Objective: (SMHC-6) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
SMHC-6 Provide opportunities for enhanced leadership skills to meet the challenges of workforce management and/or individual advancements. (Ongoing) (Output)	*2011*	Examine [EX] key area to enhance leadership skills * Study best practices in executive on-boarding to determine if there are better ways to orient new executives to NIH. [IM.2012]	N/A
	2011	Implement [IM] recommendation from prior year assessments * Create and implement a leadership development program for new supervisors and individual performers preparing for supervisory roles. [EX.2010/AS.2012]	N/A
	2011	Assess [AS] results of implementation * Assess results from the leadership development program to prepare high potential leaders for top 5 positions. [IM.2010]	N/A
	2010	Examine [EX] key area to enhance leadership skills * Conduct studies of leadership training to develop NIH leaders with a focus on moving people from individual performer into supervisory roles and enhancing skills for new supervisors.[IM.2011]	N/A
	2010	Implement [IM] recommendation from prior year assessments * Create and implement a leadership development program to prepare high potential leaders for top 5 positions. [EX.2009/AS.2011]	N/A

Measure	FY	Target	Result
	2009	Examine [EX] key area to enhance leadership skills * Conduct studies of leadership competencies, and other programs to develop NIH leaders. --1) Benchmark other scientific agencies and organizations to determine best practices in leadership development. --2) Leadership development to fill future vacancies in top 5 positions. [IM.2010]	30 senior leaders from NIH visited other scientific organizations known for leadership development in the public, private, and academic sector to determine best practices for leadership development in order to create benchmarks. These benchmarks set principles and best practices for leadership development to fill Top 5 vacancies. (Target Exceeded)

Data Source and Validation
For source validation information, please contact: Office: NIH Training Center, Workforce Support and Development Division, OHR, OM, OD at 301-443-7135

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met Efficiently. In FY09, an examination was made of leadership development needs at NIH. It was determined that retirement eligibility for people in "Top 5" positions make likely a significant drain of talent in the coming years. Top 5 leadership positions eligible to retire within three years includes:

- 67% - IC Directors
- 63% - IC Deputy Directors
- 71% - Scientific Directors
- 65%-Scientific Executives
- 48%-Executive Officers

In response, 30 senior NIH leaders made "best practices" visits to organizations (federal, academic, and private) that are known for doing leadership development well in a scientific setting. These included:

- Duke University Health System
- Federal Aviation Administration
- Johns Hopkins Medicine
- Johnson & Johnson, Inc.
- Memorial Sloan Kettering Cancer Center
- National Aeronautics and Space Administration
- University of Texas Southwestern Medical Center

Participating leaders debriefed the lessons learned and agreed upon a set of guiding principles and a set of best practices for NIH leadership development. It was also agreed that the top priority for leadership development programs was building someone to prepare high potential managers for Top 5 positions. An "Executive Development Advisory Committee" was formed to advise the NIH Training Center in building a program. The group also decided that future efforts would focus on programs for first-level supervisors and a formal orientation for new NIH executives hired from outside of the organization.

Including senior leaders in the benchmarking process was valuable both for their insight and for allowing them to see the results of effective programs in scientific environments. It helped the scientific leaders understand the importance of a focus on leadership development.

The agreed guiding principles are:

1. The NIH is committed to developing leaders at all levels.
2. Leadership development at the NIH takes place through both formal programs and developmental experiences.
3. Diversity among participants is critical in developing the strongest possible pool of future NIH leadership.
4. Development efforts will be linked to the NIH competencies and proficiencies.
5. NIH leadership development initiatives will incorporate relevant, current best practices.
6. Leaders are held accountable for their own development and the development of others.
7. Leaders are held accountable for both results and the way in which they are achieved.

These guiding principles are used to help NIH focus leadership development efforts, both in development of formal programs and in guiding discussions of building a culture of leadership development at NIH. They are not intended to fill vacancies, just to give principles around leadership development activities.

Efficiency

The FY 2009 examination of leadership development need and application of "best practice" lessons learned for the "Top 5" positions was completed early.

BACKGROUND

As the steward of medical and behavioral research for the Nation, one of NIH's keys to success lies in its people. For that reason, NIH strives to make management improvements in human capital a priority. With the ultimate goal of having a leadership cadre that can execute the agency's mission, NIH leaders and managers will collaborate to assess leadership needs and programs and develop strategies for the development and improvement of leadership competencies. As federal employees become eligible for retirement within the next few years, leadership development will be important to retaining knowledge and having available leadership talent ready to fill critical NIH leadership roles. Leadership development demands a level of strategic planning to predict and meet the needs of the NIH for a trained workforce.

Rationale

NIH values employees as a necessary organizational asset, and strives to provide the employees tools needed to succeed. NIH aims to identify and develop potential successors for mission critical and key leadership roles, which are important to science and research. As a result of a recent NIH-wide Human Capital Planning Initiative, NIH identified the creation and implementation of a leadership development program as key issues to focus on. This will ensure that the NIH has the right resources to continue to fulfill its mission, and is able to sustain operations as leadership talent retire or depart the NIH for other opportunities, or is no longer able to perform responsibilities. Appropriate leadership development is essential to the NIH to meet the continued challenges of workforce management.

TARGET CONTEXT AND CONDITIONS

The NIH plans to develop a framework to link training and leadership development to NIH mission, goals and objectives. The framework will help NIH manage leadership continuity in key positions, retain and develop intellectual and knowledge capital for the future, and encourage individual advancement. An assessment to facilitate the design, development and implementation of the framework is a first step. NIH will apply the results of the assessment, to identify the critical areas where leadership development is needed. NIH will update training policies and develop training and development plans to support the programs, mission, goals and objectives.

An ongoing process to determine the leadership competencies will be established as an initial step towards NIH leadership competency development. To carry out the process, NIH will interview leaders and form oversight

committees and outreach strategies. NIH will apply the results of the assessment to identify core competencies that are applicable across NIH, as well as specific competencies for the separate communities. This process is important to determining NIH's leadership competency demands.

The phases of NIH leadership development include: examining, implementing, and assessing key areas:

- Examine: The process of examining key area to enhance leadership skills. Studies are conducted to examine leadership competencies and discover other programs to improve the NIH leadership development program.
- Implement: Developing an implementation plan to act on the recommended leadership competencies and other programs.
- Assess: Ongoing process of assessing results of implemented plans

Long Term Objective: (SMHC-7) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
SMHC-7 Address diverse workforce recruitment needs to ascertain highly qualified staff to conduct or support biomedical research. (Ongoing) (Output)	*2011*	Examine [EX] key area to enhance recruitment * No new key areas to date	N/A
	2011	Implement [IM] recommendation from prior year assessments * Implement the incorporated new position descriptions for variety of disciplines [EX.2010/AS.2012]	N/A
	2011	Assess [AS] results of implementation * Results from NIH recruitment brand, reengineering communication plan and global recruitment strategies [IM. 2010]	N/A
	2010	Examine [EX] key area to enhance recruitment * Incorporate useful varied disciplined position descriptions into the position description library. [IM.2011]	N/A
	2010	Implement [IM] recommendation from prior year assessments * Implement NIH recruitment brand, reengineering communication plan/strategy, and standard operating procedure to improve hiring efficiency through global recruitment strategies and sharing of certificates [EX.2009 /AS.2011]	N/A
	2009	Examine [EX] key area to enhance recruitment * Develop an NIH recruitment brand, create a reengineering communication plan/strategy, and establish a standard operating procedure to improve hiring efficiency through global recruitment strategies and sharing of certificates. [IM.2010]	Developed a standard operating procedure (SOP) for Shared Certificates, prepared recommendations paper to pilot Global Recruitment, drafted a communication plan, and developed an NIH recruitment brand. (Target Exceeded)

Data Source and Validation
For source validation information, please contact: Client Services Division/OHR/OD at 301-425-3423

SUMMARY OF 2009 PERFORMANCE RESULTS

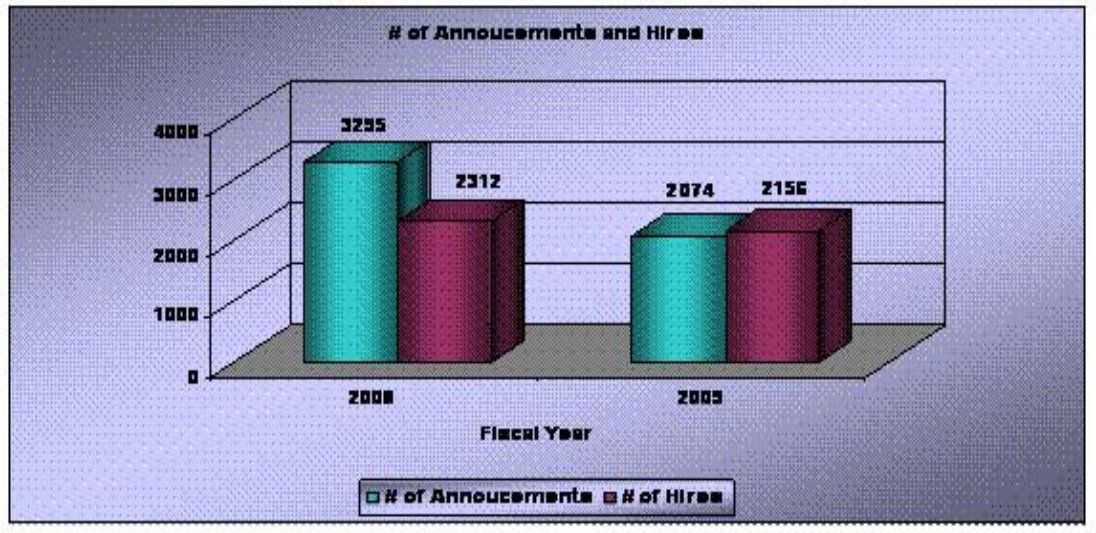
Target

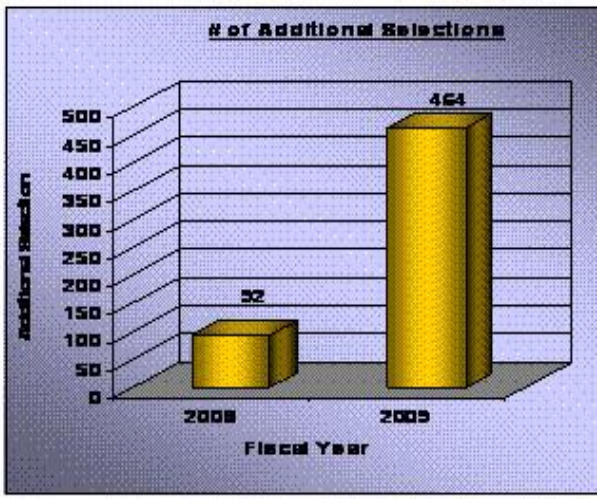
The FY 2009 target to develop an NIH recruitment brand, create a reengineering communication plan/strategy, and establish a standard operating procedure to improve hiring efficiency through global recruitment strategies and sharing of certificates has been MET Efficiently.

NIH developed a brand identity for recruitment, "Discover a Career at NIH: It's About Life". NIH then implemented the brand identity through a series online and print avenues including recruitment advertisements in prominent scientific journals and websites, transportation signs and recruiting materials for distribution at career fairs. Implementation of the brand also includes the upgrade of the OHR Jobs website which is ongoing. Reengineering groups also developed an OHR Communications plan which recommends an approach for OHR to improve communications with OHR's many customers, including hiring managers, NIH employees and potential candidates for employment. Reengineering groups for FY09 included the Global Recruitment/Shared Certificates and the Communication and Branding group. Sharing a Certificate means sharing the resumes and corresponding responses of candidates with other NIH Institutes and Centers who might be interested in recruiting for similar vacancies. This process was adopted to promote efficiency in the hiring process and contributed to the decrease in the number of announcements, increase in shared certificates, and increase in the number of additional selections, from FY08 to FY09. Recommendations for global recruitment and a Standard Operating Procedure (SOP) for shared certificates was drafted for review and comment by leadership. Global recruitment was piloted for Recovery Act positions for Program Analyst, HSAs, and Grants Management Specialists.

Advances or Other Highlights

Improvement in Hiring is summarized in the following slides:





Business Process Reengineering Results:
1. Number of Announcements decreased by 37% from FY08 to FY09
2. Number of Shared Certificates increased by 138% from FY08 to FY09
3. Number of Additional Selections increased by 504% from FY08 to FY09

Efficiency
The FY 2009 examination of key areas to enhance recruitment was completed ahead of schedule.

BACKGROUND

As the steward of medical and behavioral research for the Nation, one of NIH's keys to success lies in its people. For that reason, NIH strives to make management improvements in human capital a priority. NIH will work to develop and implement recruitment strategies to attract and hire talent consistent with the agency's mission priorities and diversity goals. By identifying early signs of potential recruitment challenges and talent availability, NIH hopes to address anticipated future staffing needs.

Rationale
NIH is committed to creating and sustaining a trained and motivated workforce to carry out its mission. NIH has taken steps to improve human capital management through appropriate staff recruitment. Improving recruitment and staffing has been identified as a key strategy for addressing human capital challenges. This activity is essential to the NIH and will be ongoing. Both the short-term and long-term recruitment goals will make provisions for recruitment of mission critical and key occupations within the NIH. The recruitment framework will support a flexible program to be implemented based on the NIH mission, structure and culture.

TARGET CONTEXT AND CONDITIONS

The NIH plans to conduct an agency-wide assessment that addresses recruitment issues in order to project short and long-term staffing needs. In order to succeed, NIH must recruit diverse or varied talent in the scientific research and medical and administrative occupations. Upon the assessment, NIH will identify the critical areas where no successor is identified in order to implement a deliberate and systematic effort to ensure continuity in key positions at all levels. Subsequently, NIH will identify areas with potential recruitment challenges, and then propose a strategic plan to meet the needs of the NIH for a trained and capable workforce.

As a first step, NIH will review and re-engineer the hiring process in order to enhance efficiency and effectiveness, and most importantly, to provide greater support for the scientific mission. NIH will examine hiring processes that are currently in use to form a starting point. Recommendations will include the OPM 45-day benchmark to aim for improved hiring practices. Specifically, the reviews of the existing processes will be

conducted for hiring of Title 5, 42(f) and 42(g) positions. Improvements will be measured incrementally as NIH's hiring improvements work towards the 45-day goal. Data will also be collected from outside agencies to serve as benchmarks for NIH.

The phases of the recruitment effort include: examining, implementing, and accessing key areas:

- Examine: The process of examining key areas to enhance efficiency and effectiveness in the recruitment process.
- Implement: Developing an implementation plan to act on the recommended recruitment activity.
- Assess: Ongoing process of assessing results of implemented plans.

Long Term Objective: (SMHC-8) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
SMHC-8 Address areas to facilitate retention of highly qualified staff to conduct or support biomedical research. (Ongoing) (Output)	*2011*	Examine [EX] key area to enhance retention * No new key areas to date	N/A
	2011	Implement [IM] recommendation from prior year assessments * Implement program to monitor telework participation [EX.2010/AS.2012]	N/A
	2011	Assess [AS] results of implementation * Results from telework communication plan implementation.[IM.2010]	N/A
	2010	Examine [EX] key area to enhance retention * Study teleworking participation [IM.2011]	N/A
	2010	Implement [IM] recommendation from prior year assessments * Implement Telework Communications Plan [EX.2009/AS.2011]	N/A
	2009	Examine [EX] key area to enhance retention * Increase knowledge about teleworking by developing a communication plan [IM.2010]	Developed an NIH telework communication plan to relay the benefits of telework for recruiting and retaining valuable highly qualified staff. (Target Met)

Data Source and Validation
NIH Telework Program Communication Strategy Overview For source validation information, please contact: NIH / OD/OM/OHR/OD/ADAM at 301.496.2288 or 301-402-7227

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to increase knowledge about teleporting by developing a communication plan was Met. An NIH telework program communications strategy was developed that uses existing resources more efficiently and effectively to promote telework, with the intent of increasing the number of program participants. The draft communications plan outlines the following goals and objectives:

- To clearly communicate the advantages and benefits of teleworking to all employees;
- To communicate the resources available through the NIH Telework Program and the value these can provide to NIH Institutes and Centers (ICs) seeking to enhance internal programs; and

- To enhance understanding of the NIH Telework policy among the program users.

The plan also lays out the proposed strategies and suggested activities for the Telework Program. Success will be measured with the annual survey that is submitted to the Office of Personnel Management at the end of the calendar year.

BACKGROUND

As the steward of medical and behavioral research for the Nation, one of NIH's keys to success lies in its people. For that reason, NIH strives to make management improvements in human capital a top priority. With the ultimate goal of retaining a talented and diverse workforce, NIH continues to review methods and policies to improve NIH as an employer of choice in this competitive and dynamic marketplace.

Rationale

NIH understands that building a premier biomedical research organization does not end with recruitment of key talent. Integrating new employees into the NIH's professional and social culture is also critical to the short and long-term success of employees and, ultimately to accomplishing the mission of the NIH. Retaining the appropriate employee for the right job is vital in warding off loss of an experienced, trained, capable employee. Talent retention is also driven by an NIH strategic approach that assesses the likely turnover in key positions to minimize the impact of turnover. It will also give early warning of any skills shortages or likely difficulties in finding suitable replacement candidates for key positions in the near and short terms. NIH understands that a strategic retention plan must include meaningful work assignments, the opportunity to utilize skills and knowledge, opportunities for increased responsibility, work that truly makes a difference, recognition for performance, and a people-oriented work culture; all factors that keep employees engaged and committed. The NIH also plans on considering future workforce needs by assessing the gaps and identifying available talent ready to fill where needed.

TARGET CONTEXT AND CONDITIONS

The NIH is working to develop means of helping managers address employee retention through management and employee partnership relationships and loyalty strategies in order to retain employee talent. NIH plans on reviewing methods and policies to improve NIH as an employer of choice. These methods will be ongoing to ensure mission accomplishment, and ensure the development of intellectual capital for the future.

Retention was identified as an area in the OPM Federal Human Capital Survey that needs to be addressed as a variant by NIH. This area is currently under review and will be identified by mid 2008.

The phases of the employee retention management activity include: examining, implementing, and accessing key areas:

- Examine: The process of examining key areas to enhance employee retention activities.
- Implement: Developing an implementation plan to act on the recommended retention program.
- Assess: Ongoing process of assessing results of implemented plans.

PROGRAM OVERSIGHT AND IMPROVEMENT

NIH takes responsibility as a steward of Federal funds seriously. Exercising careful oversight is key to demonstrating good stewardship. In addition, NIH strives to continually improve oversight procedures, policies, and systems when needed 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 'One HHS' management objectives are focusing NIH's 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, and linkage of employee performance contracts with organizational objectives.

Long Term Objective: (POI-2) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-2 Utilize performance-based contracting (PBC). (ongoing) (Output)	*2011*	Obligate the FY 2011 OMB/OFPP goal of eligible service contracting dollars to PBC. *(Baseline):* FY11 OMB/OFPP goal: TBD	N/A
	2010	Obligate the FY 2010 OMB/OFPP goals of eligible service contracting dollars to PBC *(Baseline):* FY10 OMB/OFPP goal is 47%.	N/A
	2009	Obligate the FY2009 OMB/OFPP goal of eligible service contracting dollars to PBC *(Baseline):* FY09 OMB/OFPP goal: 45%	Obligated 52% of eligible service contracting dollars through performance-based contracting. (Target Exceeded)
	2008	Obligate the FY 2008 OMB/OFPP goal of eligible service contracting dollars to PBC. *(Baseline):* FY08 OMB/OFPP goal: 43%	Obligated 43% of eligible service contracting dollars through performance-based contracting. (Target Met)
	2007	Obligate the FY 2007 OMB/OFPP goal of eligible service contracting dollars to PBC. *(Baseline):* FY07 OMB/OFPP goal: 42%	The FY07 target to obligate OMB/OFPP goal of 42% of eligible service contracting dollars to PBC was not achieved. 38% of the eligible service contracting was obligated. (Target Not Met)
	2006	Obligate FY 2006 OMB/OFPP Goal of eligible service contracting dollars through PBC. *(Baseline):* FY06 OMB/OFPP goal: 40%	Obligated 55% of the total eligible service contracting dollars through performance-based contracting. (Target Met)

Data Source and Validation
Obligations to PBC eligible service contracts are reported in DCIS. The obligations are reported throughout the fiscal year as monies were committed to various contracts throughout NIH. For source validation information, please contact: Division of Acquisition Policy and Evaluation OAMP/OA/OM/OD at 301-496-6014

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to obligate OMB/OFPP goal of 45% eligible service contracting dollars through performance-based contracting was Met and Exceeded. Fifty-two percent (52%) of the total eligible service contracting dollars was obligated to PBC service contracts. This information was reported in the Departmental Contract Information System (DCIS). These obligations were reported throughout the fiscal year as funds were committed to various contracts throughout NIH.

Advances or Other Highlights

PBC activity is tracked monthly through reports of funding activity obtained from the DCIS. Training opportunities continue to be offered to the acquisition and program community to ensure that they are properly trained in the use of PBC. Information about Government and industry sponsored events focused on PBC is regularly disseminated.

Efficiency

The 2009 expectation of 45% was far exceeded and lead to the goal being achieved efficiently at 52%. Contributing factors for the efficient included conducting presentations to each of the NIH Offices of Acquisition. In addition, a PBC Subcommittee was established to provide individual representation for each of the Offices of Acquisition to reemphasis the requirement for meeting the established goal.

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 government-wide memorandum requires that all Federal agencies use Performance Based Contracting (PBC) methods, where practicable, and match acquisition and contract administration strategies with specific requirements.

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.

NIH is committed to increasing the amount of NIH contracts that are PBC. As new contract requirements and contract renewals arise, NIH will review each situation to determine whether using PBC is appropriate. Generally, the types of contracts that can be competed as PBC are services oriented contracts such as maintenance, guard services, operational support, transportation and janitorial services. In addition to these routine services, the concept has been used for clinical center trial management resources, clearinghouse support and event management services.

Rationale

As cited in the Procurement Executives Council's Strategic Plan, over the next five years, a majority of the service contracts offered throughout the federal government will be performance-based. In other words, rather than micromanaging the details of how contractors operate, the government must set the standards, set the results and give the contractor the freedom to achieve it in the best way. As a means of maximizing agencies' endorsement of PBC, annual targets were established. The strong endorsement of PBC stems from the Government's emphasis on managing for results: by linking payments to results rather than to effort or process. PBC provides NIH with useful indicators of contactor performance and allows vendors to be innovative in responding to requirements for specific products and services.

TARGET CONTEXT AND CONDITIONS

The NIH strategy to utilize PBC incorporates three basic elements: 1) promoting the value of PBC in acquisition and contract administration/management planning; 2) ensuring that PBC planning takes place on individual requirements and contracts; and 3) making certain that NIH acquisition staff is properly trained and aware of guidance on PBC.

Under the Office of Acquisition Management and Policy's (OAMP) leadership, the acquisition and project officer community have attended training sessions promoting PBC. By fostering and facilitating these sessions as well as disseminating information about Government and industry sponsored events focused on PBC, the NIH has raised awareness and improved the organization's ability to apply PBC methods to requirements.

To ensure that PBC planning occurs, the OAMP/Division of Acquisition Policy and Evaluation (DAPE) stresses the implementation of PBC as required by the Federal Acquisition Regulation (FAR). Through publications such as the Seven Steps to Performance-Based Services Acquisition Guide, the acquisition community is reminded of the importance for considering PBC during the acquisition-planning phase. In addition, the Head of the Contracting Activity reviews solicitations submitted for Board of Contract Award reviews thereby providing the necessary oversight regarding the applicability of PBC.

As stated previously, PBC training opportunities continue to be offered to the acquisition and project officer community. In addition, consultant support has been identified to assist both contracting and project officers on their individual requirements. This effort has increased the familiarization of the community to PBC and eased the transition from traditional contracting methods to performance based contracting methods.

The monitoring of PBC activity is accomplished by the submission of monthly reports from the contracting offices and through reports of PBC funding activity from the Departmental Contract Information System (DCIS). For non-performance based contracts, the NIH uses the DCIS to collect contract related data and monitor performance. NIH institutes and centers contracting offices are being reminded of the Government-wide move toward increased use of PBC and that PBC. Contracting staff will be continually reminded that the FAR requires that contracting officers include in their acquisition plans for service contracts or orders, a description of the strategies they will use for implementing performance-based contracting methods, or provide a rationale for not using these methods. The planned strategy for performance-based contracting is to meet the targets set annually.

Long Term Objective: (POI-5) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-5 By FY 2010, enhance NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems. (Output)	*2010*	Complete goal of enhancing NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems. *(Baseline):* FY05-10 results	N/A
	2009	Transition to electronic post award processes by requiring e-mail notice of grant awards and mandating use of electronic closeout modules. *(Baseline):* Electronic post award processing not required	All grant award notices are transmitted electronically. Among closeout modules, FSR must be submitted electronically. FIS & FPR are also submitted electronically, with the exception of a very small number of FPRs in excess of 6 MB size threshold. (Target Met)
	2008	(Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY08) Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users. *(Baseline):* Prior to FY 04 all research grants has only one Principal Investigator	Project to extend multi-PI support capability throughout the grants management life cycle (from application receipt through grant closeout) completed on schedule in June. (Target Met)
	2008	(Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY08) Refine Electronic Submission of Research Grant Applications to maximize efficiency of the process for applicants. *(Baseline):* (FY04) Paper grant applications currently received.	Reduced the correction window from 5 days to 2 days effective 1/08, allowing applications to be assigned to review groups more quickly. (Target Met)

Measure	FY	Target	Result
	2008	(Target 4) Better balance workload associated with incoming grant applications while providing additional time for newer researchers to prepare grant applications (FY 2008 accomplished) (FY08) – Implement changes to standing application receipt dates *(Baseline):* (FY07) Peak receipt dates involving up to 8,000 applications.	Receipt dates realigned in spring & fall of 2007 with NOT-OD-07-001, NOT-OD-07-053, and NOT-OD-07-083. (Target Met)
	2007	(Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY07) - Accept applications that include information on more than one PI. *(Baseline):* Prior to FY 04 all research grants has only one Principal Investigator	NIH issued a new policy allowing the use of multiple investigators for most types of research grants. Over 1,500 multiple principal investigator applications have been accepted since the policy has been in effect. (Target Exceeded)
	2007	(Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY07) Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements. *(Baseline):* (FY04) Paper grant applications currently received.	An expanded pilot of 424-R&R dataset conducted using live data yielded the receipt of 37,000 applications electronically. (Target Exceeded)
	2006	(Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. *(Baseline):* In FY 2004, all research grants had only one Principal Investigator	The data structure of the system was modified to maintain data for multiple Principal Investigators (PIs) for a single application and grant in the spring of 2006. Both paper and electronic applications involving multiple PIs were received and processed by NIH. (Target Met)

Measure	FY	Target	Result
	2006	(Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY06) Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. *(Baseline):* Paper grant applications currently received.	NIH required electronic submission of applications through Grants.gov on the new form set for 19 research programs. Over 13,000 applications were accepted and processed electronically in FY06. (Target Met)
	2006	(Target 3) Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished) (FY06) ' Expand NIHMS system capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions. *(Baseline):* (FY 04) No mechanism exists to receive manuscripts	Receiving third party manuscript uploads met 12/05; Linking submissions met 2/06. (Target Met)

Data Source and Validation
The primary data sources used to evaluate this target are the IMPAC2 databse transaction records. Contact: Acting Director, Division of Communications and Outreach at 301-435-0937

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to transition to electronic post award processes by requiring e-mail notice of awards and mandating use of electronic closeout modules has been largely Met, with the caveats noted below.

All grant award notices are transmitted via e-mail, as required. Thus, the first part of this performance target has been achieved.

Performance with respect to the second component of the target is more nuanced. Grant closeout modules consist of the Financial Status Report (FSR), the Final Invention Statement (FIS), and the Final Progress Report (FPR). All three reports have been available in electronic format for several years. The FSR must be submitted electronically. Although electronic submission has not yet been mandated, almost all FISs and FPRs are voluntarily submitted electronically, given the relative convenience and cost advantages associated with electronic submittal. Due to data storage constraints still operative, electronic FPRs in excess of 6 megabytes cannot be accepted, resulting in submission of paper copies of the largest progress reports.

BACKGROUND

Over the next several years NIH will continue its efforts to enhance its ability to demonstrate benefits resulting from extramural research investments. The specific steps contributing to the achievement of this goal involve capturing information electronically that will allow NIH to better track and characterize the scientific workforce and its research portfolio in order to better inform NIH's program planning process.

There are four related areas under this measure:

- Permitting and collecting information on more than one Principal Investigator (PI) on a research grant by implementing policy and information systems that support multiple-PIs.
- Capturing standardized information digitally on electronically submitted grant applications using a new interagency grant application dataset, the Standard Form 424 [Research and Research Related (R&R)].
- Enhance public access to NIH-sponsored research findings through implementation of policy changes and electronic systems.
- Balancing workload associated with incoming grant applications while providing additional time for newer researchers to prepare grant applications.

Rationale

On average, the NIH expects to receive and process more than 60,000 grant applications each year. It is important to understand the nature of the science being funded, how that science addresses the health-needs of the nation, the community that conducts that research, and the outcome of that research. An enterprise of this magnitude needs to develop automated ways to produce the data needed to make decisions and establish priorities on a global basis, as well as by individual projects or programs. The policy changes NIH is making in this regard, in combination with the newly developed information technology, will support this goal.

TARGET CONTEXT AND CONDITIONS

At this time, planned approaches involve the following activities.

Multiple Principal Investigators: The scale and complexity of biomedical research problems increasingly require collaborative teams of scientists that frequently combine the disciplines of the physical, biological and social sciences. This approach is specifically encouraged by the NIH Roadmap Initiative called Research Teams of the Future. A critical part of this involves the recognition of all key contributors on NIH projects. Accordingly, the NIH now permits more than one PI on an NIH funded research project. This change in policy not only encourages the development of interdisciplinary approaches, it allows the NIH to recognize and acknowledge the contribution of all PIs. The White House Office of Science and Technology Policy issued a directive to all federal agencies on January 4, 2005 to begin planning to allow and recognize more than one PI. As implemented by NIH, it is now possible for more than one PI to share the responsibility for a research grant. Grant applications identify all PIs involved with a particular project. All the PIs are listed on the notice of grant award and in reports related to that particular grant. Adapting to multiple PIs required redesigning grant applications, the structure of the administrative database, and data entry modules used to process those applications and awards at all points in the grant cycle.

Research and Related Dataset: NIH is transitioning from paper submission of the PHS 398 grant application form to electronic submission of the SF424(R&R) data set through Grants.gov. The SF424 R&R dataset comprises application data elements and instructions that will be used by all Federal Agencies involved in Research and Related (R&R) grant funding. This common data set is intended to replace the data collection instruments (applications) currently maintained by each research agency, with the goal of creating a consistent application for research grant support to be used to apply for Federal research funding. Making this transition to a new application form and electronic submission requires NIH and the research community to reevaluate and make changes to policies and procedures involving the entire life cycle of the grant process, work closely with all Federal research agencies, establish aggressive communications campaigns, as well as undertake substantial information systems development. NIH has transitioned many of its research programs to require

electronic submission on the new form set in FY 06, well ahead of its original schedule. As of the end of FY 08, NIH has transitioned 83% of grant applications from a paper-based submission process to electronic submission though Grants.gov. This reflects 100% of NIH's grant programs that Grants.gov can currently accommodate. NIH will continue to work with Grants.gov to develop forms and systems to allow additional grant programs to move to electronic submission.

Public Access to Information on NIH-Sponsored Research: The NIH is using information technology systems within the NIH Commons and the National Library of Medicine's (NLM) PubMed Central (PMC) to archive publications resulting from NIH-funded research. The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central within a year of publication. This policy applies to all research grant and career development award mechanisms, cooperative agreements, contracts, Institutional and Individual Ruth L. Kirschstein National Research Service Awards, as well as NIH intramural research studies. The policy is intended to: 1) create a stable archive of peer-reviewed research publications resulting from NIH-funded research to ensure the permanent preservation of these vital published research findings; 2) secure a searchable compendium of these peer-reviewed research publications that NIH and its awardees can use to manage more efficiently and to understand better their research portfolios, monitor scientific productivity, and ultimately, help set research priorities; and 3) make published results of NIH-funded research more readily accessible to the public, health care providers, educators, and scientists.

By storing research publications from diverse sources in a searchable, electronic archive with a common format, PMC facilitates greater integration with related resources in other NLM databases, thus providing the opportunity to develop unprecedented scientific search and analysis capabilities for the benefit of science. This searchable archive will enable NIH program officials to manage their research portfolios more efficiently, monitor scientific productivity, and ultimately, help set research priorities. This strategy also will enable NIH to advance its goal of creating an end-to-end, paperless grants management process. Finally, it will make the publications of NIH-funded research more accessible to and searchable for the public, health care providers, educators, and scientists.

Changing Standard Application Receipt Dates: The transition to electronic application submission has heightened NIH's awareness of challenges posed by having very large numbers of incoming grant applications on any single day. NIH currently spreads the workload involved with receiving incoming grant applications through three annual council rounds that include multiple submission dates for each round. However, some of NIH's standing receipt dates currently allow up to eight thousand applications to come in for a single receipt date. This volume causes bottlenecks in a number of critical places: Grants.gov and eRA systems, where response time may slow under heavy volume; the Grants.gov and NIH help desks, which have to handle large spikes in call volume; the CSR Division of Receipt and Referral, which is responsible for referral of incoming applications in a timely way; and the research administration office at the applicant institution, which must now submit all applications. In addition, the principal investigator currently rushes to submit an application that sits waiting to get to the Scientific Review Administrator (SRA) while we process thousands of others. Spreading receipt dates to achieve a steady flow of applications rather than "boom and bust" cycles will allow many different groups to have a realistic approach to staffing that should minimize the need for either costly overtime or the use of less experienced part-time staff, while maximizing electronic system responsiveness. It also achieves another very important goal of providing additional time for less experienced researchers to work on their applications. Implementation of new standing receipt dates was completed in FY08.

Long Term Objective: (POI-6.1) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-6.1 Improve facility conditions in order to reach and maintain a Condition Index (CI) weighted average of 85 or above (CIwa≥85). (Ongoing) (Efficiency) (Output)	*2011*	CIwa = 76.1 (Tentative)	N/A
	2010	(2010 RA) Improve CIwa by an additional 2.2 points through Recovery Act projects	N/A
	2010	CIwa = 73.6	N/A
	2009	(2009 RA) Improve CIwa by an additional 0.6 points through Recovery Act projects	Recovery Act projects improved the CIwa by 0.3 points. (Target Not Met)
	2009	CIwa = 73.9	The condition of the portfolio (Not including RA program) reached CIwa of 73.8 in FY09. (Target Not Met)
	2008	CIwa = 85	The condition of the portfolio reached CIwa of 73.4 in FY08. (Target Not Met)
	2007	CIwa = 85	The condition of the portfolio reached CIwa of 72 in FY07. (Target Not Met)
	2006	CIwa = 85	The condition of the portfolio was maintained so that at least the average CI was 85. (Target Met)

Data Source and Validation
To obtain the summary report of the ARCHIBUS for the National Institutes of Health please contact: Program Manager, Strategic Initiatives Programs, Office of Research Facilities, Division of Technical Resources 301-496-5078

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

American Recovery and Reinvestment Act (RA) Projects:

The 2009 Recovery Act (RA) target to improve the CIwa by 0.6 points was Not Met. RA projects increased the CIwa by 0.3 points to achieve an average CIwa of 74.1 in 2009. This variance from the established target was the result of not factoring the effect of facility assessments that could potentially be completed, before the end of the fiscal year, into the condition index analyses. Absent the decrease in CI due to the larger than projected BMAR increases for the assessed buildings, the NIH CIwa would have been 0.8 higher, or 74.9, and the target would have been exceeded by 0.4.

Building and Facilities (B&F) Projects:

The 2009 performance target to maintain the condition of the portfolio to the average CIwa of 73.9 was NOT MET. NIH achieved an average CIwa of 73.8 in 2009. This represented a 0.4 increase in the facility condition compared to FY2008, or 0.1 decrease from the expected FY2009 CI. The CI improvements supported by B&F projects, fell slightly short of the targeted goals. This was attributed to not factoring the effect of facility assessments that could potentially be completed before the end of the fiscal year into the condition index

analyses. The additional facility assessments completed for Buildings 1, 4, 5, 6A, 8, 12A, 12B, 29, 29A, 37, 38, 38A, 40, 41, 45, 49, 50, 61, 61A, and 64 in 2009 resulted in slight increases in the BMAR for the buildings, including $38.5M more than expected and a corresponding decrease of 0.8 in the CI of the facilities portfolio. If the condition index analysis was calculated completely, the average CI in 2009 would have been 74.6, exceeding the target by 0.7. Thus, the targets are revised

The 2007 assessment of the Building & Facilities program cited successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. Therefore, the program continues ensuring significant progress towards the achievement of its annual objectives.

Advances or Other Highlights

NIH continued use of a Repair and Improvements Board (R&IB) consisting of cross-organization subject matter experts to review and prioritize repair and improvements program requirements to help ensure maximum utilization of resources and the best possible return on investments to improve the condition of its facilities portfolio. This management initiative supports both the continuing improvement of quality of the information in the facility assessment database as well as the improved accuracy of future year CI target goal projections and actuals.

BACKGROUND

NIH Buildings and Facilities (B&F) planning, design and construction program provide facilities to support the current and emerging requirements of NIH. The program includes planning activities and project delivery to create, expand and sustain a robust, modern and safe physical infrastructure for the conduct of basic and clinical research. The program seeks to strike a balance between future infrastructure needs of research across a broad spectrum of diseases and emergent health threats, and the need for responsible stewardship over federally owned real property assets to maximize facility investments and to reduce the potential risks of deferred maintenance. Deferred Maintenance (DM) compromises the life safety and health of the occupants and the public served in NIH facilities. The results of DM may prevent the facility from meeting all or part of its stated mission, impact the accreditation to conduct bio-medical research aimed at finding cures for the world's diseases, and reduce the intrinsic and market value of real estate assets.

Facility Condition Index (FCI) is an industry best practice for assessing and measuring the state of an individual building or an entire facilities portfolio using engineering tools to objectively analyze and quantify deferred maintenance and non-compliance with recognized building codes, guidelines and applicable standards. The FCI is defined as the ratio of the cost of deferred maintenance to the capital replacement value of a facility or portfolio of facilities. Condition Index (CI) is a related measure which converts the FCI, which is a fraction, to a whole number from 0 to 100.

FCI = (DM/RC), where DM = deferred maintenance and RC = replacement cost in current dollars; CI = 1 - (DM/RC) x100

NIH uses the weighted average of its facility condition index (CIwa) as a long the term measure of how it is providing good stewardship over its capital facility assets. The measure focuses on maintaining a weighted average CI at not less than 85 for the entire portfolio annually. A value of 85 means the facilities on average are in relatively good condition.

Rationale

NIH must ensure the capability and reliability of its facilities to support and sustain its biomedical research mission. Tools to objectively evaluate and measure the state of real property assets, and plan, budget, and monitor capital maintenance and repair programs are key to a successful program.

TARGET CONTEXT AND CONDITIONS

The R&I Program is an essential component of the NIH Buildings and Facilities Program to support, sustain and improve the CI of facilities in response to mission requirements. The key to managing NIH assets is the implementation and continued enhancement of an effective Facility Assessment Program. To enhance the accuracy of the condition of the facilities in NIH's portfolio, facility condition assessments are performed on a five -year cycle to identify and prioritize the necessary short and long-term maintenance and repair requirements. These initiatives provide the ability to forecast and prioritize the replacement of major building components and ensure optimal allocation of resources. Monitoring in-between planned reviews is performed to assess facility performance and condition. As better information is made available, modifications are made to the corresponding CI data. Lessons-learned from the past assessments and input from Subject Matter Experts was used to improve the methodology for review and assignment of CIs.

In 2002, NIH adopted a facility condition assessment protocol to manage, determine the condition of, and identify the magnitude of deferred maintenance its real estate assets and estimate deferred maintenance based on actual identified deficiencies. Surveys of the Research Triangle Park, North Carolina, and Hamilton, Montana campuses were completed in 2003. The FCI baseline was completed in 2004 when the detailed evaluative survey that underpins the facility assessment program was completed for the Bethesda, Poolesville, and Frederick, Maryland campuses. Another round of assessments began in 2007 to survey mission critical and other facilities on the Bethesda, Maryland, Poolesville, Maryland, Hamilton, Montana, and North Carolina campuses. To provide responsible stewardship, the following is done:

- Update the facility condition assessment data (continuous)
- Use facility condition data provided by building managers, engineers and trades personnel (continuous)
- Modify prior year's capital repair plan to reflect actual funds appropriated (yearly)
- Execute projects included in the funded plan (continuously)
- Develop next year's annual capital repair plan based on the facility condition data, the work funded and completed in prior years, and other criteria that optimizes the use of available capital repair funds in pursuit of short and long-term goals. (yearly)

Through this assessment process and lessons-learned during the maintenance and repair of building systems, NIH senior management enhances available knowledge of the condition of facilities and systems, the ability to prioritize repairs, and to request adequate funding to improve the condition of the NIH portfolio.

NIH's Condition Index goal is to maintain the condition of the portfolio so the average CIwa = 85* by 2017. The original CI targets were established based on 2004 CI data and expected funding streams. Since that time, the accuracy of the CI data has been reviewed and improved to better reflect current conditions. This process improvement effectively lowered the aggregate CI of the portfolio. Chiefly, the CI for the Clinical Center Complex (Building 10) was lowered from a CI of 80 to a CI of 20. However, a study is currently under way in Clinical Center Complex to correct the CI based on recent planning studies that included survey work which will produce a significant change. However, since the comparison study isn't finalized, the change is not reflected in this year's number.

An effective governance structure has been implemented to ensure that facility deficiencies are packaged into manageable projects. NIH has changed the facility condition assessment process to improve the incorporation of existing study results. NIH engages subject matter experts (maintenance staff, facility managers, and engineers and architects knowledgeable about the facilities) in the Facility Condition Assessment review and documentation process to improve the accuracy of the database. This is a continuous evaluation process which has several components that involve both in-house and consultant experts. For example, one part of the process is the integration of planning and engineering studies for Building 10 into the deficiency database. This study has not advanced enough to date to be reflected in this year's calculation, but when completed, is expected to have a significant impact on CI. Another example is the review of Facility Replacement Values (FRVs) which is also underway and when complete will be incorporated into an update of portfolio data, with an

accompanying impact on building condition indices. To further enhance the impact on improving the CI of NIH facilities portfolio, the paradigm used to score and prioritize projects to be implemented is continually re-evaluated based on lessons-learned.

Recovery Act funds allocated for NIH Buildings and Facilities Program are supporting this measure. Therefore, Recovery Act specific annual target(s) have been developed for this measure and are identified by the acronym RA.

The NIH ARRA Buildings and Facilities program consists of 15 high-priority repair, construction and improvement projects which will: enhance the capability of NIH to perform biomedical research by providing additional research space; improve NIH facility energy efficiency to reduce operating costs; improve infrastructure condition to support existing scientific research programs; and create jobs for the local and national economies. NIH's ARRA projects will result in an additional improvement in the CI of NIH's overall facilities portfolio beyond previously planned activities. After project identification has been completed, NIH prepares and posts pre-solicitation announcements, completes final scope of work, and conducts additional design work in some cases to incorporate sustainability features to meet ARRA requirements. The NIH post solicitations for an appropriate period of time – usually 30 days, and accepts and reviews proposals. After completing technical analysis of the best value proposals and oral discussions with offerors, a final proposal is approved, and the contract for construction can be awarded. NIH will not reflect the CI impact on our buildings of a specific ARRA project until the project is actually awarded for construction. This is because the chief practical role of the Condition Index is to indicate to planners the amount of funds which should be expended for repairs, and to which buildings these funds should be directed. In this context, the construction contract award is the point at which the CI improvement represented by the project is assured and should be taken into account in subsequent decision making (barring an extremely rare project termination, in which case there is a manual adjustment).

Long Term Objective: (POI-6.2) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-6.2 By 2017, maintain the annual condition of buildings and facilities portfolio so that no less than 95% of occupied gross square feet (GSF) will have a CI greater than 65. (Ongoing) (Efficiency) (Output)	*2011*	Target = 69.4%	N/A
	2010	Target = 69.3%	N/A
	2009	Target = 73.8% *(Baseline):* (FY08) 71.3%	The FY09 target of 73.8% of occupied GSF was not achieved. Only 69.3% of the occupied space reached a CI > 65. (Target Not Met)
	2008	Target = 91.5% *(Baseline):* (FY07) 67.5%	The FY08 target of or 91.5% of occupied GSF was not achieved. Only 71.3% of the occupied space reached a CI > 65. (Target Not Met)
	2007	Target = 90.0% *(Baseline):* (FY06) 91%	The FY07 target of 90% of occupied GSF was not achieved Only 67.5% of the occupied space reached a CI > 65. (Target Not Met)
	2006	Target = 88.5% *(Baseline):* (FY05) 87.0%	The FY06 target of 88.5% occupied GSF was met and exceeded by 2.5%. 91% occupied space (GSF) had a CI greater than 65. (Target Exceeded)

Data Source and Validation
To obtain the summary report of the ARCHIBUS for the National Institutes of Health please contact: Program Manager, Strategic Initiatives Programs, Office of Research Facilities, Division of Technical Resources 301- 496-5078

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The 2009 target to ensure that not less than 73.8% of occupied gross square feet (GSF) will have a Condition Index (CI) greater than 65 was Not Met. In 2009, 69.3% of NIH square footage reached a CI > 65. This represented a 2% CI decrease from reported FY2008 accomplishments and a 4.5% variance compared to 2009 projections.

For a large portfolio of buildings such as NIH's, consisting of over 200 owned assets, the projections of changes in how much square footage will be above a CI of 65 are affected by multiple and cumulative factors such as: changes in which projects are actually funded, CI changes stemming from completed facility assessments, the addition or removal of assets from the inventory, and building area adjustments based on resurveys or other refinements. While the cumulative effect of such factors at the end of 2009 resulted in the variance of 4.5%, NIH is closer to meeting the goal than the data indicates. Specifically: for Buildings 13 and 6, the CI will be raised to above 65 in the next portfolio data submission due to accomplishments completed by November 2009 but not included in the final FY2009 facilities data submission; this will increase by 2.4% the amount of NIH square footage having a CI of 65 or above. Buildings 38 and NIHAC T01 together had $2M in

requirements identified that were not funded. In addition, a number of such projects were not funded due to the redirection of available R&I dollars to emergent requirements such as a series of floods that occurred in January, 2009. The repairs in buildings 38 and NIHAC T01, if implemented, would have resulted in a 1.7% increase in the amount of NIH square footage having a CI of 65 or above. Combined, the above two effects total 4.1% (2.4% + 1.7%). In addition, Recovery Act (RA) project support for Buildings 3 and 16A, planned for award in 2009, will not be awarded until 2010, increasing by 0.4% the amount of NIH square footage having a CI of 65 or above. Thus the combined effect of progress made but not reported at the end of FY2009, repairs identified but not funded, and factors which will be reportable next quarter, accounts for a 4.5% variance in the percentage of square footage having a CI above 65. In consideration of these factors, the 2010 and 2011 targets have been adjusted.

The Building & Facilities Program was assessed in 2007. The assessment cited successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. Therefore, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

This Buildings and Facilities (B&F) measure sets the minimum quality level for NIH buildings and facilities increases each year. This is measured as the percent of gross square feet (GSF) within the portfolio with a Condition Index (CI) value above 65. Detail information on the NIH facilities Condition Index (CI) can be found in the *GPRA Performance Measure: POI-6.1, Improve facility conditions in order to reach and maintain a Condition Index (CI) weighted average of 85 or above (CIwa≥85*). Performance Measure, POI-6.1 focuses on maintaining the square feet weighted average condition index (CIwa) at 85 for the entire portfolio year after year. The need to achieve this highly ambitious CI level is the reason the minimum CI measure was established to ensure facilities condition index does not fall below a value of 65 which borders on only fair condition.

Rationale

NIH must ensure the capability and reliability of its facilities to support and sustain its biomedical research mission. Tools to objectively evaluate and measure the state of real property assets, and plan, budget, and monitor capital maintenance and repair programs are key to a successful program.

TARGET CONTEXT AND CONDITIONS

The original CI targets for NIH were established based on 2004 CI data and expected funding streams. Since that time, the accuracy of the CI data has been reviewed and improved to better reflect current conditions. In 2009 there was an unusually high demand for change in use of facilities, thus allowing less funding for reduction in deficiencies. NIH engages subject matter experts (maintenance staff, facility managers, and engineers and architects knowledgeable about the facilities) in the Facility Condition Assessment review and documentation process to improve the accuracy of the database. This is a continuous evaluation process which has several components that involve both in-house and consultant experts. For example, one part of the process is the integration of planning and engineering studies for Building 10 into the deficiency database. This study has not advanced enough to date to be reflected in this year's calculation, but when completed, is expected to have a significant impact on CI. Another example is the review of Facility Replacement Values (FRVs) which is also underway and when complete will be incorporated into an update of portfolio data, with an accompanying impact on building condition. Both of these efforts are expected to be completed in time for incorporation in the reporting of 2010 performance results. In addition, building usage and time increases the backlog of maintenance and projects associated with aging facilities. The targeted CI achievement is heavily dependent on the levels of available repair and improvement (R&I) resources.

Long Term Objective: (POI-7.1) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-7.1 Manage all Buildings and Facilities (B&F) line item projects so it is completed within 100% of the final approved project cost. (Ongoing) (Output)	*2011*	(2011 RA) 13 active Recovery Act funded projects	N/A
	2011	10 active projects initiated (Tentative)	N/A
	2010	(2010 RA) 15 active Recovery Act funded projects initiated	N/A
	2010	16 active projects initiated	N/A
	2009	(2009 RA) 10 active Recovery Act funded projects initiated	Eleven (11) active Recovery Act funded projects were initiated within the approved budget. (Target Met)
	2009	25 active projects	21 of the 25 active projects were managed within the approved budget. . One project scope was expanded due to program changes and the complexity of commissioning of high containment facilities. One project scope was expanded to meet more stringent safety and HVAC requirements. Two projects incurred costs due to scheduling delays within existing occupied facilities. (Target Not Met)
	2008	29 active projects	28 of the 29 active projects were managed within the approved budget. One project scope was expanded using DHHS Facility Project Approval Authorization process and reprogramming actions. (Target Not Met)
	2007	24 active projects	23 of the 24 Active Projects were managed within budget tolerances. One project scope and budget was expanded to 2008 using the Facility Project Approval Authorization form approved by HHS. (Target Not Met)
	2006	20 active projects	All twenty (20) active projects were managed within the approved budget. (Target Met)

Data Source and Validation
NIH Quarterly Report to DHHS HHS Facility Project Approval Agreement (N-05-001) and N-05-104 Contact: Program Manager Strategic Initiatives Programs, Office of Research Facilities, Division of Technical Resources at 301-496-5078

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

American Recovery and Reinvestment Act (RA) Projects:

The 2009 target was Met and Exceeded. Eleven (11) RA projects were initiated in 2009. Design was initiated for one (1) project, construction contracts were awarded for five (5) projects, construction contracts were advertised for three (3) projects, and market surveys were completed for two (2).

NIH remains committed to managing its project portfolio consistent with the FY2007 B&F Program assessment objectives to meet its annual performance goals.

Building and Facilities (B&F) Projects:

The 2009 performance target to manage all B&F line item projects to completion within 100% of the final approved project cost was NOT MET. Of the 25 B&F reportable projects scheduled to be completed, 21 or 84% of the portfolio fully met this objective. For the balance of the projects in the portfolio, programmatic changes, the complexity of commissioning high containment facilities, more stringent safety and HVAC requirements, and scheduling delays associated with working within confined spaces, resulted in managing additional project costs. The request for the additional scope was approved and increases in the total project budgets were authorized.

Advances or Other Highlights

Use of the Office of Research Facilities (ORF) Earned Value Management System (EVMS) was expanded to include all projects in the portfolio eligible for evaluations. This was a function of project cost, complexity and the estimated duration.

The Building & Facilities Program was assessed in 2007. The assessment cited successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. Therefore, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

The design and construction processes are complex, and vulnerable to outside influences including market forces, material shortages, weather, and building codes, standards, and guideline changes. Thus, managing the design and construction of capital facilities within the approved budget and schedule is an ambitious goal. Under current practice as defined by OMB Circular A-11, federal construction projects are to be fully funded in advance. In this situation, it is critically important to manage each Building & Facilities (B&F) project identified as a line item within appropriated amounts.

NIH actively manages and tracks its 'line item B&F' projects to deliver the scope within the approved appropriated budget. This is consistent with guidelines issued by the Department of Health and Human Services and federal real property asset management principles. To accomplish this ambitious goal, NIH annually manage funded projects to meet schedule and cost management targets. This involves development and execution of specific management plans for each project that will include as a minimum:

- Use of Earned Value Management to assess risk and variance and to help ensure completion of projects on schedule and within budget
- Construction management and quality assurance programs
- Commissioning to validate that the facility is fully operational for the intended use

Criteria for optimal performance (to be assessed as annual targets):

- Manage all B&F reportable line item projects so it is completed within 100% of the final approved total project cost.
- No more than 10% of the projects may incorporate plus or minus 10% adjustments of the authorized budget.

TARGET CONTEXT AND CONDITIONS

NIH is committed to managing design and construction of capital facility projects funded by the Building and Facilities (B&F) appropriation to ensure the approved scope of work meets the requirements. This process supports the research mission of the NIH and complies with OMB Circular A-11. Earned Value Management is one of the key tools used to accomplish this objective. The baseline for the budget control measure is the number of active projects; this will change from year to year. It is a function of the number of carryover active projects, the number of projects completed and the number of new starts.

Recovery Act funds allocated for NIH Buildings and Facilities Program will support this measure. Therefore, Recovery Act specific annual target(s) have been developed for this measure and is identified by the acronym RA (Recovery Act). The entire Recovery Act facilities portfolio is included for performance reporting purposes.

Long Term Objective: (POI-7.2) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-7.2 Manage design and construction of capital facility projects funded by B&F so that no more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (Ongoing) (Output)	*2011*	(2011 RA) 13 active Recovery Act funded projects / 10% ≤ 1	N/A
	2011	10 active projects (Tentative) / 10% ≤ 1	N/A
	2010	(2010 RA) 15 active Recovery Act funded projects initiated / 10% ≤ 1	N/A
	2010	15 active projects / 10% ≤ 1	N/A
	2009	(2009 RA) 10 active Recovery Act funded projects initiated (Tentative) / 10% ≤ 1	Ten (10) projects were managed within the approved scope. (Target Met)
	2009	25 active projects / 10% ≤ 1	21 of the 25 active projects were managed without adjustments of the approved scope. 4 or 16% of the active projects experienced a 10% scope variance due to operational requirement changes approved by HHS. (Target Not Met)
	2008	29 active projects / 10% ≤ 2	Twenty-eight of the projects were managed within the approved scope. 1 or 3.4% of the 29 active projects experienced a scope increase related to increased security requirements. (Target Met)
	2007	24 active projects / 10% ≤ 2	Twenty three (23) of the active projects were managed within the approved scope. 1 or 4% of the 24 active projects experienced a 10% scope variance due to operational requirement changes approved by HHS. (Target Met)
	2006	20 active projects / 10% ≤ 2	All twenty (20) of the active projects were managed within the approved scope. (Target Met)

Data Source and Validation
NIH Quarterly Report to DHHS HHS Facility Project Approval Agreement (N-05-001) and N-05-104 For more information, contact: Program Manager Strategic Initiatives Programs, Office of Research Facilities, Division of Technical Resources at 301- 496-5078

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

American Recovery and Reinvestment Act (RA)Projects:
The 2009 target to manage the facilities portfolio so that no more than 10% of the projects incorporate a plus or minus 10% adjustment of the approved scope was Met. None of the projects in the NIH facilities portfolio experienced a scope variance of 10% or greater. This is documented by the HHS Facility Project Approval Authorization (FPAA) form. Projects in the NIH RA portfolio were supported on the Bethesda, and Hamilton, Montana campuses.

Building and Facilities (B&F) Projects:
The 2009 performance target to manage the facilities portfolio so that no more than 10% of the projects incorporate a plus or minus 10% adjustment of the approved scope was NOT MET. Twenty-one (21) of the twenty-five (25) projects in NIHs facilities portfolio experienced a scope variance of 10% or greater. This scope adjustment was required to support operational requirements and to enhance the safety and reliability of an NIH facility. This is a 16% program variance. Project variances were reviewed and approved by DHHS. This is documented by the HHS Facility Project Approval Authorization (FPAA) form. Projects in NIHs portfolio were on the Bethesda, North Carolina, Hamilton, Montana, and Frederick, Maryland campuses.

BACKGROUND

NIH actively manages its 'line item B&F' projects to complete them with a scope variation of ≤ 10%. To accomplish this goal, NIH develops project specific management plans to include as a minimum:

- Acquisition Planning
- Formation of an Integrated Project Team that includes stakeholders
- Pre-project planning to manage potential project risks
- Development and approval of a program of requirements as a basis for design
- Design management to include peer reviews and approvals

Criteria for optimal performance (to be assessed as annual targets):

- No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope.

TARGET CONTEXT AND CONDITIONS

NIH is committed to monitor and track on-scope delivery of facilities project to support and sustain the NIH biomedical research mission. NIH monitors specific performance of individual capital projects throughout the design, construction, and commissioning processes with the aim of delivering the project scope on-time and within budget. The baseline for the scope management measure is 10% of the active projects and the approved scope of work for each project.

Recovery Act funds allocated for NIH Buildings and Facilities Program will support this measure. Therefore, Recovery Act specific annual target(s) have been developed for this measure and is identified by the acronym RA (Recovery Act).

Long Term Objective: (POI-8.1) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-8.1 By 2013, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval. (Output)	*2011*	(2011 RA) Ensure that 100% of 18 grantees have met all construction requirements.	N/A
	2010	(2010 RA) AWARD 110 extramural construction grants in 2010 with construction requirements met by 2013, as specified in the measure.	N/A
	2009	(2009 RA) AWARD 37 extramural construction grants in 2009 with construction requirements met by 2012, as specified in the measure.	AWARDED 37 extramural construction grants for Core Facility Renovation, Repair, and Improvement (G20) and Extramural Research Facilities Improvement Program (C06). (Target Met)
	2009	Ensure that 100% of grantees have met all construction requirements *(Baseline):* (FY09) 0 grantees	100% of projects under construction have approved design and construction documents and ensured the Notice of Federal Interest has been recorded. (Target Met)
	2008	Ensure that 100% of 21 grantees have met all construction requirements *(Baseline):* (FY08) 21 grantees	100% of projects under construction have approved design and construction documents and ensured the Notice of Federal Interest has been recorded. (Target Met)
	2007	Ensure that 100% of 35 grantees have met all construction requirements *(Baseline):* (FY07) 35 grantees	54% of projects under construction have approved design and construction documents and ensured the Notice of Federal Interest has been recorded. Corrective strategies have been taken to ensure that the remaining projects will meet the construction requirements. (Target Not Met)
	2006	Ensure that 100% of 50 grantees have met all construction requirements *(Baseline):* (FY06) 50 grantees	66% of projects under construction have approved design and construction documents and ensured the Notice of Federal Interest has been recorded. Corrective strategies have been taken to ensure that the remaining projects will meet the construction requirements. (Target Not Met)

Data Source and Validation
NCRR Construction Grants Management System. For more information please contact Patricia Newman at (301) 435-0864.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

2009 RA Target

Due to Recovery Act funding, the measure have been extended to 2013. Recovery Act fund for construction grant awards are being issued in 2009 and 2010. After the award, construction design requirements monitoring will begin in 2012 and complete by 2013.

During FY2009, 37 extramural construction grants were AWARDED with funding from the Recovery Act. The awards were issued to institutions proposing renovations, repairs, improvements or construction of core research facilities. The objective of the award is to upgrade or construct core facilities to support the conduct of PHS supported biomedical and/or behavioral research while creating and/or maintaining American jobs. Consistent with Recovery Act guidance, consideration was given to applications that generate energy-saving and beneficial environmental effects.

2009 Regular Target

100% of grantees met all construction requirements, including having NIH approved design and construction documents, and having a Notice of Federal Interest filed or recorded. Grantees took necessary actions to provide construction design documents and ensured the Notice of Federal Interest has been recorded.

The Extramural Construction Research Program was assessed in FY 2008. The assessment cited a successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

The NIH Extramural Construction Grant Program has policies and/or procedures in place to obtain sufficient knowledge of grantee activities throughout the project period and during the 20-year usage requirement associated with a funded award. The NIH Grants Policy Statement addresses the unique requirements for progress reporting under construction grants or grants supporting both construction activities, including acquisition or modernization and nonconstruction activities. Therefore, Institutes and/or Centers (IC) provide grantees with reporting requirements during the performance of the project (project design and construction).

NIH developed a self-certification process to monitors the use of grant-supported space and to also remind grantees of the usage requirement and prior approval requirements if changes in use should occur during the 20-year period. If there is evidence through this self-certification process or other means that NIH may question a grantee’s compliance with the facility usage obligation, NIH will conduct a site visit(s) to ensure the proper use of grant-supported space or take corrective action.

TARGET CONTEXT AND CONDITIONS

The objective of this measure is to protect NIH's interest in real property supported under the extramural construction grant program by ensuring that grantees meet program requirements.

To protect the federal interest in real property that has been constructed or undergone major renovations with the use of NIH grant funds, grantees shall record a Notice of Federal Interest (NFI) in the appropriate official records of jurisdiction in which the property is located.
The Recovery Act Extramural Construction program objectives aligns with the objective of the existing

Extramural Construction program, which is to facilitate and enhance the conduct of biomedical and behavioral research by supporting the costs of designing and constructing non-Federal basic and clinical research facilities to meet the biomedical or behavioral research, research training, or research support needs of an institution or a research area at an institution. The Recovery Act expects that all awards be expanded expeditiously and that grantees will consider green/sustainable technologies and design approaches.

The construction grants awarded under the Recovery Act are on a 2-3 years post award design and documentation review timeline, whereas regular awards are on a 3-4 year monitoring timeline. Ten year post construction monitoring will be conducted to ensure that Recovery Act construction grant recipients use the grant-supported facilities for scientific research purposes.

Awards are expected to create and/or maintain American jobs. The citizens of the United States will benefit from these awards through improved biomedical and behavioral research capacity.

Recovery Act extramural construction grants are monitored in the same manner of our normal extramural research program with the exception of the post construction monitoring period. That is, 10 years rather than the normal 20 years.

Long Term Objective: (POI-8.2) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-8.2 By 2015, report the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research. (Output) (Output)	*2011*	95% of 182 projects are in compliance *(Baseline):* No. of projects occupied in past 20 years: (FY11) 182 prjs	N/A
	2010	95% of 196 projects are in compliance *(Baseline):* (Target 2) No. of projects occupied in past 20 years: (FY10) 196 prjs	N/A
	2009	95% of 179 projects are in compliance *(Baseline):* (Target 2) No. of Projects occupied in past 20 years: (FY09) 179 prjs	99% of the extramural construction projects were in compliance with the post award 20 year usage requirement. (Target Met)
	2008	95% of 164 projects are in compliance *(Baseline):* (Target 2) No. of Projects occupied in past 20 years: (FY08) 164 prjs	95% of the extramural construction projects were in compliance with the post award 20 year usage requirement. (Target Met)
	2007	95% of 143 projects are in compliance *(Baseline):* Target 2: No. of Projects occupied in past 20 years: (FY07) 143 prjs	98% of the extramural construction projects were in compliance with the post award 20 year usage requirement. (Target Met)
	2006	95% of 123 projects are in compliance *(Baseline):* No. of Projects occupied in past 20 years: (FY06) 123 prjs	97% of the extramural construction projects were in compliance with the post award 20 year usage requirement. (Target Met)

Data Source and Validation
Official documents are located in the Grants Management Office at the respective Institute or Center or the NCRR Construction Grants Management System. * For more information, please contact: Patricia Newman at (301) 435-0864.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target was Met. During FY 2009, 99% (177/179) of the extramural construction projects were in compliance with the post award 20 year usage requirement to conduct research. NIH received one of the following from each grantee ensuring research was being conducted: a signed document, a publication, photos or other grant support verifying the 20 year usage requirement. For some projects, verification was attained through an NIH staff site visit to the facility.

At the end of the 20 year monitoring period, a final acceptance letter is sent to the grantee with the encouragement to continue to use the space for the purposes(s) of the award.

The Extramural Construction Research Program was assessed in FY 2008. The assessment cited a successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

BACKGROUND

The National Institutes of Health's (NIH) extramural construction grant program supports construction and renovation projects that facilitate and enhance the conduct of PHS-supported biomedical and behavioral research. The extramural construction grant program supports the costs of designing, constructing and/or renovating non-Federal basic and clinical research facilities to meet the biomedical and behavioral research, research training, or research support needs of an institution or a research area at an institution.

Although there are ten NIH Institutes and Centers (IC), including the Office of AIDS Research, that have construction or modernization grant authority, in FY 2005 only two ICs had appropriated funds for extramural construction and have actively awarded construction grants over the past 5 years. The National Center for Research Resources (NCRR) and the National Institute of Allergy and Infectious Diseases (NIAID) actively support the program through the issuance of grants and/or cooperative agreements (hereafter referred to as grants).

The principal objective of NCRR's program is to facilitate and enhance the conduct of PHS-supported biomedical and behavioral research by supporting the costs of designing and constructing non-federal basic and clinical research facilities to meet the biomedical or behavioral research, research training, or research support needs of an institution or a research area at an institution.

The principal objective of NIAID's program is to support the construction of National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs) at research institutions across the country. The NBLs will serve as a national and regional resource for research on biodefense and emerging infectious disease agents that require biosafety Level 2, 3 or 4 (BSL-2/3/4) biocontainment, while the RBLs will serve as a regional resource for research requiring BSL-2/3 biocontainment. The NBLs and RBLs will complement and support the research activities of NIAID's Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, and will be made available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

Rationale

The administration of construction grants has unique controls in place to protect the interest of the Federal Government. Although there are many unique requirements applicable to the construction grant program, the focus here is on those requirements pertinent to the protection of the Federal Government's interest in grant-supported real property.

To protect the Federal interest in real property that has been constructed or has undergone major renovation using NIH grant funds, the NIH must ensure the awardee's compliance with additional requirements that are unique to the program.

When the grantee receives their award, the awardee must obtain NIH approval of all plans and specifications at each stage of design to ensure the grant-supported space is designed in accordance with NIH Design Policy and Guidelines and Good Laboratory Standards. The proper design of the facility will ensure the safety of NIH grant-supported researchers who will occupy the completed facility. In addition, at the time construction begins the awardee is also required to file a Notice of Federal Interest (Notice) in the local land records in the

jurisdiction in which the property is located. Filing of this Notice results in a lien on the property to ensure that the property will not be: used for any purpose inconsistent with that authorized by the grant program statute, mortgaged or otherwise used as collateral, or sold or transferred to another party without written permission of the NIH. The Notice ensures the Federal interest in the property will not subordinate to those of non-Federal parties unless a deviation is approved. The baseline for Target 1 is the number of projects under construction during the target year.

After construction is complete, the awardee must ensure that they are using the grant-supported space for its intended purpose throughout the usage obligation. The authorization and/or appropriation language for construction grant programs requires construction grant recipients to use the grant-supported space for the research purposes for which the space was built for a 20 year period after completion of construction. In order to ensure the awardee's compliance with the usage obligation and to protect the NIH's interest in grant-supported property, NIH monitors this usage in a variety of ways, including periodic facility use certifications or reports, site visits, or other appropriate means for the duration of the required usage period. The baseline for Target 2 is the number of projects completed in the 20 years prior to the end of the target year (e.g. FY05 baseline is number of projects completed during October 1, 1985 to September 30, 2005).

NIH staff also provides additional oversight related to environmental impact issues, design specifications, and financial management of construction projects.

NIH's grants compliance program works to ensure that the ICs adhere to NIH construction-specific grants oversight policies through a management controls initiative that examines IC policies and procedures, their compliance with NIH policy, and if IC staff follow the required procedures.

TARGET CONTEXT AND CONDITIONS

NIH has collected data on IC compliance with certain policy requirements including monitoring the use of research space supported by NIH construction grants for the 20 year period specified in the Notice of Grant Award. Based on the findings of the data analysis, NIH staff is working closely with ICs to ensure that they have systems in place that meet policy requirements. NIH will reevaluate IC systems by re-administering a management controls questionnaire self assessment tool to validate continued compliance.

The objective of this measure is to protect NIH's interest in real property supported under the extramural construction grant program by ensuring compliance with construction and 20 year usage requirements.

Long Term Objective: (POI-9) Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.

Measure	FY	Target	Result
POI-9 By 2015, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors. (Output)	*2011*	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources. *(Baseline):* BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments.	N/A
	2010	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources. *(Baseline):* BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments.	N/A
	2009	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources. *(Baseline):* BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments.	25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated. (Target Met)
	2008	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources *(Baseline):* BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments	25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated. (Target Met)
	2007	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources *(Baseline):* BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments	25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated. (Target Met)

Measure	FY	Target	Result
	2006	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources *(Baseline):* BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments	25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated. (Target Met)

Data Source and Validation
The NIH Manual Issuance 3005 - Review and Evaluation of Intramural Programs describes policy for the scientific review process for Principal Investigators within the intramural programs. * For additional information, contact Larry Chloupek at (301) 594-3992.

SUMMARY OF 2009 PERFORMANCE RESULTS

Target

The FY 2009 target to conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources was Met. To assess quality of science, 25% of Principal Investigators were reviewed resulting in 25% of resources recommended to be reallocated. The NIH Manual Issuance 3005 – Review and Evaluation of Intramural Programs requires BSC reviews and recommendations in writing and distributed to the Deputy Director for Intramural Research (DDIR) and the Director, NIH. Members of the DDIR's Office of Intramural Research attend the BSC reviews monitoring specific reviews and resulting recommendations. The written reviews and recommendations are also provided annually to the ICs National Advisory Council.

The Intramural Research Program was assessed in FY 2007. The assessment cited a successful program management and appropriate achievement of progress toward the measure as a strong attribute of the program. As a result of the program assessments, the program continues ensuring significant progress towards the achievement of its annual objectives.

Advances or Other Highlights

The annual meeting of the Chairs of the Boards of Scientific Counselors met on October 2, 2009 to discuss issues relating to the BSC reviews. The discussions included intramural-extermural differences, Scientific Management Review Board, enhancing mentoring and training of fellows, enhancing clinical research at NIH, encouraging high-risk research at NIH, tenure and team science, and specific issues from BSC chairs. The Director, NIH (via phone) and DDIR, NIH attends the meeting and presents current intramural issues.

The annual cost savings realized in FY 2008 was $2,886,000; this amount was reallocated within the Intramural Research Programs in FY 2008. Annual cost savings for FY 2009 will be available in 2010.

BACKGROUND

The NIH is the steward of medical and behavioral research for the Nation whose mission is science in pursuit of fundamental biological knowledge and the application of that knowledge to improve public health. The Intramural Research Program at NIH conducts distinctive, high-risk, high impact laboratory, clinical and population-based research and trains new researchers to support this mission. There are 27 Institutes and Centers (ICs) at NIH and of those, 22 ICs have intramural research programs. The Intramural Research Programs have resources allocated to individual tenured and tenure-track investigators.

Rationale

Intramural research at NIH has been reviewed by committees of scientists from outside the NIH since 1956. The committees are called Board of Scientific Counselors (BSCs) and constituted to assist the Scientific Directors (SDs) of each IC in evaluating the quality of the intramural programs for which they are responsible. It is the policy of the NIH that all research conducted intramurally must be reviewed at regular intervals by highly qualified outside scientists. Every independent intramural scientist (Principal Investigator) on a tenured appointment must be reviewed and evaluated at a minimum of every four years. Although the principal purpose of these independent evaluations is to advise the SDs, the reports of the BSCs are distributed to the Director, National Institutes of Health (NIH), Deputy Director for Intramural Research (DDIR), the appropriate Institute or Center (IC) Director, and the Board of SDs. The BSC also reports annually to the National Advisory Council or Board of the IC. The composition of BSCs is based primarily on scientific qualification; members shall be international recognized as an authority in one of the fields of research under review. While the primary criterion for all appointments to the BSCs should be scientific excellence, each BSC should exhibit reasonable balance in membership in terms of points of view (scientific interests/disciplines) and with respect to gender, ethnicity, and geographical distribution of members' institutions.

BSC members serve for five-year terms, if possible, to allow them to be involved more than once in the regular quadrennial review of some programs. An effort should be made to have some BSC members (approximately one-third) who are not primarily funded by the IC on whose BSC they serve.
A BSC may make use of ad hoc reviewers when the Chair of the BSC, in consultation with the SD, deems it necessary. Such ad hoc reviewers should be selected by the BSC Chair, with the advice of the other BSC members, the SD, and the IC Director.

TARGET CONTEXT AND CONDITIONS

The review process used by BSCs will take into consideration the special nature of NIH intramural research made possible by stable funding, that high-risk research should be encouraged, and that the review process will emphasize past performance. The review will address the accomplishments of individual scientists and the quality and productivity of their research. The BSCs make recommendations to the Scientific Director and IC Director regarding the allocation of resources. Recommendations regarding resources are explicit as possible, with a clear indication as to which resources (budget, space, and personnel) should remain the same, be increased, or decreased. The BSCs shall meet often enough (ordinarily two or three times each year) to assure that the work of each tenured and tenure-track intramural scientist and each Laboratory or Branch is reviewed at least once every four years. The BSC members meet face-to-face at the site visits and BSC review meetings to complete the Principal Investigators' review process.

The review cycle for each scientist is every four years indicating that 25% of the Principal Investigators will be reviewed each year. The BSCs will recommend the reallocation of resources at that time resulting in 25% reviewed resources being recommended for reallocation as a result of the reviews.

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NIH SUPPORT FOR HHS STRATEGIC PLAN

As mentioned previously, NIH performance measures are representative and serve as proxies for performance on the larger, research portfolio. The measures are representative, not comprehensive, and taken together represent the breadth of NIH's portfolio including basic, prevention, diagnostic, and treatment research. Because NIH takes a representative approach, the measures included in the GPRA plan are not meant to cover all programs, projects, or aspects of NIH performance. The performance measures selected for inclusion in the GPRA plan are all key measures and serve as NIH strategic goals.

In addition to supporting the Agency mission and Core Strategic Vision, the NIH budget request supports the HHS Strategic Plan (http://www.hhs.gov/strategic_plan/), Department-Wide Objectives, and Healthy People 2010 (http://www.healthypeople.gov/). In particular, NIH substantially contributes to HHS Strategic Goal 4: *Advance scientific and biomedical research and development related to health and human services* and the goals subcomponents.

Strategic Objective 4.1: Increase basic scientific knowledge to improve human health and human development.
Strategic Objective 4.2: Strengthen the pool of qualified health and behavioral science researchers.
Strategic Objective 4.3: Conduct and oversee applied research to improve health and well-being.
Strategic Objective 4.4: Communicate and transfer research results into clinical, public health and human service practice.

The NIH Functional Area categories provide evidence of linkages between NIH activities and the HHS mission. While not directly determined or limited by HHS Strategic Goal 4 subcomponents, the expected performance of NIH targets supports each aspect of the overall goal.

NIH Link to HHS Strategic Goal 4 and Objectives

NIH Strategic Goals	**HHS Strategic Objective** 4 1 Strengthen the pool of qualified health and behavioral science researchers	**HHS Strategic Objective** 4 2 Increase basic scientific knowledge to improve human health and human development	**HHS Strategic Objective** 4 3 Conduct and oversee applied research to improve health and well-being	**HHS Strategic Objective** 4 4 Communicate and transfer research results into clinical, public health, and human service practice
Scientific Research Outcomes Measures				
SRO-1.3: By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement.			X	
SRO-1.4: By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders.		X		
SRO-1.5: (RA) By 2012, develop a comprehensive IT platform that can facilitate evaluation of diverse behavioral interventions to promote health			X	
SRO-1.6: (RA) By 2012, present preliminary findings from the three-pronged approach to curtail the HIV pandemic.			X	
SRO-1.7: (RA) By 2012, incorporate scientific human development concepts, in order to develop and rigorously test at least 2 childhood learning approaches that can be integrated into science, technology, engineering and mathematics (STEM) K-12 educational programs.		X		
SRO-1.8: (RA) By 2012, identify three research findings that will advance understanding of the biological basis underlying the heterogeneity of autism spectrum disorder (ASD) and conduct initial testing of three treatment or service delivery strategies.		X		
SRO-2.1: By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.			X	
SRO-2.2: By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.			X	

NIH Strategic Goals	HHS Strategic Objective 4 1 Strengthen the pool of qualified health and behavioral science researchers	HHS Strategic Objective 4 2 Increase basic scientific knowledge to improve human health and human development	HHS Strategic Objective 4 3 Conduct and oversee applied research to improve health and well-being	HHS Strategic Objective 4 4 Communicate and transfer research results into clinical, public health, and human service practice
SRO-2.4: By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life.			X	
SRO-2.5: By 2011, identify and evaluate 5 novel molecular-targeted interventions for cancer, and determine suitability for use in early phase clinical trials.		X		
SRO-2.6: By 2011, develop one field deployable sensor device for use in human studies and develop one biomarker to characterize the impact of environmental exposures on biological pathways.		X		
SRO-2.7: By 2011, complete clinical testing of one candidate medical countermeasure that could be used to diagnose or treat victims of a chemical terrorist attack or accident, and complete preclinical testing for two others.			X	
SRO-2.8: By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials.		X		
SRO-2.9: By 2015, advance understanding of social determinants of health and health disparities using multilevel, transdisciplinary team science approaches by developing intervention models of how various factors affect individual health outcomes and their distribution in populations.			X	
SRO-2.10: By 2014, identify three clinical candidate compounds for rare or neglected diseases.		X		
SRO-2.11: By 2014, conduct studies of young children to determine whether the plant estrogens in soy formula produce hormone-like effects.			X	
SRO-3.1: By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD).			X	
SRO-3.2: By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.		X		
SRO-3.3: By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.			X	
SRO-3.4: By 2015, evaluate an HIV vaccine candidate in a test of concept (phase IIB) efficacy trial in order to move towards an HIV/AIDS vaccine.			X	
SRO-3.5: By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies.		X		
SRO-3.6: By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.		X		
SRO-3.7: By 2019, develop at least two novel therapies for immune-mediated disease.		X		
SRO-3.8: By 2016, determine the optimal tailored treatment regimen for patients with early stage breast cancer that maximizes the benefits of chemotherapy while minimizing the side-effects of unnecessary treatment.			X	
SRO-3.9: By 2020, identify two molecular-targeted therapies for disorders of the immune system in children.		X		
SRO-3.10: By 2017, advance two candidate medications for treatment of substance use disorders to clinical studies in humans.			X	
SRO-4.3: By 2009, evaluate the safety and efficacy of two new treatments for nonalcoholic steatohepatitis (NASH) in adults.			X	
SRO-4.4: By 2011, identify or study additional genes involved in communication disorders in humans and animal models.		X		
SRO-4.5: By 2011, identify genetic and environmental factors which predispose to three complex diseases.		X		
SRO-4.6: (RA) By 2012, develop a technology to facilitate patient-controlled, secure image sharing between medical centers and at least one clinic operating in an underserved community.			X	
SRO-4.7: (RA) By 2011, evaluate at least one novel animal model of type 1 diabetes.		X		
SRO-4.8: (RA) By 2011, develop and/or test at least one strategy for improving end-of-life care or palliative care.			X	
SRO-4.9: (RA) By 2011, enhance the capacity of researchers to investigate genetic causes of disease by DNA sequencing of participants in well-phenotyped cohorts.		X		

NIH Strategic Goals	**HHS Strategic Objective** 4 1 Strengthen the pool of qualified health and behavioral science researchers	**HHS Strategic Objective** 4 2 Increase basic scientific knowledge to improve human health and human development	**HHS Strategic Objective** 4 3 Conduct and oversee applied research to improve health and well-being	**HHS Strategic Objective** 4 4 Communicate and transfer research results into clinical, public health, and human service practice
SRO-4.10: (RA) By 2011, accelerate progress toward identifying relevant genomic alterations in 10 tumor types.			X	
SRO-4.11: (RA) By 2011, analyze oral cancer genomes using high throughput methods to develop a blueprint of genetic alterations.		X		
SRO-4.12: (RA) By 2011, demonstrate the feasibility of a new therapeutic strategy in a preclinical model of a neurological disease.		X		
SRO-5.2: By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).			X	
SRO-5.3: 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.		X		
SRO-5.6: By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.		X		
SRO-5.7: By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy.		X		
SRO-5.8: By 2012, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies.			X	
SRO-5.9: By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.		X		
SRO-5.10: By 2011, conduct studies of girls aged 6 through 8 years to determine the associations between the age of onset of puberty and progression through puberty with 12 environmental exposures.			X	
SRO-5.11: By 2012, develop and test at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes.			X	
SRO-5.12: By 2013, identify several potential targets and/or molecules that modulate or enhance the extinction of learned behaviors and conditioned associations supporting addiction, compulsion, or anxiety disorders.		X		
SRO-5.13: By 2014, establish a process to prioritize compounds that have not yet been adequately tested for more in-depth toxicological evaluation.		X		
SRO-5.14: By 2013, reduce tobacco prevalence among youth by preventing initiation and increasing rates of cessation.		X		
SRO-6.1: By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.		X		
SRO-6.2: 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.			X	
SRO-6.4: By 2014, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.		X		
SRO-6.5: By 2014, develop and evaluate two new interventions for the prevention and/or treatment of HIV disease utilizing the newly restructured HIV/AIDS clinical trials networks.			X	
SRO-6.6: By 2015, provide at least one new or significantly improved minimally-invasive treatment for clinical use in patients using image-guided interventions.		X		
SRO-7.4: By 2009, create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis.		X		
SRO-7.7: By 2011, assess community-based methods for facilitating cancer research and providing patients access to optimal cancer care.			X	
SRO-7.8: (RA) By 2011, create genomic resources to identify rare genetic variants that contribute to primary open angle glaucoma.		X		
SRO-7.9: (RA) By 2011, enhance understanding of the characteristics of differentiated heart, lung, and blood cells derived by reprogramming human embryonic and induced pluripotent stem cells.		X		

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SRO-7.10: (RA) By 2011, create a publically accessible database of cell images, videos, and animations from a variety of organisms to better understand the molecular and biochemical activities of cells and subcellular components, as well as on the role of cellular dysfunction in disease.		X		
SRO-7.11: (RA) By 2012, gather sufficient data to support the development of a national standard for normal fetal growth.		X		
SRO-8.2: 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.		X		
SRO-8.4: 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.		X		
SRO-8.5: By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.			X	
SRO-8.6: By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES).		X		
SRO-8.7: By 2012, identify three (3) effective implementation strategies that enhance the uptake of research-tested interventions in service systems such as primary care, specialty care and community practice.			X	
SRO-8.8: By 2012, identify at least one candidate intervention that extends median lifespan in an animal model.		X		
SRO-8.9: By 2014, identify 12 pathogen and/or host factors critical for understanding the molecular and cellular basis of pathogenesis of Category A-C biodefense pathogens and/or pathogens causing emerging infectious diseases.		X		
SRO-9.1: 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).			X	
SRO-9.2: By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities.			X	
SRO-9.3: By 2011, characterize the progression of normal, healthy brain development in a nationally representative sample of children in the United States by creating a database of MRI and clinical/behavioral data and analytical software.		X		
SRO-9.4: By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.		X		
SRO-9.5: By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.			X	
Communication and Transfer of Results Measures				
CTR-1: By 2014, 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).				X
CTR-6: By 2010, improve the efficiency and reduce the unit cost of producing authoritative serials cataloging records used to improve access to the biomedical literature in libraries worldwide.				X
CTR-7: By 2010, establish the feasibility of sharing information from already-conducted scientific studies of warfarin (coumadin^{R}) anti-coagulation, through the knowledge base PharmGKB.				X
CTR-8: By 2012, increase communication efforts and enhance centralized outreach strategies regarding extramural research funding policy, compliance and administration as demonstrated by the type and frequency of communications and related activities.				X

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CTR-9: By 2012, increase awareness of the NIH SBIR and STTR funding opportunities available for women-owned and socially and economically disadvantaged small business concerns (SBCs).				X
CTR-10: By 2014, expand the scope of the Hazardous Substances Data Bank to include 14 nanomaterials.				X
Capacity Building and Research Resources Measures				
CBRR-1.1: By 2012, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds the relevant comparison groups within 10 years of graduation.	X			
CBRR-1.2: By 2012, ensure that the proportion of post-doctoral fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups within 10 years of fellowship completion.	X			
CBRR-2: Promote data sharing and provide information in real time through the NIH Business System (NBS) by developing, integrating, deploying and maintaining business modules. (By FY 2014, the NBS will be in an ongoing status)			X	
CBRR-4: By 2013, provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic Research Administration (eRA) system.			X	
CBRR-6.1: By 2011, construct or renovate 153 biomedical research facilities in order to build the capacity to conduct the proposed research.			X	
CBRR-6.2: By 2012, complete 15 biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases.			X	
CBRR-7: By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research.			X	
CBRR-8: By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management.	X			
CBRR-9: By 2011, achieve average annual cost savings of managing construction grants by expanding the use of electronic project management tools that enhance oversight and 20 year usage monitoring.			X	
CBRR-10: By 2013, make freely available to researchers the results of 300 high-throughput biological assays screened against a library of 300,000 unique compounds, and the detailed information on the molecular probes that are developed through that screening process.				X
CBRR-11: (RA) By 2010, determine the number of shared instrumentation grants awarded that will contribute to the success of many NIH-funded research projects.			X	
Strategic Management of Human Capital Measures				
SMHC-4: Ensure NIH reports tracked commercial functions and cost savings from completed commercial services studies efficiently and on time. (Ongoing)	X			
SMHC-5: By 2011, improve and monitor the use of human resource services by providing real-time access to tools via the NIH portal.	X			
SMHC-6: Provide opportunities for enhanced leadership skills to meet the challenges of workforce management and/or individual advancements. (Ongoing)	X			
SMHC-7: Address diverse workforce recruitment needs to ascertain highly qualified staff to conduct or support biomedical research. (Ongoing)	X			
SMHC-8: Address areas to facilitate retention of highly qualified staff to conduct or support biomedical research. (Ongoing)	X			
Program Oversight and Improvement Measures				
POI-2: Utilize performance-based contracting (PBC). (ongoing)	X			
POI-5: By FY 2010, enhance NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems.				X
POI-6.1: Improve facility conditions in order to reach and maintain a Condition Index (CI) weighted average of 85 or above (CIwa≥85). (Ongoing)			X	
POI-6.2: By 2017, maintain the annual condition of buildings and facilities portfolio so that no less than 95% of occupied gross square feet (GSF) will have a CI greater than 65. (Ongoing)				

NIH Strategic Goals	**HHS Strategic Objective** 4 1 Strengthen the pool of qualified health and behavioral science researchers	**HHS Strategic Objective** 4 2 Increase basic scientific knowledge to improve human health and human development	**HHS Strategic Objective** 4 3 Conduct and oversee applied research to improve health and well-being	**HHS Strategic Objective** 4 4 Communicate and transfer research results into clinical, public health, and human service practice
POI-7.1: Manage all Buildings and Facilities (B&F) line item projects so it is completed within 100% of the final approved project cost. (Ongoing)			X	
POI-7.2: Manage design and construction of capital facility projects funded by B&F so that no more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (Ongoing)				
POI-8.1: By 2013, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval.			X	
POI-8.2: By 2015, report the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research. (Output)			X	
POI-9: By 2015, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors.	X			

FULL COST TABLE

Summary of Full Cost for NIH[1]

(Budgetary Resources in Millions)

HHS Strategic Goals and Objectives	FY 2009	FY 2010	FY 2011[2]
1 Health Care Improve the safety, quality, affordability and accessibility of health care, including behavioral health care and long-term care.	$0	$0	$0
1.1 Broaden health insurance and long-term care coverage.	$0	$0	$0
1.2 Increase health care service availability and accessibility.	$0	$0	$0
1.3 Improve health care quality, safety and cost/value.	$0	$0	$0
1.4 Recruit, develop, and retain a competent health care workforce.	$0	$0	$0
2 Public Health Promotion and Protection, Disease Prevention, and Emergency Preparedness Prevent and control disease, injury, illness and disability across the lifespan, and protect the public from infectious, occupational, environmental and terrorist threats.	$0	$0	$0
2.1 Prevent the spread of infectious diseases.	$0	$0	$0
2.2 Protect the public against injuries and environmental threats.	$0	$0	$0
2.3 Promote and encourage preventive health care, including mental health, lifelong healthy behaviors and recovery.	$0	$0	$0
2.4 Prepare for and respond to natural and man-made disasters.	$0	$0	$0
3 Human Services Promote the economic and social well-being of individuals, families, and communities.	$0	$0	$0
3.1 Promote the economic independence and social well-being of individuals and families across the lifespan.	$0	$0	$0
3.2 Protect the safety and foster the well being of children and youth.	$0	$0	$0
3.3 Encourage the development of strong, healthier and supportive communities.	$0	$0	$0
3.4 Address the needs, strengths and abilities of vulnerable populations.	$0	$0	$0
4 Scientific Research and Development Advance scientific and biomedical research and development related to health and human services.	$30,554	$31,247	$32,247
4.1 Strengthen the pool of qualified health and behavioral science researchers.	1,432	1,489	1,516
4.2 Increase basic scientific knowledge to improve human health and human development.	16,509	16,705	17,462
4.3 Conduct and oversee applied research to improve health and well-being.	12,483	12,917	13,107
4.4 Communicate and transfer research results into clinical, public health and human service practice.	130	136	162
Total	$30,554	$31,247	$32,247

1. Distribution of funds may change once NIH Program Level is finalized
2. FY 2011 funding level is based on NIH Settlement Level.

Methodology for Full Cost

NIH does not have an account or collection of accounts dedicated to program management. To allocate costs for program management, the Research Management and Support (RMS) line item was selected from the NIH mechanism display and Office of the Director Operations, a line item in the appropriation for the Office of the Director. Methodology used to allocate NIH total budget to HHS strategic goals and objectives was refined to ensure programmatic alignment. The totals were reduced by the direct costs of the performance measures that are funded through RMS or OD operations. This calculated level for Program Management was allocated across GPRA measures and the unsampled program on a pro-rata basis.

SUMMARY OF FINDINGS AND RECOMMENDATIONS FROM PROGRAM EVALUATIONS

A summary of the findings and recommendations from NIH program evaluations completed during FY 2008 can be found in the HHS Performance Improvement Database (http://aspe.hhs.gov/pic/performance/).