DEPARTMENT of HEALTH and HUMAN SERVICES

National Institutes of Health

FY 2012 Online Performance Appendix

INTRODUCTION

The FY 2012 Online Performance Appendix is one of several documents that fulfill the Department of Health and Human Services' (HHS) performance planning and reporting requirements. 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 2012 Congressional Justifications and Online Performance Appendices, the Agency Financial Report, and the HHS Summary of Performance and Financial Information (SPFI). These documents are available at http://www.hhs.gov/budget/.

The FY 2012 Congressional Justifications and accompanying Online Performance Appendices contain the updated FY 2010 Annual Performance Report and FY 2012 Annual Performance Plan. The Agency Financial Report provides fiscal and high-level performance results. The HHS SPFI summarizes key past and planned performance and financial information.

TRANSMITTAL LETTER

I am pleased to present the FY 2012 Annual Performance Plan for the National Institutes of Health (NIH). This plan supports the Administration's priority initiatives and the goals of the FY 2010-2015 Strategic Plan for the Department of Health and Human Services and is consistent with the Government Performance and Results Act (GPRA). NIH uses GPRA performance measures and many other monitoring tools, such as peer review, site visits, and performance-based contracting, to assess program performance. The performance data provided in this plan is accurate, complete, and reliable.

In FY 2010, NIH research led to major new insights and advances in human health and disease and paved the way for improved diagnosis, therapy, and prevention. Four of many examples are:

- NIH's genome sequencing centers have reduced the fully-loaded cost of sequencing a genome from over $95 million in FY 2001 to about $31,000 in FY 2010, enabling more rapid research results and conserving resources to support more research. As NIH continues to reduce genome sequencing costs, truly personalized medicine—making medical decisions on an individualized genomic knowledge basis as a routine part of clinical care—can become a reality.

- NIH funded researchers expanded knowledge of genomic rearrangements associated with specific cancers. The researchers submitted over 3,000 cases to the NIH Cancer Genome Atlas and added eight new cancer genomes, including breast, colon, rectal, and lung cancers. These comprehensive datasets are available online, and enable the research community to identify specific genetic changes linked to specific clinical outcomes.

- NIH research helped advance understanding of an antiviral drug that targets viral receptors on the host cell surface. The study showed that the drug may be useful for treating and preventing infection by all variations of influenza and parainfluenza viruses that share the same viral entry mechanism.

- NIH scientists began validation testing of a compact new device that uses saliva samples, instead of blood samples, to detect oral and systemic diseases. This research may improve detection of a number of diseases, as well as reduce the cost and risk associated with blood-based diagnostics.

These are only a few examples of the exciting and life-changing research supported by NIH. Ongoing support for biomedical research will help save lives, reduce the burden of chronic illness and health care costs, and improve the Nation's global competitiveness.

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

NATIONAL INSTITUTES OF HEALTH
FY 2012 ONLINE PERFORMANCE APPENDIX

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PRIORITY GOAL

Resources and Performance (dollars in millions)

Program	FY 2010 Enacted	FY 2011 Continuing Resolution	FY 2012 Request
Large Scale Sequencing Program (1)	110	110	100
Total	110	110	100

(1) This amount corresponds to the RFAs for NHGRI large scale sequencing centers which carry out DNA sequencing for multiple NIH projects. The centers fall under several categories of the Basic Genomics NHGRI CJ budget line.

Large Scale Sequencing Program

Performance Measure	FY 2009 Result	FY 2010 Result	FY 2011 Target	FY 2012 Target
Reduce the fully-loaded cost of sequencing a human genome to $15,000.	N/A	$31,125	$25,000	$15,000

NIH has made significant progress on the achievement of its Priority Goal to *reduce the fully-loaded cost of sequencing a human genome to $15,000*.

The reduction of sequencing costs will be enabled through the NIH-funded large-scale DNA sequencing centers that are engaged in medical sequencing to discover disease-related genomic changes. A key activity of these centers, which complements and enables a high rate of data production, implements newly emerging technologies in a real-world setting to achieve the highest efficiency of DNA sequence production. Achievement of the 2012 goal stated here requires support for technology and process enhancements in NIH's large-scale sequencing centers, enhancements that will then propagate to the research community by publications and collaborative ventures, and is dependent on secondary effects of NIH activities in medical sequencing. In the area of basic research, large NIH projects for advancing methods, pushing down costs, and demonstrating the value of comprehensive genomic analysis are ongoing. Sequencing center feedback, in addition to basic research discoveries whose origins were supported by an NIH technology development program, is the feedstock for continued ambitious cost reductions that are exemplified by this goal, and that likely will occur as commercial vendors refine and optimize sequencing systems. The feedback circuit of supply and demand for DNA sequencing, and competition in the marketplace, together with routine incremental cost improvements, will lead to achievement of the 2012 cost goal.

Specific measures were developed to quantify the full cost of production genomic sequencing to ensure consistent quarterly reporting from different genome sequencing centers funded by NIH. These cost measures have evolved over time with input from the Scientific Advisors to the Large-Scale sequencing program. There are two very important caveats regarding use of the measures:

1. Cost measure sophistication has improved with experience. For example, as sequencing production pipelines have evolved, on occasions it has become apparent that new components should be included in what NIH considers to be "production" activities. In addition, NIH historically has tracked a unit cost in terms of base pairs of production. NIH only recently could consider routinely tracking cost per re-sequenced human genome (the metric for the goal reported on here) because it has only recently become routinely possible to rapidly sequence multiple human genomes.
2. Cost measures are only one of several factors that NIH uses in managing the program. In particular, NIH makes a distinction between "production costs" and non-production activities. NIH tracks all costs, but only includes "production" activities in the cost of sequencing a genome. In addition, NIH judges the program on several non-quantifiable measures that are just as critical to success, most importantly designing and executing the most significant scientific projects that can be addressed with large-scale sequencing.

Included in “production” costs towards the high-priority goal (cost per re-sequenced human genome) are:

- Labor, administration, and center management
- Reagents and consumables
- Informatics activities directly related to sequence production (e.g., lab information management systems; initial data processing)
- Utilities
- Construction of DNA fragment libraries (this is a step required for preparing DNA to be sequenced, and is a significant cost)
- Sequencing machines and other large lab equipment (amortized over three years)
- Data submission to a public database (required by award terms and NIH policy)

Tracked, but not included in production costs are:

- Quality assurance and/or quality control for different projects
- Technology development to improve sequencing pipelines
- Development of bioinformatics/computational tools to improve sequencing pipelines, or to improve downstream analysis
- Management of individual sequencing projects
- IT equipment
- Data analysis downstream of initial data processing (for example, genome assembly, alignments, identifying genomic variants, interpretation of results)

All categories listed above include allocated F&A (indirect) costs.

Where there is a question of costs being significantly subsidized (for example, a grantee institution may provide funds for purchasing large equipment, a benefit to the Government), NIH attempts to identify those additional funds so they can be excluded from the analysis in order to obtain a comparable cost.

More information about NIH’s Priority Goal can be found in NIH’s GPRA measure CBRR-12.

OVERVIEW

The National Institutes of Health (NIH) FY 2012 Online Performance Appendix contains initial FY 2010 performance details and FY 2011 and FY 2012 performance planning information for each of NIH's performance measures. It includes reporting as required by the Government Performance and Results Act (GPRA). NIH's approach to performance involves representative trans-NIH performance measures and annual targets that are milestones toward the achievement of the measures. The selected measures support a balanced research portfolio of extramural/intramural and basic/clinical activities and present the story of scientific discovery for each measure.

FUNCTIONAL AREAS FOR NIH ACTIVITIES

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. To achieve this mission, NIH carries out activities in five functional areas. Accordingly, NIH categorizes performance in the GPRA Plan under these functional areas with representative trans-NIH performance measures.

- *Scientific Research Outcomes (SRO).* The SRO functional area includes measures and targets with a focus on supporting and conducting investigations across the full range of the biomedical research continuum, including basic and applied research in the biomedical and behavioral sciences.

- *Communication and Transfer of Results (CTR).* The CTR functional area includes measures and targets with a focus on disseminating the knowledge resulting from NIH's research activities to clinicians, public health systems, health organizations, and the public at large. This functional area also encompasses activities to transfer knowledge to the private sector for use 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 CBRR functional area includes measures and targets with a focus on developing the strength of NIH's talent pool, and the research resources needed for scientific inquiries.

- *Strategic Management of Human Capital (SMHC).* The SMHC functional area includes measures and targets with a focus on developing and retaining a qualified workforce to conduct NIH's research programs effectively and efficiently.

- *Program Oversight and Improvement (POI).* The POI functional area includes measures and targets with a focus on ensuring that NIH's activities and strategies are carried out effectively and in compliance with all applicable laws and regulations.

The NIH Online Performance Appendix includes six years of performance information – the current performance reporting year (FY 2010), two planning years, and three years of past performance.

SUMMARY OF PERFORMANCE MEASURES PER FISCAL YEAR BY FUNCTIONAL AREA

Functional Area	FY07	FY08	FY09	FY10	FY11	FY12
Scientific Research Outcomes	36	45	48	58	55	38
Communication and Transfer of Results	4	5	4	5	4	4
Capacity Building and Research Resources	7	7	11	12	10	8
Strategic Management of Human Capital	3	3	5	5	5	5
Program Oversight and Improvement	7	6	9	9	8	8
Total	57	66	77	89	82	63

For each of the performance measures, a table of annual targets and results is included. If available, a summary of FY 2010 performance results is provided (along with an efficiency description if a target is met and exceeded). In addition, each measure includes a narrative that describes the impetus for the measure as well as the implementation plan to achieve

the intended objective. The narrative contains background information, rationale for the measure, and the target context and conditions. When applicable, scientific rationales for adjusted targets are also provided. (Please note that performance measures that will begin in FY 2011 or FY 2012 are also included.)

NIH PERFORMANCE MEASURE CRITERIA

NIH supports a wide spectrum of scientific endeavors and engages in a full range of activities that enable research and its management. Thus, a number of factors must be considered in the development, selection, and management of NIH's performance measures.

- *Measure Selection Criteria*. NIH selects measures that are representative of its extensive portfolio and that are useful for tracking progress in achieving performance priorities. The measures were selected based on the following criteria:
    - *Representative.* Taken together, the measures should represent the breadth of NIH's portfolio.
    - *Objective*. The measures should permit comparisons between actual achievement levels and those targeted by the measures.
    - *Reportable.* The measures must lend themselves to annual reporting, including the reporting of incremental progress.
    - *Not obviously attainable.* The measures should be recognized as outcomes that *could* be achieved in the future, but may not be reachable for any number of reasons, including the unpredictable progress of science, funding, and/or development of new tools needed to achieve the objectives.
    - *Specific.* The measures should be as specific to a disease or definable problem as possible, with reference to a metric, and/or a date for measurable progress or completion.
    - *Meaningful.* The measures must be credible to the research community and the public, and important to NIH and its 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 next section) to show the nature and extent of its portfolio.

- *Budget/Performance Integration.* To support performance management, it is insufficient to monitor measures without linking them to planning and budgeting processes. For measures to be useful, they must provide substantive information about program performance to assist in management and resource prioritization.

Target Adjustments. The prospective target-based approach for science requires flexibility to reflect the discovery process. Adjusting an annual target allows NIH to incorporate new knowledge and redirects performance towards conducting or funding the best science.

SUMMARY OF TARGETS AND RESULTS TABLE

NIH tracks its performance against a set of performance measures with performance targets for each measure specified for each fiscal year. As appropriate, the measures are retired when they are no longer relevant and new measures are added. The following table provides summary data on NIH's overall performance against its established targets. For example, of the 89 measures applicable to FY 2010, there were 99 performance targets. NIH met 91 of these targets, or 92% of the targets for which data were available.

Fiscal Year	Total Targets	Targets with Results Reported	Percent of Targets with Results Reported	Total Targets Met	Percent of Targets Met
2007	76	74	97%	66	87%
2008	80	79	99%	72	90%
2009	85	84	99%	74	87%
2010	99	99	100%	91	92%
2011	94	N/A	N/A	N/A	N/A
2012	74	N/A	N/A	N/A	N/A

PERFORMANCE DETAIL
GPRA PERFORMANCE MEASURE NARRATIVES BY FIVE FUNCTIONAL AREAS

SCIENTIFIC RESEARCH OUTCOMES

NIH supports and conducts biomedical and behavioral research on the nature and behavior of living systems and the application of that knowledge to extend healthy life and to reduce the burdens of illness and disability. 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, most of the ICs conduct their own research in NIH's intramural laboratories.

All research supported by NIH is subjected to rigorous review. The Extramural Program, which encompasses the largest category of NIH-funded research, utilizes a two-level peer review process in evaluating grant applications. The first level consists of chartered review groups composed of experts in particular scientific disciplines. The second level is conducted by National Advisory Councils. Approximately 50,000 grants are awarded each year to the most promising and productive scientists throughout the country and, where special opportunities exist, to scientists abroad. For the Intramural Program, an external Board of Scientific Counselors (BSC) evaluates the research productivity of individual intramural scientists. Occurring once every four years, these BSC reviews provide ongoing assessments of all intramural laboratories and the accomplishments of the scientists who contribute to them. It is through this well-honed system of external peer review that NIH has been able to support research of the highest quality.

NIH has selected 62 specific, representative research measures as proxies for its extensive portfolio. Central to this approach is a risk/difficulty and time matrix that depicts the portfolio of funded research studies. The matrix includes a continuum of risk (low, medium, and high), and a corresponding timeline for achievement (1-3, 4-6, and 7-10 years. There are a number of challenges in developing useful measures to track the progress of scientific programs. In many instances, research outcomes cannot be foreseen with certainty, but progress may be captured with milestones toward the planned objectives. Unplanned results also are common in scientific studies; at times, they can provide new information to redirect the course of research. Moreover, the full value of any given research finding may not be apparent at the time of discovery. The implications or applications of some findings may only occur after many years or in combination with other advances. In some cases, the downstream impact of scientific knowledge generated by basic research is not known without further development by the private sector, public agencies, universities, or research institutions. Research is an inherently collaborative endeavor, and partnerships are crucial to achieving NIH’s mission.

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. **2.5** 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 2016, 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. **3.11** By 2015, advance the discovery of high need cures through the development of novel compounds, the repurposing of abandoned products, and innovations in the therapeutics discovery and development process.

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
Medium	**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). **5.7** 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 2015, establish and evaluate 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 2015, 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	**7.7** 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.	**8.6** By 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 2015, identify three (3) key factors influencing the scaling up of research-tested interventions across large networks of services 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 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 generally unknown. Achievement of a high-difficulty measure in the early stages cannot be guaranteed and may be based on hypotheses which prove to be incorrect. In contrast, low-difficulty measures usually have a long history associated with the scientific effort, and the knowledge base has known parameters. With low-difficulty measures, only a few steps may remain to translate the knowledge into an application that could benefit public health. NIH also uses performance measures that span the middle of the continuum. For the medium-difficulty measures, a foundation of knowledge may have been established but not extensively developed. These measures are pursued because achievement is deemed probable.

This continuum of scientific discovery affirms the need for a balanced portfolio with high-risk/ambitious measures, as well as low-risk/probable measures, and all those in between. NIH recognizes that all of its research measures involve some degree of uncertainty because of the inherent difficulty embedded in the scientific discovery process. NIH promotes ambitious measures because they address a critical need toward improving the health of the Nation. However, the pathway to discovery is seldom linear, and the building blocks needed to make a scientific breakthrough may still need to be determined. The complex portfolio highlights the difficulties of assessing research. However, by using ambitious and achievable 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.

SRO-1.3 By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement. (Outcome)

FY	Target	Result
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.	Developed a portable pneumatic robotic exoskeleton for clinical rehabilitation of upper extremity movement in stroke patients, and completed safety and feasibility testing to enable use in a home or clinical setting. (Target Met)
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
Klein J, Spencer S, Allington J, Bobrow JE, Reinkensmeyer D. Optimization of a parallel shoulder mechanism to achieve a high-force, low-mass, robotic-arm exoskeleton. Robotics, IEEE Transactions, Aug. 2010, 26(4): 710-715. URL: http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=5497202&isnumber=5540533 Duff M, Chen Y, Attygalle S, Herman J, Sundaram H, Qian G, He J, Rikakis T. An adaptive mixed reality training system for stroke rehabilitation. IEEE Trans Neural Syst Rehabil Eng. Oct 2010, 18(5): 531-41. URL: http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=5497185&isnumber=5596181

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 Target was Met and the Measure was Achieved. Researchers have developed a portable robotic exoskeleton that can be tested for clinical rehabilitation among certain stroke patients to improve upper extremity movement, such as reaching for objects. The device has been tested on stroke patients for safety and feasibility. Because the device is powered by pneumatics, it is portable and could be used in a clinical setting or in the home. With initial guidance from a physical therapist, the robot can be programmed to assist a patient in completing a movement, and based on biofeedback, recalculates when and how much assistance is needed. In addition, the device includes a graphic user interface to provide visual feedback to the patient about his/her performance.

Measure

NIH research recently led to the development of an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement. The device is a portable pneumatic exoskeleton that can be fastened around a patient's torso and arm. Researchers developed software that enables the device to control rehabilitative movements, assess progress, and advance the therapy program as the patient regains the ability to perform upper arm movements. The robotic system was tested in a clinical setting and in a home setting on stroke survivors for safety and feasibility of setting up and operation. These steps led 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.

Advances or Other Highlights

Researchers also developed a mechanism that improves the capacity of a device to provide more naturalistic shoulder movements, which could be used to improve rehabilitation outcomes. In another project, researchers developed a mixed reality rehabilitation system that could be used to help improve the reaching movements of

certain stroke patients. The system provides a novel visual and musical environment in which to provide therapy to stroke patients. The system shows promise as a tool for therapists to enrich rehabilitation programs.

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.

SRO-1.4 By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders. (Outcome)

FY	Target	Result
2012	Complete gene expression studies with peripheral tissues and identify signature gene expression profiles. *(Baseline):* The effects of ethanol exposure on gene expression continue to be analyzed.	N/A
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.	Standardized cell culture techniques were established, validated and refined. (Target Met)

Data Source and Validation
Edenberg HJ, Koller DL, Xuei X, Wetherill L, McClintick JN, Almasy L, Bierut LJ, Bucholz KK, Goate A, Aliev F, Dick D, Hesselbrock V, Hinrichs A, Kramer J, Kuperman S, Nurnberger JI Jr, Rice JP, Schuckit MA, Taylor R, Todd Webb B, Tischfield JA, Porjesz B, Foroud T. Genome-wide association study of alcohol dependence implicates a region on chromosome 11. Alcohol Clin Exp Res. 2010 May;34(5):840-52. Epub 2010 Mar 1. http://onlinelibrary.wiley.com/doi/10.1111/j.1530-0277.2010.01156.x/pdf

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH investigators have established and validated standard techniques to culture cells from peripheral tissues, including immortalized lymphoblastoid cell lines (LCLs), that are enabling studies of gene expression profiles in individuals with and without alcohol use disorders. Recently, a genome wide association study (GWAS) was conducted in a search for new genetic variations that confer risk for alcohol dependence. Of the genetic variations found, those that had the strongest association to alcohol dependence were examined for differences in gene expression in ethanol exposed lymphoblastoid cells. Data from the lymphoblastoid cells, GWAS and a family study were consistent and suggest a possible association between alcohol dependence and a cluster of genes on chromosome 11. The association of this chromosomal region and alcohol dependence warrants further analysis.

NIH investigators also are continuing to refine standardized techniques for use of LCLs. One underlying issue in the use of immortalized cell lines, such as LCLs, is that gene expression may be affected by the process of immortalizing cells. To explore this possibility in depth, gene expression in lymphocyte cells that were not immortalized were compared that of LCLs. Differences were observed suggesting immortalization does affect gene expression in LCLs. However, it may be possible to treat these gene expression effects as "baseline" expression in LCLs, and subtract them from changes that occur in response to ethanol exposure.

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.

SRO-1.5 (RA) By 2012, develop a comprehensive IT platform that can facilitate evaluation of diverse behavioral interventions to promote health (Outcome)

FY	Target	Result
2012	Conduct at least 1 pilot project to test the functionality of the IT platform. *(Baseline):* Initial development phase completed	N/A
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.	The design phase of this project was completed and the development phase is well underway. (Target Met)

Data Source and Validation
For further information, contact Jonathan W. King, Ph.D., kingjo@nia.nih.gov.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. The design phase of this project was completed and development of the platform is well under way. Investigators designed and completed initial development of the Way to Health web-based portal including deploying and testing of hardware and virtual machines, and finalization of technical integration of device-originated data with the portal for several peripheral home-based and hand-held health measurement devices. Programmers also developed automated features of the web portal for researchers such as ability to customize randomization, participant tracking, survey creation, and data downloads for analysis; these features will be tested and debugged in an ongoing Beta launch of the platform.

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 established a plan to create and test a prototype platform. During the first year (FY2010), investigators conceptualized the platform, which consists 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 also integrates with financial service and payment vendors. In the second year (FY2011), development of the platform will be completed. The platform is being 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 addition, pilot projects will be conducted to test the functionalities of the Way to Health platform in a variety of clinical contexts of importance to the health of older adults such as obesity, smoking cessation, exercise, management of congestive heart failure, use of continuous positive airway pressure (CPAP) for sleep apnea, and medication adherence. These projects are on schedule to be completed in 2012.

SRO-1.6 (RA) By 2012, present preliminary findings from the three-pronged approach to curtail the HIV pandemic. (Outcome)

FY	Target	Result
2012	Present preliminary findings from the three-pronged approach to curtail the HIV pandemic, which includes Test, Link to Care, Plus Treat (TLC-Plus) and Pre-Exposure Prophylaxis (PrEP) studies, and basic research to eliminate HIV reservoirs. *(Baseline):* Studies have been initiated to address each of the areas of research that comprise the "three-pronged" approach.	N/A
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.	Enrollment was completed for HPTN 061 and HPTN 064. HPTN 061 enrolled 1,548 participants and HPTN 064 enrolled 2,099 participants. (Target Met)

Data Source and Validation
HPTN 061: Feasibility of a community-level, multi-component intervention for Black MSM in preparation for a Phase IIB community-level randomized trial to test the efficacy of the intervention in reducing HIV incidence among Black MSM. http://www.hptn.org/research_studies/hptn061.asp HPTN 064: The Women's HIV SeroIncidence Study (ISIS). http://www.hptn.org/research_studies/hptn064.asp

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. Enrollment was completed for HPTN 061 and HPTN 064. HPTN 061 completed enrollment of a total of 1,548 participants. The enrollment process for HPTN 061 included media campaigns and community outreach that targeted black men who have sex with men (MSM) friendly venues to advertise the study and find potential participants.

The HPTN 064 study team completed enrollment of a total of 2,099 female participants across 10 communities. Strategies used by the HPTN 064 team to enhance recruitment included the following:

- Ethnographic assessment of communities prior to study initiation and throughout implementation to ensure that appropriate recruitment venues were selected,
- Ongoing community engagement activities at each site to ensure community and stakeholder support and involvement,
- Regular call updates from the principal investigators (PIs) of sites whose accrual was slower than protocol required expectations,
- Monthly site-specific calls and across site calls,
- In person visits and refresher training.

BACKGROUND

While there has been a decline in HIV/AIDS mortality as a result of the increased availability of antiretroviral treatment worldwide, new infections continue to impede efforts to curtail the epidemic. Progress continues to be

made in lowering the number of new HIV infections, but new infections still remain at unacceptably high levels in the US and throughout the world. In addition, AIDS-related illnesses remain a significant cause of morbidity and premature mortality. Existing prevention methods such as education, counseling, and condom use are important in reducing the number of HIV infections, but thus far, have been unable to halt the spread of the epidemic on their own or in combination. Therefore, additional potential prevention methods, new treatment strategies, and approaches to completely eliminate HIV infection must be developed in the coming years as they are still essential to successfully stopping the epidemic.

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 in 2008 even though the number of new infections per year decreased among children from 460,000 in 2001 to 430,000 in 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 with 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 methods. There are three new approaches for controlling the HIV/AIDS pandemic that are being discussed in medical and public health communities; pre-exposure prophylaxis (PrEP), universal testing and treatment (test and treat), and elimination of persistent HIV reservoirs.. Although these approaches are still in the early stages of research and evaluation, when used in combination, their potential for curtailing the HIV pandemic shows great promise.

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), HPTN 064 and HPTN 061, will help determine ways to increase voluntary 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. Together 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 recruitment methods to increase voluntary 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 it may also reduce the overall risk of HIV transmission by lowering viral load among many individuals within a broader community.

Importantly, the Test and Treat strategy has been further streamlined and is now being called “Test, Link to Care, Plus Treat” or the TLC-Plus strategy. The biggest difference between “Test and Treat” and “Test, Link to Care, Plus Treat” is that in the “Test and Treat” approach, all HIV-positive individuals would be treated with antiretroviral therapy , but in the “Test, Link to Care, Plus Treat” approach, only HIV-positive individuals who qualify for antiretroviral therapy according to the current treatment guidelines would receive treatment. Research is ongoing and will address the many factors that could impact the potential value of the TLC-Plus approach,

including: 1) the relationship between stage of infection and transmission, 2) efficacy of antiretroviral therapy (ART) in preventing 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.

Another strategy being studied is pre-exposure prophylaxis (PrEP) which provides therapy prior to exposure to prevent HIV rather than administering treatment after the incidence of infection or illness. Recent studies demonstrated that treatment with antiretroviral HIV 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 a similar effect 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 aimed at eliminating HIV reservoirs in HIV-infected individuals undergoing highly active antiretroviral therapy (HAART). Reservoirs are pockets of latent and persistent HIV in people using 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. Several ongoing research projects seek to characterize residual HIV in treated individuals and develop techniques for its eradication. Better model systems (animal models or simple assays) must be developed to study residual HIV to address the challenge of identifying potential unknown cellular and anatomic reservoirs of HIV. A new initiative was developed to address the issue of HIV persistence and several awards were made in FY 2009.

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)

FY	Target	Result
2012	Complete testing of at least 2 childhood learning approaches for integration into science, technology, engineering and mathematics (STEM) K-12 educational programs. *(Baseline):* Data collected for studies	N/A
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.	A rigorous study protocol of STEM learning in at-risk children was developed and 50% of the 300 participants needed were enrolled. (Target Met)

Data Source and Validation
RC1-HD-063534 Improving fine motor skill development to promote mathematical ability (http://projectreporter.nih.gov/project_info_description.cfm?projectnumber=1RC1HD063534-01). RC1-HD-063522 Efficacy of the core knowledge approach to math and science preschool instruction (http://projectreporter.nih.gov/project_info_description.cfm?projectnumber=1RC1HD063522-01).

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. Researchers designed a study to evaluate whether improving fine motor skills improves math achievement in children. Of the approximately 300 participants needed, 50% were enrolled. The study is an evaluation of two fine motor skill interventions. One intervention is widely used and commercially available that combines increasingly complex fine motor exercises in workbooks with music. The second intervention is designed and administered by occupational therapists that use their diagnostic skills and professionally approved methods to improve fine motor skills. The study participants will be evenly divided between the two interventions and a control group.

Advances or Other Highlights

In another study, researchers will assess the efficacy of an intervention in promoting the math and science skills of children ages 3-5, who are at risk for academic difficulties. Nearly 90% of the preschool teacher participants have been recruited and the child participants are being recruited.

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 provided 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 offered a great opportunity to use biomedical discoveries to inform the development and rigorous testing of interventions to improve classroom achievement.

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)

FY	Target	Result
2012	Build upon research findings to advance understanding of the biological basis underlying the heterogeneity of autism spectrum disorder (ASD) and complete initial testing of three treatment or service delivery strategies *(Baseline):* Several studies are underway to address causal factors and trajectories of ASD, and to test screening, diagnostic, treatment and service delivery strategies.	N/A
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.	Researchers initiated testing of more than six novel treatment or service delivery approaches to address symptoms or improve functioning for individuals with Autism Spectrum Disorder (ASD). (Target Met)

Data Source and Validation
Contact Keisha Shropshire, Health Science Analyst, NIMH, 301-451-0292 or kshropsh@mail.nih.gov R01 HD065272-01 - Improving and Streamlining Screening and Diagnosis of ASD at 18-24 Months of Age – Wetherby, Amy (FL) R01HD065277-01 -- Development of a Screening Interview for Research Studies of ASD – Bishop, Somer (OH) R01HD039961-06A2W1 -- Early Detection of Pervasive Developmental Disorders – Fein, Deborah (CT) R21 HD065275-01 -- Initial Investigation of Prevention of ASD in Infants at Risk – Rogers, Sally (CA) R01 HD065282-01 -- Neural Dissection of Hyperactivity/Inattention in Autism – Castellanos, Francisco (NY) R34 HD065270-01, R34HD065274-01, R34HD065284-01 -- CBT for Anxiety Disorders in Autism: Adapting Treatment for Adolescents – Wood, Jeffrey (CA), Storch, Eric (FL), Ehrenreich-May, Jill (FL) R01 HD065291-01 -- Treatment as usual and peer engagement in teens with High Functioning Autism – Orlich, Felice (WA) R21 HD065276-01 -- The effects of oxytocin on complex social cognition in autism spectrum disorders – Bartz, Jennifer (NY) R01-MH089607-02 -- Behavioral Treatment for Autism in Community Settings Using A Telehealth Network – Lindgren, Scott (IA) RC1-MH089760-02 -- Randomized Study of Training in Autism – Ruble, Lisa (KY) R21-MH085904-02 -- Virtual Reality and Augmented Social Training for Autism – Mundy, Peter (CA)

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH researchers initiated testing of more than six novel treatment or service delivery approaches to address symptoms or improve functioning for individuals with Autism Spectrum Disorder (ASD). Below is a sample of 6 studies that have been initiated.

NIH researchers are conducting studies aimed at developing and testing a variety of interventions designed to enhance clinicians' and families' ability to determine the onset of ASD as early as possible. For example,

researchers are developing and testing an intervention for infants as young as 6-11 months old, who are at risk for ASD and show some early symptoms of the disorder. Such early diagnosis enables early intervention; these studies aim to improve and maximize treatment outcomes for infants and children with ASD. Other researchers are developing interventions for young adults, including cognitive behavioral therapy for adolescents with ASD and co-morbid anxiety disorder, and comparative school-based and community-based interventions to improve peer relationships in adolescents with ASD.

In the area of novel treatment development, one NIH-supported study will determine whether a certain hormone improves social cognition in adults with ASD—a potentially new treatment for social impairment linked to ASD. Another study is investigating the efficacy of a computer-based virtual reality classroom training program to improve the social attention and interaction skills of high functioning children with ASD (HFA). The study has the potential to help improve our understanding of the attention difficulties that children with HFA have in both classroom learning and social interaction settings. Preliminary preparation to conduct the studies is complete, and the researchers continue to be on track to achieve their targeted participant recruitment and enrollment goals.

In the area of service delivery, an NIH study is evaluating how effective telehealth networks are at giving behavioral specialists and parents in rural communities the skills necessary to reduce disruptive behaviors and improve positive social behaviors among children with ASD. A similar investigation is evaluating the effect of three models of professional development training (online only; face-to-face consulting and in-classroom teacher coaching; and, face-to-face consultation and web-based teacher coaching), on basic indicators of ASD symptoms, diagnostic criteria, and evidence-based treatments and services. The study will examine the different effects of these approaches on child and teacher outcomes.

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 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.

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)

FY	Target	Result
2012	Complete data collection for Phase II studies. *(Baseline):* The total number of patients enrolled through FY11.	N/A
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.	303 subjects have been enrolled for assignment into 5 Phase II clinical trials and 2 Phase III clinical trials. (Target Met)
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)

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 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Researchers enrolled 303 subjects across the seven trials, with assignment occurring at the time that a pancreas became available for transplant. In addition, a total of 73 islet transplants have been performed across the seven trials by the end of FY2010. Of these, 33 transplant procedures were performed in subjects enrolled in the phase III trials, and the remainder in subjects enrolled in the pilot trials.

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

Transplantation of pancreatic islets for the treatment of type1 diabetes has the potential for improving control of blood glucose levels and reducing long-term complications as compared to the use of insulin injections. However, recipients of islet transplants must take anti-rejection drugs to prevent immune destruction of the islets, and the long-term benefits of islet transplantation remain unproven.

Prevalence/Incidence

Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys the insulin-producing islets of the pancreas. Approximately, 120,000 people with type 1 diabetes are younger than 20 years of age, making this one of the most common chronic diseases of childhood. 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 pre-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 2008-2011, 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 pilot studies that achieve complete enrollment, the

primary endpoint data are expected to be available for analysis in FY2012. For the Phase III studies, the primary endpoint data will be available for analysis in FY2012 (islet alone) and FY2013 (islet after kidney) 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.

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)

FY	Target	Result
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.	NIH investigators identified three novel targeted cancer interventions: HLI373, englerin, and Tdp1 inhibitors. (Target Met)
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
Dexheimer TS, et al. 4-Pregnen-21-ol-3,20-dione-21-(4-bromobenzenesulfonate) (NSC 88915) and related novel steroid derivatives as tyrosyl-DNA phosphodiesterase (Tdp1) inhibitors. J Med Chem. 2009 Nov 26;52(22):7122-31. PMID: 19883083 http://www.ncbi.nlm.nih.gov/pubmed/19883083 Weidlich IE, et al. Inhibitors of human tyrosyl-DNA phospodiesterase (hTdp1) developed by virtual screening using ligand-based pharmacophores. Bioorg Med Chem. 2010 Jan 1;18(1):182-9. Epub 2009 Nov 11. PMID: 19963390 http://www.ncbi.nlm.nih.gov/pubmed/19963390

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY10 target was Met. NIH investigators identified three novel targeted cancer interventions; 1) HLI373, 2) englerin and 3) Tdp1 inhibitors. HLI373 is an inhibitor of Hdm2. Englerin is a natural product. Tyrosyl-DNA phosphodiesterase (Tdp1) is an enzyme involved in the repair of topoisomerase-mediated DNA damage. 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.

NIH investigators are pursuing inhibitors of specific RING finger ubiquitin ligases whose activity may play an important role in cancer. This work has led to the discovery of a family of inhibitors of Hdm2, an E3 that plays a critical role in regulating levels of p53, a critical tumor suppressor and the 'guardian of the genome'. Investigators have discovered HLI373, a highly soluble potent member of this family. This compound represents a potential “drug-able” lead for the development of therapeutically efficacious inhibitors of Hdm2.

Advances or Other Highlights

Investigators are also carrying out structure-function and structural studies on the transmembrane prometastatic endoplasmic reticulum (ER)-associated degradation (ERAD) ubiquitin ligase gp78. The team determined that the G2BR binds to a region of Ube2g2 distinct from where the RING finger binds this E2 and increases the affinity of Ube2g2 for the gp78 RING finger and therefore stimulates ubiquitination. Researchers predict that this is likely to be the first of many such binding sites on the backside of E2s and that these types of interaction may represent a

general means by which the affinity of E2s for RING finger E3s is increased. Continued evaluation of the means by which gp78 functions as an E3 and development of possible inhibitors is ongoing.

Using an NIH 60-cell panel, NIH investigators found the natural product extract from Phyllanthus engleri --a plant found in East Africa, particularly Tanzania and Zimbabwe --selectively inhibited the growth of renal cancer cell lines. New analogs of englerins were prepared and are now being evaluated for testing in kidney cancer cell lines. Preliminary results show that cells with 1 of 3 genetic lesions are sensitive to englerin A, indicating that it may be useful in therapy.

Human tyrosyl DNA phosphodiesterase I (Tdp1) as been identified an emerging anticancer target. Tdp1 is a DNA repair enzyme involved in the repair of lesions. The development of Tdp1 inhibitors as anticancer agents can be envisioned as combinations of Tdp1 and Top1 inhibitors. Moreover, Tdp1 inhibitors might also be effective by themselves as anticancer agents. To this end, NIH investigators have identified a series of novel inhibitors of Tdp1.

BACKGROUND

The NIH provides a unique community of researchers who work together to advance our knowledge of cancer and AIDS and to translate fundamental discoveries into novel therapies for patients. The NIH is committed to advancing clinical practice and bringing improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects.

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.

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)

FY	Target	Result
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.	A wearable sensor measuring personal exposure to total hydrocarbon and total acid was validated and a high-throughput assay for detecting DNA damage in blood and buccal cells is being validated. (Target Met)
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
Negi et al, Novel monitor paradigm for real-time exposure assessment. JESEE 2010, epub doi:10.1038/jes.2010.35 http://www.ncbi.nlm.nih.gov/pubmed?term=10.1038/jes.2010.35 Single cell trapping and DNA damage analysis using microwell arrays Proc Natl Acad Sci U S A. 2010 Jun 1;107(22):10008-13 http://www.pnas.org/content/107/22/10008.abstract

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. A wearable sensor measuring personal exposure to total hydrocarbon and total acid was validated for its response to several environmental factors in intra- and inter-laboratory settings as well as various field deployment conditions. A high-throughput assay for detecting DNA damage in blood and buccal cells is being validated through inter-laboratory collaborations and is being applied to studies of arsenic-exposed individuals.

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) aimed to accelerate the understanding of genetic and environmental contributions to health and disease. It had two components: the genetic component which focused on identifying major genetic susceptibility factors and the environmental component which focused 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 has created 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 has also developed 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.

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)

FY	Target	Result
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	Completed preclinical studies for the approval of an intramuscular formulation of midazolam for chemical agent induced seizures. (Target Met)
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
Shih, Y1-AI-6178-03: Interagency Agreement "Chemical Affecting the Nervous System – Anticonvulsant /Neuroprotectants. Progress Report Barsan, U01-NS056975: Neurological Emergencies Treatment Trials Network: Clinical Coordination Center. Progress Report. (for period 8/01/2009 – 7/31/2010) Palesch, U01-NS059041: Neurological Emergencies Treatment Trials Network Statistical and Data Management. Progress Report (for period 8/01/2009 – 7/31/2010) Website for Neurological Emergencies Treatment Trials Network (NETT) (http://www.nett.umich.edu/nett/welcome) Contact: Cara Allen, NINDS Office of Science Policy and Planning. Email: allencar@ninds.nih.gov; Tel: 301-496-9271

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH researchers, in partnership with the Department of Defense, completed preclinical studies for the use of intramuscular (IM) midazolam as a drug treatment for chemical agent induced seizures. The candidate drug is being advanced along the FDA Animal Rule regulatory pathway. This regulatory process is designed for circumstances, such as chemical agent exposure, in which human efficacy studies are not feasible or not ethical. In several meetings with the FDA and concerned federal and private organizations, it has been determined that three datasets will be used to seek approval of midazolam for treatment nerve agent seizure under this regulatory pathway. These data include 1) human safety Phase 1 trials (completed), 2) definitive GLP (FDA Good Laboratory Practice) animal efficacy studies (completed, with possible add-on studies), and 3) human efficacy clinical trial of IM midazolam to treat emergency seizures lasting more than five minutes in people who are being transported by emergency medical services (underway and nearing completion).

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. Prompt treatment of lasting seizures is essential to prevent brain damage. The NIH Neurological Emergency Treatment Trial Network (NETT) is conducting the trial, which is designated RAMPART (Rapid Anticonvulsant Medications Prior to Arrival Trial). NETT is a multi-site network that brings together experts from neurology, emergency medicine, and other disciplines to conduct trials of neurological emergencies, such as lasting seizures. RAMPART began recruiting patients in June 2009, and completed the original enrollment target of 800 patients in 2010, ahead of schedule. A new revised target of 1024 patients, with possible extension to pediatric patients, is targeted for completion in early 2011.

Cobinamide, a new cyanide antidote, is in the final stages of preclinical testing. A GMP (FDA Good Manufacturing Practices) manufacturer has been identified and placed under contract. Advanced formulation studies are scheduled for completion by the end of 2010. An Investigational New Drug (IND) application to the FDA, to allow clinical trials to be initiated, is scheduled for 2011. If the IND application is approved, cobinamide could enter phase I clinical testing shortly thereafter.

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 (Investigational New Drug) meeting was held with the FDA in FY 2009 to discuss what studies would be required for an IND. In 2010, the NINDS awarded an SBIR (Small Business Innovation Research) grant (R44NS068049) to complete these studies.

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. New studies have shown that a major contributor to the acute and chronic lung damage caused by sulfur mustard may be due to the formation of fibrin casts in the airways. AEOL 10150 prevents the formation of these casts. 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. In addition, CounterACT investigators have shown that this drug also protects against the toxicity of cholorine, another high priority chemical threat agent. Finally, 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.

SRO-2.8 By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials. (Outcome)

FY	Target	Result
2012	Test an antisense oligonucleotide-based therapeutic strategy that could be applicable to multiple MD-causing mutations that require exon skipping. *(Baseline):* Trials to test strategy for one mutation and preclinical studies to inform use for other mutations are underway.	N/A
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	Multiple small molecules have been shown to be efficacious and result in functional improvement in animal models. (Target Met)
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
Sweeney U01- NS058572: Development of novel small molecules for delaying the progression of muscular dystrophies. Progress Report (for period 07/01/2009 – 06/30/2010). Guttridge U01- NS058451: NF-KB inhibition therapy for Duchenne Muscular Dystrophy. Progress Report (for period 03/01/2009 – 02/28/2010). Fallon U01- NS06429: Development of biglycan as a therapeutic for Duchenne Muscular Dystrophy. Progress Report (for period 08/01/2009 – 06/01/2010). Wang Z, Storb R, Lee D, Kushmerick MJ, Chu B, Berger C, Arnett A, Allen J, Chamberlain JS, Riddell SR, Tapscott SJ. Immune responses to AAV in canine muscle monitored by cellular assays and noninvasive imaging. Mol Ther. 2010 Mar:18(3):617-24. Epub 2009 Dec 29. PMID: 20040912.http://www.nature.com/mt/journal/v18/n3/full/mt2009294a.html Contact: Cara Allen, NINDS Office of Science Policy and Planning. Email: allencar@ninds.nih.gov; Tel: 301-496-9271

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH-supported researchers have tested small molecules in multiple cell-based assays and animal models and have demonstrated that these compounds show activity and functional improvement in the animals. These compounds represent exciting progress toward development of new therapies for muscular dystrophy. While additional animal studies are needed, a number of these compounds are getting closer to the point of preparedness for clinical trials.

One of these studies, a public-private partnership, has made significant progress in identifying and optimizing small molecules that alter the levels of two protein targets: utrophin, a component of muscle that has been suggested as a therapeutic substitute for the protein dystrophin; and myostatin, a protein that inhibits muscle growth. Using high-throughput screening technology, the research team identified a number of compounds that either increased utrophin or inhibited myostatin in cell-based assays. They chose two chemical scaffolds each from the utrophin and myostatin assays to further characterize and synthesize. Using medicinal chemistry, each scaffold is being optimized to generate compounds with the best drug properties and efficacy profile. Recent results have shown that selected compounds based on the scaffolds for the utrophin target showed safety and efficacy in mice. These selected compounds also resulted in a reduction in injury to muscle and improvement in muscle strength in the diaphragm muscle in the mdx mouse model (a strain of mice arising from a spontaneous mutation (mdx) that exhibits many of the same features as Duchenne muscular dystrophy). Similarly, the scaffolds selected for the myostatin target have been optimized using medicinal chemistry with some compounds in the series showing an increase in muscle mass and strength and a decrease in the number of degenerated muscle fibers in mdx mice.

Another team of NIH-supported researchers have been working to improve the efficacy in mouse models of a small protein (peptide) that inhibits the NF-KB signaling pathway. NF-KB is a protein involved in regulating multiple cellular processes both during development and in the disease state. Chronic activation of this pathway has been shown to result in DMD (Duchenne Muscular Dystrophy) pathology specifically by increasing inflammation and inhibiting muscle cell differentiation. The researchers have demonstrated that this peptide blocked NF-KB signaling and thereby significantly improved function of the diaphragm muscle in mdx mice. The peptide also rescued cardiac function in a more severely affected mouse model of DMD.

A third research project supported by NIH has begun work to develop biglycan – a protein that contributes to the dystrophin-glycoprotein complex at the cell surface – into a useable form to test as a therapy for DMD. The research team has shown that one form of biglycan is active in a cell-based assay, increases the expression of utrophin in muscle, and improves muscle function in mdx mice.

Advances or Other Highlights

In FY 2010, NIH-supported investigators also tested a strategy to suppress or evade the immune response to gene therapy. They had hypothesized that modifying proteins on the surface of a virus used to deliver therapeutic genes would cause less of an immune response than unmodified virus. When they made the changes to the virus to block interactions between the virus and a class of molecules thought to be involved in the immune response [heparan sulfate proteoglycans (HSPG)], however, the modified virus still provoked an immune response in dogs. This finding demonstrates that activation of the dogs' immune system was not related to the virus binding to HSPG. Furthermore, the study also demonstrated that magnetic resonance imaging is a sensitive, non-invasive method to detect local muscle inflammation after gene therapy injections—a finding that will be useful for subsequent gene therapy studies.

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. The NIH data compiled in 2009 indicate 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 workshop convened by NIH in June 2007 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 therapy 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. The NIH supports 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 supported research on muscular dystrophy pathogenesis and therapies, and preclinical therapy development research for neurological conditions. The NIH supports a Cooperative Program in Translational Research for Neuromuscular Disease focused on the development of novel therapies for muscular dystrophy. Researchers in the Cooperative Program have focused on multiple forms of muscular 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 make the blood vessel walls permeable 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 supported 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 a patient voluntary organization as well as a biopharmaceutical company to support this project, thereby creating a public-private partnership.

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)

FY	Target	Result
2012	Build teams of transdisciplinary scientists, including those newly trained, to conduct cross-center analysis to understand and address health inequities. *(Baseline):* New comprehensive training strategies and programs for junior scientists have been developed.	N/A
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.	NIH funded 10 new Centers for Population Health and Health Disparities grant awards at academic institutions across the United States. (Target Met)

Data Source and Validation
Centers for Population Health and Health Disparities (CPHHD) program website: http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html NCI Press Release: NIH Announces Ten Awards for Centers for Population Health and Health Disparities http://www.cancer.gov/newscenter/pressreleases/CPHHD

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. The National Institutes of Health (NIH) funded 10 Centers for Population Health and Health Disparities (CPHHD) around the country, designed to better understand and address inequities associated with the two leading causes of death in the United States – cancer and heart disease. The CPHHD program uses a transdisciplinary approach involving social, behavioral, biological, and genetic research to improve knowledge of the causes of health disparities and devise effective methods of promoting health and preventing, diagnosing, and treating disease. In addition, each center plays a major role in the training of a new generation of transdisciplinary researchers in collaborative team science. The applications that were selected for funding were those that received the top scores during NIH peer review.

The value added by transdisciplinary approaches to traditional health disparity research models, typically characterized by isolated specialty foci or "silos," is clearly evident within the CPHHD and across the program as a whole. NIH's CPHHD program has provided a single, network-based organizational structure that supports and encourages the unique type of research required to address health disparities. By providing this structure, the CPHHD program has established new ground in health disparities research never explored fully before the program existed.

Research conducted through the NIH CPHHD program is unique not only because it is moving science from "bench to trench," but because it includes underserved and minority communities as partners to identify, address, and ultimately reduce health disparities. As a central feature of the CPHHD, members of the community are involved in the development, execution, and dissemination of research that impacts them directly. NIH's CPHHD researchers have established a wide variety of successful relationships between academic researchers and community groups.

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. Therefore, 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.

SRO-2.10 By 2014, identify three clinical candidate compounds for rare or neglected diseases. (Outcome)

FY	Target	Result
2012	Begin pilot projects on the selected rare disease lead compound series to assess their capabilities as potential therapeutics. *(Baseline):* Pilot projects on the selected rare disease lead compound series to assess their capabilities as potential therapeutics are needed	N/A
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

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

Performance Results for the FY11 GPRA Performance Target will be reported in February, 2012.

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.

SRO-2.11 By 2016, conduct studies of young children to determine whether the plant estrogens in soy formula produce hormone-like effects. (Outcome)

FY	Target	Result
2012	Enroll an additional 112 mothers prenatally or at birth. Complete 70 prenatal visits, 80 birth visits and 80 2-week examinations. Enroll an additional 200 Toddlers and complete their 1 year evaluations. *(Baseline):* (FY11) Data collection initiated.	N/A
2011	Enroll 112 mothers prenatally or at birth. Complete 70 prenatal visits, 80 birth visits and 80 2-week examinations. Enroll 200 Toddlers and complete their 1 year evaluations. *Previous target:* *Enroll 112 mothers and complete 99 birth and 2 week examinations and specimen collections from the children. Enroll 240 toddlers and do 1 year evaluations.* *(Baseline):* Detection of hormonal influences on infants possible	N/A

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

Performance Results for the FY11 GPRA Performance Target will be reported in February, 2012.

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.

In planning the study for this measure, the NIH expected to identify at least 2 study sites capable of conducting the research based on previous experience with similar observational studies. However, out of the 4 proposals received, only 1 site was appropriate and technically adequate. Enrollment and evaluation of study participants is proceeding at this site, but the overall progress is approximately half of the originally anticipated progress. Participant enrollment will be extended by 2 years to develop a cohort with originally planned and sufficient statistical power to complete the observational study. The measure completion year and targets have been adjusted to reflect the new pace of enrollment.

The measure will be extended by two years, to 2016 to reflect the additional time needed to complete participant enrollment and evaluation. Overall performance will be maintained as the final cohort size will be the same as originally planned. Annual performance targets will reflect the incremental progress expected from the participating study site. The original budget has been reduced appropriately to compensate for the change to one study center but the budget is currently planned to continue funding until the completion of the study.

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.

The 2011 and 2012 targets for the Infant Phase have been modified to reflect a shift in recruitment strategy. The accrual totals remain the same but the focus for recruitment will shift more to the prenatal period rather than the post delivery period. The study team has determined that recruitment during the 3rd trimester will be more successful than at birth visits. This decision is based on the researchers' recent study experience, which includes cultural sensitivity considerations. They have discovered that introducing the mother to the study during the 3rd trimester is less challenging and more predictable than during the 48 hours post-delivery. There are a number of logistical and ethical issues that may occur during post-delivery, e.g., is the mother sleeping, will the baby be circumcised, etc. On the other hand, mothers in the 3rd trimester are more relaxed and better prepared for the birth visit, which is a required baseline visit, if they are pre-enrolled. The modification regarding toddler enrollment is due to resources and logistics, which had to be adjusted due to staffing and clinic patient flow as a result of the scientific aim regarding the shift in recruitment described above.

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)

FY	Target	Result
2012	Complete baseline imaging studies to facilitate analysis of the effects of IVIg on relevant biomarkers of AD. *(Baseline):* Relevant biomarkers of disease have been identified for Alzheimer's disease.	N/A
2011	Complete recruitment to a Phase III clinical trial of intravenous immunoglobulin (IVIg) for the treatment of mild to moderate AD. *(Baseline):* People who receive IVIg treatment for other conditions are at reduced risk of developing AD later in life, but IVIg's direct effects on AD are unknown.	N/A
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.	NIH established a phase III clinical trial of intravenous immunoglobulin (IVIg) for the treatment of mild to moderate Alzheimer's disease. (Target Exceeded)
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.	Investigators found that changes in tau and beta-amyloid levels in the cerebrospinal fluid may signal early AD; elevated brain beta-amyloid may denote increased risk of the disease. (Target Met)
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)
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)

Data Source and Validation
Shaw LM et al., Cerebrospinal fluid biomarker signature in Alzheimer's Disease Neuroimaging Initiative subjects. Annals of Neurology e-pub 18 March 2009. http://www3.interscience.wiley.com/cgi-bin/fulltext/122266379/HTMLSTART Morris JCet al. Pittsburgh Compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer's disease. Archives of Neurology 66: 1469-1475, 2009. Storandt M et al.Cognitive decline and brain volume loss are signatures of cerebral amyloid beta deposition identified with PiB. Archives of Neurology 66: 1476-1481, 2009. IVIg Trial Description at clinicaltrials.gov: http://www.clinicaltrials.gov/ct2/show/NCT00818662?term=alzheimer%27s+disease+AND+IVIg&rank=3

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Researchers with the Alzheimer's Disease Neuroimaging Initiative have established a method and standard of testing levels of AD's characteristic *tau* and beta-amyloid proteins in the cerebrospinal fluid (CSF). The researchers correlated levels of these proteins in the CSF with changes in cognition over time and determined that changes in these two protein levels in the CSF may signal the onset of mild AD. This is a significant step forward in developing a test to help diagnose the early stages of Alzheimer's disease earlier and more accurately so that treatment efforts may begin and potentially delay the development of more severe AD symptoms.

In a separate study, NIH-supported investigators used positron emission tomography with Pittsburgh Compound B (an agent developed to detect levels of beta-amyloid in the living brain), magnetic resonance imaging, and standardized cognitive tests to explore the relationship between brain beta-amyloid and dementia risk in cognitively normal people. The study found that higher amounts of the protein deposits in dementia-free people were associated with an increased risk of developing dementia over time and with loss of brain volume and subtle declines in cognitive abilities. These findings suggest that brain beta-amyloid may in fact be a preclinical sign of disease even among individuals who appear cognitively normal.

Taken together, these findings will greatly facilitate less expensive and more efficient drug trials for AD. AD pathology may be apparent in the brain long before clinical symptoms appear, and these findings may open the door to the discovery of an entire panel of CSF biomarkers that will not only predict people at risk of developing AD, but also assess how the disease responds to therapies rapidly and efficiently, well before the advent of clinical symptoms.

In addition, the FY 2011 target was Met Efficiently. NIH established a phase III clinical trial of intravenous immunoglobulin (IVIg) for the treatment of mild to moderate Alzheimer's disease. IVIg is a type of immune therapy in which antibodies from thousands of plasma donors are pooled, purified, and administered to a patient in order to boost the immune system. IVIg carries antibodies against beta amyloid, the accumulation of which leads to the formation of the AD characteristic amyloid plaques. Research has shown that people who receive IVIg treatment for other conditions (e.g., autoimmune disease) may also have a reduced risk of developing AD later in life.

An important component of this study is the analysis of the effects of treatment on biomarkers of disease to assess amyloid burden and changes to the brain structure and function. All participants will undergo magnetic resonance imaging (MRI) and a subset will undergo serial positron emission tomography (PET) and cerebrospinal fluid (CSF) collection.

Advances or Other Highlights

NIH has made other important advances toward the overall achievement of this measure. Notably, ADNI has

entered its second phase, ADNI2, in which approximately 1,000 people aged 55 to 90 will be followed to define any changes in brain structure and function as people transition from normal cognitive aging to mild cognitive impairment (MCI), often a precursor to Alzheimer's, to Alzheimer's dementia. The study will use imaging techniques and biomarker measures in blood and cerebrospinal fluid specially developed to track changes in the living brain. Researchers hope to identify who is at risk for Alzheimer's, track progression of the disease and devise tests to measure the effectiveness of potential interventions.

In addition, the advent of genome wide association studies (GWAS) and other high throughput technologies has facilitated the identification of several other strong candidate genes, including CR1, CLU, PICALM and SORL1; the first three of these were identified and confirmed in studies that used pooled genetic data from a number of U.S. and European research groups. Identification of new pathways that contribute to the development of AD will provide novel avenues for drug targeting.

Efficiency

FY 2011 target: NIH was able to initiate the Phase III clinical trial of IVIg sooner than anticipated based on the success of early phase (I / II) clinical trials. In these clinical trials, AD patients who were treated with IVIg demonstrated improvement in cognition and reduced amyloid load in the brain. These study results will be tested in the larger-scale Phase III trial that will now complete patient recruitment in FY 2011.

BACKGROUND

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. Estimates of how many people in the United States currently have AD vary, but experts suggest that between 2.6 million and 5.1 million Americans aged 65 years and older may have AD, and these numbers are predicted to increase to 13.2 million by 2050 unless more effective ways to treat and prevent AD are found according to prevalence estimates research created using the 2000 US Census.

Disease Burden

In 2010, the projected healthcare spending for people with Alzheimer's and other dementias is $174 billion. Medicare and Medicaid spend the majority of those health care dollars. But even a delay in the progression of AD by a few years could significantly decrease the amount of health care spending, as well as the cost of care provided by families according to a report by the Alzheimer's Association.

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

As this measure enters its final years, NIH is moving toward completion of the goal through the establishment of a phase III clinical trial of intravenous immunoglobulin (IVIg) for the treatment of mild to moderate Alzheimer's disease. IVIg is a type of immune therapy in which antibodies from thousands of plasma donors are pooled, purified, and administered to a patient in order to boost the immune system. IVIg carries antibodies against beta amyloid, the accumulation of which leads to the formation of the AD characteristic amyloid plaques. Research has shown that people who receive IVIg treatment for other conditions (e.g., autoimmune disease) may also have a reduced risk of developing AD later in life. In previous early phase clinical trials, AD patients who were treated with IVIg demonstrated improvement in cognition and reduced amyloid load in the brain; however, these were small studies whose results require confirmation in a larger-scale trial.

An important component of this study is the analysis of the effects of treatment on biomarkers of disease to assess amyloid burden and changes to the brain structure and function. All participants will undergo magnetic resonance imaging (MRI) and a subset will undergo serial positron emission tomography (PET) and cerebrospinal fluid (CSF) collection. It is anticipated that baseline imaging of all participants will be completed by the end of FY2012.

Since this measure was established in 2003, researchers have made important progress 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. Research is ongoing 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 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.

Genetics

Until recently only one risk factor gene for late-onset AD – the ε4 allele of the APOE gene – had been validated. However, the advent of genome wide association studies (GWAS) and other high throughput technologies has facilitated the identification of several other strong candidate genes, including CR1, CLU, PICALM and SORL1. The AD Genetics Initiative was established 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. In addition, NIH has created an AD Genetics Consortium to collaboratively use the collective resources of the AD research community to identify the remaining susceptibility genes for late-onset AD; data from a number of GWASs have been pooled to facilitate this analysis. Consortium investigators are also using these data to identify genes that influence

specific aspects of AD that vary among patients, such as the amount of amyloid plaques or neurofibrillary tangles in the brain, concentrations of amyloid beta and tau in cerebral spinal fluid, rate of disease progression, and responses to environmental factors (drugs, non-pharmaceutical factors) that may either slow or hasten the disease's onset or progression.

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.

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 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 supports a major translational research effort to expand the range of novel compounds to be tested for cognitive decline, MCI, and AD, and to more quickly move research from the laboratory to clinical trials in humans. Over 40 compounds are currently under study as part of this effort, including agents that may inhibit the development of neurofibrillary tangles (a hallmark of the disease) as well as anti-inflammatory drugs and neuroprotective agents. NIH also supports preclinical testing of natural products such as grape seed extract, which has been shown to reduce cognitive deterioration in a mouse model of AD. Other preclinical development projects focus on the repurposing of drugs to treat other disease conditions – for example, studies are ongoing to determine whether anti-hypertensives and diabetes drugs can improve cognition.

In many cases, compounds for which NIH funded preclinical development have been picked up by industry partners for clinical testing.

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. Successful pilot trials may be followed by full-scale clinical trials conducted by NIH or academic or industry partners. 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 clinical trials of diabetes drugs such as metformin and insulin. Finally, investigators on epidemiological and longitudinal studies sometimes observe that interventions for other conditions (for example, cholesterol-lowering statins and nonsteroidal anti-inflammatory drugs) appear to be associated with a reduction of risk of AD. Although such interventions have not always fared well in controlled clinical trials for AD, questions remain about the optimal timing of administration of some of these drugs. For example, some forms of hormone therapy, when given to postmenopausal women, may increase risk of cognitive decline; however, some research suggests that a "window of opportunity" may exist, during which estrogen may exert a long-term protective effect on the brain. This is currently an active area of study for NIH-supported investigators.

NIH currently supports 38 clinical trials of a wide range of interventions to prevent, slow, or treat AD. A particular emphasis is on prevention trials in presymptomatic individuals using biomarkers identified through ADNI (or elsewhere, as appropriate). Interventions under study include:

- treatments to stimulate the immune system to fight AD
- drugs for common health conditions such as diabetes and cardiovascular disease
- hormonal treatments
- antioxidants
- physical and mental exercise
- commonly used psychiatric drugs

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.

SRO-3.2 By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. (Outcome)

FY	Target	Result
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.	Conducted Phase Ib study of DAS181-F02 and determined it was safe and well-tolerated in healthy adults. (Target Met)
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)

Data Source and Validation
Dr. Helen Schiltz – hschiltz@niaid.nih.gov, 301-451-3245

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met and the measure was Achieved. NIH researchers conducted a Phase Ib study of DAS181-F02 for safety and tolerability. DAS181-F02 is an antiviral that targets viral receptors on the host cell surface and thus is potentially useful for treating and preventing infection by all variations of influenza and parainfluenza, viruses from two different families that share the same viral entry mechanism.

The need for novel antiviral drugs against influenza has been highlighted by the emergence of H5N1, the pandemic H1N1 virus and the development of multi-drug resistant strains of influenza. An ideal candidate would work with a novel mechanism, be effective against all variants of influenza viruses (IFV) and limit the emergence of drug resistance. DAS181 (Fludase®), a sialidase fusion protein, is one such new therapeutic candidate. DAS181(Fludase®), targets sialic acid viral receptors on the host cell surface and thus is potentially useful for treating and preventing infection by all variations of influenza and parainfluenza viruses that share the same sialic acid receptor-based viral entry mechanism. Together with industry, the NIH developed DAS181. DAS181 has proven, both in tissue culture and in various animal models, to have strong inhibitory activity against a large number of seasonal influenza strains, pandemic H1N1, and highly pathogenic avian influenza (HPAI) strain H5N1, as well as activity against parainfluenza. In 2010, an additional phase I clinical trial, Phase Ib, was completed. This further demonstrated safety in normal and healthy adults using a formulation of DAS181, DAS181-F02.

The Phase Ib study was conducted as a double-blind, randomized, placebo-controlled, single and multiple dose-

escalating study in healthy adults ages 18 to 65. This study enrolled a total of 45 subjects who were randomized into five cohorts of nine individuals. The primary endpoints were safety and tolerability of DAS181-F02 as measured by a battery of clinical and laboratory parameters. Unlike the Phase Ia first in man safety study that was completed previously, the drug dosages tested in the Phase Ib trial were in dose ranges that will support future efficacy studies in humans. This Phase Ib trial demonstrated both single dose and multiple doses of DAS181-F02 were safe and well-tolerated with no significant safety concerns observed. Based on these favorable findings, a Phase IIa human efficacy trial of DAS181-F02 has subsequently been initiated in human subjects with confirmed non-complicated influenza infection. The Phase IIa study is currently enrolling patients at numerous clinical sites across the US.

Measure

The NIH supports product development through the pipeline from basic research through clinical trials. The development of DAS181-F02 is an excellent example of this wide-ranging commitment. Initially NIH supported drug discovery and preclinical development that led to the filing of an investigational new drug application and the initiation of a first-in-man human safety clinical trial. NIH has also supported subsequent product development in nonclinical and clinical activities, including the Phase Ib clinical trial referenced in this report. Regulatory support enabled the conduct of regulatory compliance audits, which were crucial to the success of the Phase Ib trial. The development of DAS181-F02 is an excellent example of how Federal commitment can positively affect the drug development process.

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. It is also 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. This includes 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.

SRO-3.3 By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease. (Outcome)

FY	Target	Result
2012	Demonstrate the clinical value of the compact instrument by collecting and testing saliva samples from 80 patients with head or neck cancer against 120 control samples. *(Baseline):* No large-scale clinical validation studies have been conducted.	N/A
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.	A validation study of salivary samples from 102 patients was completed. Salivary protein biomarkers and mRNA biomarkers were confirmed to discriminate Sjogren's Syndrome from systemic lupus erythematosus and healthy saliva. (Target Met)
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)
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)

Data Source and Validation
Patent filed: "Salivary Biomarkers for Primary Sjogren's Syndrome." UCLA Case # 2008-303. US application filed 05/20/2009, Patent # 12/475,347. http://portal.uspto.gov Paper under revision for Arthritis Care Research. Hu S, Gao K, Pollard R, Arellanno-Garcia M, Zhou H, Zhang L, Elashoff D, Kallenberg CGM, Visser R, Wong DT. Validation of salivary biomarkers for primary Sjogren's syndrome.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. Thirty-four patients with primary Sjogren's Syndrome, 34 patients with systemic lupus erythematosus, and 34 healthy individuals were enrolled for validation studies. Analyses of salivary samples revealed a panel of protein and mRNA biomarkers that discriminated primary Sjogren's Syndrome from both the lupus and healthy patients. Identification of these biomarkers may help develop a simple yet highly discriminatory clinical tool for the diagnosis of Sjogren's Syndrome.

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.

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)

FY	Target	Result
2012	Develop one or more alternative macaque models that more accurately reflect human exposure and that can be used to determine the ability of candidate vaccines to provide protection against challenge viruses that are genetically distinct from the vaccine (i.e., a heterologous challenge) *(Baseline):* Current animal models do not reflect HIV infection in humans making it difficult to determine the potential effectiveness of an HIV vaccine candidate.	N/A
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.	Researchers initiated three phase I studies of new HIV vaccine approaches: a DNA vaccine, an adenovirus-based HIV vaccine regimen, and a novel, preventive HIV vaccine. (Target Met)
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)
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)

Data Source and Validation
HIV Vaccine Regimen Demonstrates Modest Preventive Effect in Thailand Clinical Study. http://www3.niaid.nih.gov/news/newsreleases/2009/ThaiVaxStudy.htm HIV/AIDS Vaccines. http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines Abstracts from AIDS Vaccine 2010 Selected abstracts include: Analysis of the relative risk of HIV acquisition among Step study participants with extended follow up 1. Beneficial effects of protective HLA class I allele expression on HIV viral load are not mediated through increased vaccine-induced immunity. 2. Susceptibility of Epithelial cells from the human female upper reproductive tract to infection by transmitted/founder HIV-1 3. Phase III HIV Vaccine Trial (RV144): Preliminary Immunogenicity findings. NIAID Press Release: NIH-Led Scientists Find Antibodies that Prevent Most HIV Strains from Infecting Human Cells NIAID Media Availability: NIH Scientists Freeze Virus Fragment in Shape Recognized by Immune System

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. During the past fiscal year, NIH initiated three small phase I trials of new vaccine approaches. Two studies were initiated within the HIV Vaccine Trials Network (HVTN), HVTN 080 and HVTN 083, and one was initiated through an Integrated Preclinical/Clinical AIDS Vaccine Development program award -- Ad5HVR48.

HVTN 080 is assessing a DNA vaccine, PENNVAX-B, given with and without an IL-12 adjuvant, enhancing agent, and delivered via electroporation (*Electroporation is a mechanical method that allows molecules like DNA to pass into a host cell through the cell membrane.).* The study will assess the safety and level of immune response in 48 healthy volunteers. The vaccine targets HIV gag, pol, and env proteins. Previous research in non-human primates, conducted by an NIH researcher, showed a 100-fold enhancement in immune responses resulting from the vaccine when delivered via *in vivo* electroporation compared to syringe injection without electroporation.

HVTN 083 is a phase 1 clinical trial that will evaluate the safety and immune response of an adenovirus-based HIV vaccine regimen that includes two vaccines given at different time points to HIV uninfected adults. The study utilizes a prime-boost vaccine approach, which is when two vaccines are given sequentially at different time points in order to stimulate different parts of the immune system and enhance the body's overall immune response to HIV. The trial will test the ability of this heterologous-insert prime-boost vaccine regimen using env inserts from different HIV clades to increase T-cell responses. The trial will then compare the degree of polyfunctionality of insert specific T cells after vaccination within heterologous and homologous (similar in structure and origin) vector vaccine regimens. Participants will receive the two HIV vaccines three months apart. Heterologous-insert prime-boost vaccine regimens, which use the same gene from different HIV subtypes, may be more effective than traditional homologous insert prime-boost vaccine regimens at eliciting immune responses directed at epitopes (binding sites on antigens) that are highly prevalent, possibly leading to a more effective immune system response to the vaccine.

Recombinant adenovirus serotype vectors have been shown to elicit strong immune response from both CD4 and CD8 cells. The third study is designed to determine the safety and immunogenicity (ability to create an immune response) of a novel, modified recombinant adenovirus serotype 5 preventive HIV vaccine, Ad5HVR48. The study is being conducted in healthy adults and will last 18 to 24 months.

BACKGROUND

The development of a universal HIV/AIDS vaccine continues to be a priority to control the pandemic. While, progress has led to the development of valuable medical treatments, such as highly active antiretroviral therapy (HAART), there is still no cure. Most importantly, antiretroviral therapy does not prevent the spread of HIV. 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 2008, 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 2008, 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 2008, while the number of children newly infected HIV (430,000) was decreased by 18% in that same time frame.

In the United States, the most recent statistics from the Centers for Disease Control and Prevention revealed that from 2004 through 2007, the estimated number of newly diagnosed HIV/AIDS cases in the 34 states with confidential name-based HIV infection reporting increased 15%. This is most likely due to changes in state reporting regulations and an increase in HIV testing. In 2007, the estimated overall rate of newly diagnosed HIV/AIDS infections in the 34 states was 21.1 per 100,000 people. African-Americans continue to face the greatest burden of HIV/AIDS. At 76.7 per 100,000, the rate of new HIV infections among African-Americans in the United States is seven times the rate among whites. In 2007, African-Americans accounted for 51% of all diagnosed cases of HIV/AIDS. Men who have sex with men (MSM) accounted for 53% of all diagnosed cases.

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, thereby weakening the social stability and threatening 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.

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 advance HIV vaccine research. This dialogue revealed a broad scientific consensus that designing a safe and effective preventive HIV vaccine will require enormous advances in fundamental research beyond present-day knowledge. As such, NIH supports basic research, non-human primate research and other clinical research that may contribute to vaccine discovery. In addition, NIH continues 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 research 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's vaccine research program includes fundamental research to better understand how HIV interacts with the human immune system and the clinical testing of promising vaccine candidates when appropriate. Basic research in HIV pathogenesis, immunology, virology and animal model development helps inform and guide the identification of new vaccine concepts. Clinical testing is conducted to address important scientific questions and for product development purposes.

NIH continues to support and strengthen its fundamental research efforts through several programs. Two programs in particular were initiated in 2008: the Basic Vaccine Discovery Program and Highly Innovative Technologies to Interrupt Transmission of HIV (HIT-IT). In 2009 NIAID made 20 awards to the Basic Vaccine Discovery program, which was designed to accelerate vaccine discovery efforts by generating new knowledge to inform new conceptual approaches to vaccine design. In that same year, 16 awards (five of which focused on vaccine discovery research) were made for Highly Innovative Technologies to Interrupt Transmission of HIV (HIT-IT), which aims to stimulate the development of novel, unconventional, high-risk, high-impact approaches.

Two other programs also important for advancing NIH's vaccine discovery efforts include the Phased Innovation Awards in AIDS Vaccine Research Program, which supports highly innovative early stage AIDS vaccine research and the B-cell Immunology Partnerships for HIV Vaccine Discovery Program. The B-cell Immunology Program, initiated in late 2009, is designed to foster cross-fertilization between B-cell immunologists and HIV vaccinologists to facilitate discovery of novel vaccine design and immunization strategies for eliciting broadly protective anti-HIV antibodies. Several awards to this program are anticipated in the coming year. NIH also continues to support the Center for HIV/AIDS Vaccine Immunology (CHAVI), a virtual center designed to support intensive and highly collaborative projects that address key immunological obstacles to the discovery and development of a safe and effective HIV vaccine.

Plans are also underway for NIH to initiate a new program – the Consortia for AIDS Vaccine Research in Nonhuman Primates – to investigate SIV mucosal infection in nonhuman primate (NHP) models. This consortium will address deficiencies in NHP models, such as the Simian Human Immunodeficiency Virus in the macaque model not correlating with the results seen in a human clinical trial (i.e., STEP). Additionally, this should provide understanding of events that occur very early during sexual transmission of HIV in humans and insight into the immune response needed by an HIV vaccine to block infection at mucosal sites, prevent establishment of systematic infection and reduce the pathogenic effects of infection.

In addition, efforts are underway to improve or develop alternative macaque models that better reflect human HIV infection. In the macaque model the homologous challenges are administered into the muscle of the animal and the challenge virus is exactly matched in genetic composition to the vaccine. In most HIV infections in humans the infecting HIV is highly unlikely to contain the exact HIV genetic sequences that are used in preparing the vaccine and most infections are acquired through mucosal exposure.
The HVTN Laboratory Program (LP) will continue to expand its portfolio of immune assessments to include more comprehensive B-cell, T-cell and innate immune analyses to define vaccine immunogenicity in order to better predict protective immune responses. Also, the HIV Vaccine Research and Design Program (HIVRAD) will continue to support targeted research that translates basic research concepts into prototype vaccine/prevention candidates.

To date, NIH has supported 114 HIV vaccine clinical trials, involving 67 different products and 18 adjuvants. Currently, NIH is supporting 15 HIV vaccine trials through its HIV Vaccine Trials Network, Vaccine Research Center and in collaboration with the U.S. Military HIV Research Program (MHRP) and other collaborating partners. Of note is an exploratory HIV vaccine clinical study that was initiated this past year. This phase II study is examining whether a two-part vaccine regimen can decrease viral load (the amount of HIV in the blood) in study participants who later become infected with HIV (HVTN 505). HVTN 505 employs a prime-boost strategy of two investigational vaccines developed by scientists at NIAID's Vaccine Research Center (VRC). In this approach one

vaccine is used to prime the immune system and another vaccine is used to boost the immune response. This type of strategy generally induces different types of immune system responses compared with vaccine regimens in which only one type of vaccine is administered. Although the study is not intended to lead to the licensure of the vaccine regimen being tested, it will answer important scientific questions that could lead to the discovery and development of new and improved HIV vaccines in the future.

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)

FY	Target	Result
2012	Initiate replication and refinement of genome wide association and functional analysis data. *(Baseline):* Genome wide association studies have identified variations linked to alcohol dependence, and functional analyses have been conducted.	N/A
2011	Conduct functional studies of candidate genes in different populations. *Previous Target:* *Replicate previously identified functional differences in various ethnic populations.* *(Baseline):* Variations identified from fine mapping studies continue to be characterized. Genome wide association studies are also being used to identify variants.	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.	Functional differences were characterized for sequence variations in genes encoding serotonin receptors and transporters, the oxidative stress enzyme SOD2, and nicotinic receptor subunits. (Target Met)
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)

Data Source and Validation
Bevilacqua L, Doly S, Kaprio J, Yuan Q, Tikkanen R, Paunio T, Zhou Z, Wedenoja J, Maroteaux L, Diaz S, Belmer A, Hodgkinson CA, Dell'Osso L, Suvisaari J, Coccaro E, Rose RJ, Peltonen L, Virkkunen M, Goldman D. A Population-Specific Htr2b Stop Codon Predisposes to Severe Impulsivity. Nature, In Press. Srivastava V, Buzas B, Momenan R, Oroszi G, Pulay AJ, Enoch MA, Hommer DW, Goldman D. Association of SOD2, a mitochondrial antioxidant enzyme, with gray matter volume shrinkage in alcoholics. Neuropsychopharmacology. 2010 Apr;35(5):1120-8. Epub 2009 Dec 30. http://www.nature.com/npp/journal/v35/n5/pdf/npp2009217a.pdf Hong LE, Hodgkinson CA, Yang Y, Sampath H, Ross TJ, Buchholz B, Salmeron BJ, Srivastava V, Thaker GK, Goldman D, Stein EA. A genetically modulated, intrinsic cingulate circuit supports human nicotine addiction. Proc Natl Acad Sci U S A. 2010 Jul 27;107(30):13509-14. Epub 2010 Jul 19. http://www.pnas.org/content/107/30/13509.full.pdf+html Enoch MA, Gorodetsky E, Hodgkinson C, Roy A, Goldman D. Functional genetic variants that increase synaptic serotonin and 5-HT3 receptor sensitivity predict alcohol and drug dependence. Mol Psychiatry. 2010 Sep 14. [Epub ahead of print] PMID: 20838391 [PubMed - as supplied by publisher] http://www.nature.com/mp/journal/vaop/ncurrent/full/mp201094a.html

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH researchers examined sequence variations in genes encoding serotonin receptors and transporters, the oxidative stress enzyme SOD2, and nicotinic receptor subunits. The results of the studies suggest the variants tested are likely to be associated with increased vulnerability for substance use and behavioral disorders in individuals who carry them. The sequence variants may be useful in the future as markers to predict risk of developing alcohol and other drug dependence and related disorders.

The neurotransmitter serotonin influences many behaviors, including impulsivity, and plays important roles in substance use addiction. In a recent search for genes that influence impulsive behavior, NIH collaborated with international scientists to conduct a high throughput genomics study on severely impulsive Finnish criminal offenders and matched controls. The researchers identified a functional polymorphism in a serotonin receptor gene, HTR2B, which was predictive of impulsive behaviors, including homicide and other violent crimes. Study participants who both carried the polymorphism and committed violent offenses committed 94% of the crimes under the influence of alcohol. The HTR2B polymorphism, also called a genetic variant, prematurely terminates synthesis of the receptor. It is only present in the Finnish population where it has a relatively high frequency (1 in 50 Finnish people carry the variant). The findings were replicated in mice which became more impulsive when the mouse HTR2B gene was made nonfunctional.

In previous studies of the serotonin pathway, a polymorphism in the promoter region of the serotonin transporter gene, 5-HTTLPR, was associated with changes in neuronal circuitry as well as risk-taking behavior. In a recent study, a functional polymorphism in the 5-HT3 serotonin receptor gene (HTR3B) was analyzed in treatment-seeking African-American men with single and comorbid DSM-IV lifetime diagnoses of alcohol, heroin and/or cocaine dependence. A variant in the HTR3B gene that confers gain-of-function in the 5-HT3 receptor predicted alcohol dependence and had no effect on heroin or cocaine dependence. A 5-HTTLPR functional polymorphism that confers low activity of the serotonin transporter gene predicted heroin and cocaine dependence but was not associated with alcohol dependence. However, individuals who had both the HTR3B and 5-HTTLPR functional variants were six times more likely to have alcohol and comorbid drug dependence compared with those individuals who had neither variant.

Oxidative stress caused by the accumulation of free radicals, such as reactive oxygen species, has been linked to various disorders and diseases such as diabetes, atherosclerosis, neurodegenerative disorders and psychiatric disorders. Chronic alcohol use produces reactive oxygen species in the brain, which are associated with changes in

brain structure and shrinkage in the white and gray matter regions of the brain. SOD2 is an enzyme in the mitochondria which protects against oxidative stress and is less active in the brain and liver of individuals with alcohol dependence or withdrawal. This led NIH researchers to investigate SOD2 as a protective mechanism against brain shrinkage caused by alcohol-induced reactive oxygen species. In the current study, MRI scans were used to measure brain volume. Alcohol dependent individuals had lower gray matter and white matter volumes as compared to controls. Genomic studies with DNA isolated from the alcohol-dependent individuals indicated the SOD2 variant, Ala16Val which appears to reduce SOD2 activity, was associated with reduced gray matter volume in those who had lower levels of lifetime alcohol consumption. These results reveal a mechanism for how alcohol-induced reactive oxygen species results in brain degeneration and may lead to the discovery of therapeutic targets to protect against brain shrinkage.

NIH researchers also investigated a brain circuit that is associated with nicotine addiction. Studies have replicated the association between gene variants in the CHRNA5-CHRNA3-CHRNB4 gene cluster and alcohol dependence and smoking. These genes encode nicotinic acetylcholine receptor subunits involved in nicotine dependence. In the current study, the Asp398Asn variant of the CHRNA5 gene was associated with reduced function of a brain circuit involved in nicotine addiction and psychiatric disorders.

Advances or Other Highlights

NIH is also exploring genetic variations that predict positive drinking outcomes in individuals in response to medications such as odansetron (which blocks the action of serotonin) and naltrexone (FDA approved for alcohol dependence). Previous studies of naltrexone revealed a single nucleotide polymorphism (SNP), the mu opioid receptor A118G (Asn40Asp) variant, was associated with reduced alcohol consumption in patients treated with the medication. This finding was replicated in several animal and human studies and has led to a Phase IV clinical trial that is measuring response to naltrexone in alcohol dependent individuals. Phase IV trials are conducted after a drug has been approved by the FDA to gain additional information about the effects and optimal use of a drug.

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 has 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.

Due to unforeseen circumstances, few functional differences have been identified and the replication of these differences in various ethnic populations is not expected at this time. The FY11 target has been revised to more narrowly focus on candidate genes associated with vulnerability for substance use disorders and improves the likelihood of identifying functional variants for further characterization.

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)

FY	Target	Result
2012	Develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues. *(Baseline):* The efficacy of encapsulated MSCs in enhancing arteriogenesis, and the capacity of imaging techniques to track MSC efficacy non-invasively, are unknown.	N/A
2011	Using a rat hind limb 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	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.	Encapsulated and non-encapsulated mesenchymal stem cell (MSC) survival was tested in a rabbit model. (Target Met)
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)

Data Source and Validation
Progress report: Project number 5 R33 HL089029-04 Additional information on this grant can be found at: http://projectreporter.nih.gov/project_info_description.cfm?aid=7905794&icde=6147966 National Heart, Lung, and Blood Institute program contact: Dr. Denis Buxton, db225a@nih.gov

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Encapsulated and non-encapsulated mesenchymal stem cell (MSC) survival was tested in a rabbit model. Hind limb ischemia was created in 20 rabbits, randomized to receive non-encapsulated stem cells, encapsulated stem cells, empty capsules, or sham injections of saline.

Registration (comparing locations of the capsules determined by different methods) of XMRCap capsules between CT, MRI, and post-mortem tissue analysis has been performed, and a good correlation between *in vivo* imaging and

post-mortem analysis was found. Repeated assessments of XMRCap volume by CT analysis at injection time, and 3 and 7 days post-injection have shown no shrinking of capsules over time – suggesting that at least in the short term, no rejection of the capsules is occurring. Contrast and non-contrast magnetic resonance angiography are currently being tested for evaluation of reflow in the ischemic limbs.

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 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, 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 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 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 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. 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 (isotopes that are radioactive and are used as imaging agents) 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 developed 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. Current research includes testing the hypothesis that encapsulation lead to enhanced MSC survival in normal and disease-model environments.

SRO-3.7 By 2019, develop at least two novel therapies for immune-mediated disease. (Outcome)

FY	Target	Result
2012	Complete data analysis of the study of rabbit and horse ATG in the treatment of severe aplastic anemia and publish results. *(Baseline):* Treatment completed in study of rabbit and horse ATG in the treatment of severe aplastic anemia.	N/A
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	Marked differences in cytokine profiles were observed between patients treated with two types of ATG, and antibody levels were correlated with serum sickness. (Target Met)
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
Xingmin Feng, Phillip Scheinberg, Olga Nunez, Angelique Biancotto,J. Philip McCoy, Jr, and Neal S. Young, *Serum sickness and plasma cytokine profiles after treatment with antithymocyte globulin in severe aplastic anemia patients***,** abstract submitted for American Society of Hematology Annual Meeting, 2010. http://www.hematology.org/Meetings/Annual-Meeting

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Laboratory studies were conducted involving multiplex analysis of plasma cytokine (proteins involved in immune response) levels and also measurement of anti-horse and anti-rabbit antibodies from patient samples.

Marked differences in cytokine profiles were observed between patients treated with two types of ATG, and antibody levels were correlated with serum sickness (an immune reaction). Further studies of subsets of cells defined by multiple surface markers and flow cytometry are in progress.

BACKGROUND

This goal is one of several new trans-NIH initiatives created, 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, 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 NIH Clinical Center; establishment of specific core facilities, as examples, generating valuable reagents and facilitating 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 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 developed and is testing 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.

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)

FY	Target	Result
2012	Complete hormone receptor scoring for 30% of all cases *(Baseline):* Performed central testing of hormone receptors per amended protocol.	N/A
2011	Perform central testing of hormone receptors per amended protocol. *(Baseline):* Completed accrual of participants for the trial.	N/A
2010	Complete accrual of additional patients per the amended protocol. *(Baseline):* Additional participants needed to compensate for higher than anticipated rate of non-compliance	Completed accrual of additional patients per the amended protocol for a total of 6908 randomized participants. (Target Met)
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)

Data Source and Validation
Cancer Trials Support Unit website *https://www.ctsu.org/public/*

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. The TAILORx trial completed accrual to the amended protocol and randomized 6908 patients. The quality assurance for the hormone receptors has been completed and the actual staining of the material has begun. This is on target for completion in 2011 as scheduled, and for scoring to commence in 2012.

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 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. In order to adapt to higher than anticipated non-compliance, additional patients were needed in the trial than originally planned 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. The trial successfully completed accrual and 6908 women were randomized. 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.

SRO-3.9 By 2020, identify two molecular-targeted therapies for disorders of the immune system in children. (Outcome)

FY	Target	Result
2012	Complete genetic, biochemical, or cellular studies aimed at identifying a molecular pathway underlying the disease in each of the two patient cohorts. *(Baseline):* Cohorts are assembled for the purpose of discovering genetic, biochemical, or cellular markers that are unique, and therefore attributable, to their disease.	N/A
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.	Two cohorts are being accrued by NIH investigators – one with neonatal-onset multisystem inflammatory disease and another with systemic-onset juvenile idiopathic arthritis. (Target Met)

Data Source and Validation
Data provided directly by intramural primary investigators. Contact NIAMS OSPP (Dr. Branden Brough, 301-496-8271, broughb@mail.nih.gov) for more information.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH investigators are recruiting two patient cohorts – one for Neonatal-onset multisystem inflammatory and another for Systemic-onset JIA. Neonatal-onset multisystem inflammatory disease (NOMID) is a rare monogenic autoinflammatory disease. NIH clinical investigators recently demonstrated that daily injections with an IL-1 inhibitor called anakinra have a dramatic effect on the manifestations of NOMID. However, these injections are frequently quite painful and may not completely control the manifestations of NOMID. In order to identify additional targeted therapies that may be better tolerated and provide better control of inflammatory symptoms, NIH investigators are actively recruiting NOMID patients to the NIH Clinical Center. To date over 50 patients have been recruited, making this cohort one of the largest in the world. For each patient, extensive clinical and laboratory data are collected, including the use of advanced imaging techniques.

Systemic-onset JIA (SoJIA, or Still's disease) is a genetically complex autoinflammatory disease. Within the last several years, new therapies that inhibit cytokines have shown promise in SoJIA, but these treatments are not effective in all patients or may be only partially effective, and have significant toxicities. Genome-wide association studies have the potential to reveal new causative pathways that could be targeted for novel therapies for SoJIA. NIH investigators are coordinating a large international effort to collect samples from a sufficient number of SoJIA patients (approximately 1000) to conduct a genome-wide association study. To date, samples from over 500 well-characterized SoJIA patients and 200 ethnically matched controls have been collected, and each of these samples has been genotyped for almost one million genetic markers spanning the human genome.

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.

Systemic-onset JIA (SoJIA, or Still's disease) is a genetically complex autoinflammatory disease that is more common than NOMID, and is characterized by high fevers with daily spikes, an evanescent salmon-colored skin rash, inflammation of the lining of the abdominal and/or chest cavities, generalized swelling of the lymph nodes, enlargement of the liver or spleen, and a chronic destructive inflammatory arthritis. Some patients develop a complication known as macrophage-activation syndrome, which is potentially fatal. Although SoJIA does not behave as a simple dominant or recessive disease, it does tend to run in families. Within the last several years, new therapies that inhibit cytokines have shown promise in SoJIA, but these treatments are not effective in all patients or may be only partially effective, and have significant toxicities.

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.

SRO-3.10 By 2017, advance two candidate medications for treatment of substance use disorders to clinical studies in humans. (Outcome)

FY	Target	Result
2012	Test one compound in proof-of-concept trials. *(Baseline):* Preclinical/clinical studies have identified compounds that show promise and warrant testing in proof-of-concept studies for substance use disorders.	N/A
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.	Researchers identified a candidate compound for treatment of fatty liver and one new molecular target for treatment of problem drinking. (Target Met)

Data Source and Validation
Tam J, Vemuri VK, Liu J, Bátkai S, Mukhopadhyay B, Godlewski G, Osei-Hyiaman D, Ohnuma S, Ambudkar SV, Pickel J, Makriyannis A, Kunos G. Peripheral CB1 cannabinoid receptor blockade improves cardiometabolic risk in mouse models of obesity. J Clin Invest. 2010 Aug 2;120(8):2953-66. PMID: 20664173 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2912197/?tool=pubmed Neasta J, Ben Hamida S, Yowell Q, Carnicella S, Ron D. Role for mammalian target of rapamycin complex 1 signaling in neuroadaptations underlying alcohol-related disorders. Proc Natl Acad Sci U S A. 2010 Nov 16;107(46):20093-20098. Epub 2010 Nov 1. http://www.pnas.org/content/107/46/20093.full.pdf+html

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH-supported researchers identified one candidate compound for treatment of fatty liver, a precursor to advanced alcoholic and non-alcoholic liver disease, and one new molecular target for treatment of problem drinking.

Endoannabinoids are naturally occurring substances in the brain and other tissues in the body and have similar psychoactive properties as marijuana. Previous studies of obesity have shown that blockade of the CB1 class of endocannabinoid receptors has multiple effects including weight loss and reduced cardiovascular and metabolic risks in obese mice and overweight or obese humans. CB1 inhibitors, such as rimonabant, were shown to be effective for reducing heavy drinking in animal studies and were pursued for testing in humans. However, blockade of brain CB1 receptors led to psychiatric side effects such as anxiety, depression and suicide thoughts. As a result, rimonabant was not approved by the FDA as a medication and preclinical testing of compounds that were similar to rimonabant was no longer pursued. Recently, NIH developed a novel CB1 receptor inhibitor that does not cross from the bloodstream into the brain and bind brain CB1 receptors. In a mouse model of obesity, the novel inhibitor promoted weight loss as the earlier inhibitors did and improved obesity-related metabolic complications such as diabetes and insulin-resistance, changes in blood lipid profiles and fatty liver. Fatty liver is the initial stage in liver disease caused by obesity and heavy alcohol use, and these results suggest this class of CB1 receptor inhibitors may be effective for liver disease treatment. Further testing is warranted for similar CB1 inhibitors and for treatment of fatty liver.

In addition, NIH scientists identified a new molecular target that affects drinking behavior in mice. The mammalian target of rapamycin complex 1 (mTORC1) is involved in a signaling pathway that affects processes related to learning and memory in the nucleus accumbens of the brain, part of the brain's reward system.

Disruption of learning and memory are thought to play roles in the development of alcohol and other drug dependence. In the current study, alcohol consumption and heavy alcohol use increased expression of proteins within the mTORC1 signaling pathway in the mouse nucleus accumbens, indicating that alcohol activated the mTORC1 pathway. In contrast, rapamycin, a FDA-approved immunosuppressant that inhibits mTORC1, reduced excessive alcohol consumption and alcohol seeking. These results suggest that the mTORC1 pathway in the nucleus accumbens of mice is a molecular mechanism that is involved in regulating alcohol consumption, and may provide a new molecular target for future drug development.

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 Control 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.

SRO-3.11 By 2015, advance the discovery of high need cures through the development of novel compounds, the repurposing of abandoned products, and innovations in the therapeutics discovery and development process. (Outcome)

FY	Target	Result
2012	Establish mechanisms to operationalize the Cures Acceleration Network *(Baseline):* Congress authorized the Cures Acceleration Network through the Patient Protection and Affordable Care Act of 2010 (P.L. 111-148).	N/A

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

Performance Results for the FY 2012 GPRA Performance Target will be reported in February, 2013.

BACKGROUND

Translating basic discoveries into new diagnostics and treatments is essential for realizing the promise of fundamental biomedical research, but today developing new therapeutics for human disease has become an exceedingly complex, costly, and risk-laden endeavor. The process involves many phases beginning with basic research to understand the disease process and pre-clinical studies to identify a specific aspect of the disease to target, e.g., a gene or signaling pathway. After validating the target, in itself a multi-faceted process, thousands of chemical or molecular compounds must be screened to find promising candidates for further study. Significant pre-clinical research involving animal models of the disease is also needed to assess the safety, toxicity, pharmacokinetics, and metabolic properties of the candidate compounds. Unfortunately, only a few compounds will ultimately prove safe or promising enough for clinical studies in humans. The multi-phase clinical trial process is also fraught with significant challenges with most compounds failing to reach market, the ultimate goal of the process. According to 2004 and 2008 research on the drug discovery process, 90 to 95 percent of new medicines entering clinical testing do not succeed. As for the costs of developing a new drug, estimates range from $500 million to $2 billion. Moreover, despite greater investments in research and development, FDA approval of new compounds declined from an average of 33 per year in the late 1990s to 22 in the 2000-2009 period.

The problems in the therapeutics discovery and development enterprise have adverse impacts on the search for treatments and cures for the many diseases and conditions affecting human health today. Moreover, for certain health problems, such as drug resistant infections, nervous system disorders and drug addiction, and global health problems such as malaria and tuberculosis, waning interest on the part of industry is further limiting prospects. For example, in the last decade, industry efforts to develop new antibiotics for drug resistant infectious diseases affecting Americans, e.g., Methicillin-resistant Staphylococcus aureus (MRSA), have declined significantly. According to 2007 research on the drug market, since 1999, 10 of the 15 largest companies have fully abandoned, or cut down significantly, discovery efforts in this field. In 2010, two pharmaceutical companies decided to end drug discovery work on pain, depression, anxiety, schizophrenia, and bipolar disorder. Therapeutic development for rare diseases has always lacked broad private sector support.

Rationale

Several recent and noteworthy scientific developments and advances in technological capabilities have created an unprecedented opportunity to transform the therapeutic development pipeline. First, recent discoveries have uncovered the molecular basis of hundreds of diseases and, thereby, generated a substantial inventory of potential new therapeutic targets. More than 2,000 rare diseases have had their molecular bases identified, but, according to FDA, effective therapies are available for only about 200 of those diseases. According to an NIH catalog of genome wide association studies, more than 800 new targets have emerged from genome wide association studies for common diseases, far more than can be further developed by the private sector alone. In the area of neglected diseases that are indigenous to the developing world, the recent derivation of genome sequences of pathogens, vectors, and hosts has opened up a broad array of potential targets for the development of new therapeutics.

Second, academic investigators, in large part through support from NIH, now have access to high throughput

technologies that make possible the rapid screening of hundreds of thousands of compounds and accelerate the identification of the most promising candidates for further development. These NIH-supported resources are critical to progress in translating fundamental discoveries about the molecular basis of disease into effective approaches to diagnosis and treatment.

Third, there is growing recognition of the need for new and innovative approaches to therapeutics development that takes advantage of specific strengths and skill sets of different sectors. These approaches cannot be successful without novel partnerships between and among government, academia, industry, venture capital, and non-profit organizations. This interest is the outgrowth of several factors. One factor is the increasing pressure on the pharmaceutical and biotechnology industries to surmount the slow pace of therapeutics discovery and to reap more rapid returns on the billions of dollars they invest in research and development. Another factor is widespread dissatisfaction with the traditional model of therapeutics discovery and its low success rate. Capitalizing on sector strengths through innovative public-private partnerships among government, academia, industry, venture capitalists, will improve the quality and efficiency of the development process and distribute the cost and risk of the enterprise across all sectors.

Fourth, NIH has the capability to conduct and to support research in the early, preclinical stages of therapeutics discovery and development—research that industry and venture capital are increasingly reluctant to pursue. NIH also has a key role to play in identifying new techniques and technologies that enhance the predictive value of work done at the preclinical stages of therapeutics discovery. As such, NIH can both conduct the essential preclinical work and help prevent the attrition of compounds and failure at later, more expensive, stages of clinical testing by discovering and disseminating innovative approaches to preclinical development.

These current challenges and opportunities have prompted calls for action by stakeholders across all sectors, including Congress, as well as recommendations for organizational change from NIH's Scientific Management Review Board. Accordingly, NIH is proposing to take a new approach to therapeutics discovery and development, an approach that would benefit greatly from a focused organizational structure dedicated to translational science. The proposed National Center for Advancing Translational Sciences (NCATS) would contain cross-cutting programs, including the Cures Acceleration Network (CAN), to support a streamlined approach to therapeutics discovery and development.

TARGET CONTEXT AND CONDITIONS

CAN was authorized by Congress in the Affordable Care Act of 2010 (P.L. 111-148) to strengthen NIH's ability to advance the development of "high need cures" through the reduction of barriers between research discovery and clinical trials. "High need cures" are defined in the law as any drug, biological product, or device that the NIH Director determines to be a) a priority to diagnose, mitigate, prevent, or treat harm from any disease or condition, and b) for which the incentives of the commercial market are unlikely to result in its adequate or timely development.

NIH will exploit new opportunities made possible by scientific advances in genomics and molecular biology and help overcome the many challenges currently facing the medical product development system in order to advance the discovery of high need cures through the development of novel compounds, the repurposing of abandoned products, and the innovation of the therapeutics discovery and development process. The NIH will be able to add an important new program to the agency's renewed and refocused commitment to speed the development of new, urgently needed products and catalyze fundamental improvements in the process of therapeutics discovery and development.

CAN would be an important component in NIH's translational science efforts because of its focus and the flexible authorities it provides for conceiving and executing projects in therapeutics development. Its functions are to:

- support revolutionary advances in basic research and translate scientific discovery from bench to bedside;
- provide resources to accelerate the development of high need cures;
- reduce barriers between laboratory discoveries and clinical trials for new therapies; and
- facilitate review in FDA for the high need cures funded by the CAN.

In addition to standard funding mechanisms such as contracts, grants, and cooperative agreements, the CAN's flexible funding authorities will enable new partnerships and collaborative teams to be forged and to operate openly with broad sharing of research results, whether positive or negative. CAN's authorities also will allow NIH to move nimbly to initiate new projects and, when needed, to cancel and redirect efforts quickly. With CAN, NIH will have a more "hands-on" role in directing each project, setting and monitoring specific milestones, and managing the scientific and administrative dimensions of projects--as well as the ability to terminate the project as necessary. These capabilities are critical in translational medicine, where product development is the goal and the specific strategy and approach needed to realize it cannot be fully anticipated in advance. CAN will involve close coordination with FDA and strong partnerships with private sector stakeholders working in a transparent and collaborative environment. CAN's specific focus, flexible operational strategies, and collaborative approaches will also constitute a completely new approach to therapeutic development, and, thereby, exemplify, and be a force for, innovation in the research and development enterprise.

The steps that will need to be taken to operationalize CAN include the following:

- Set priorities for "high need cures," by developing criteria and consensus building in light of the broad definitions provided by Congress.
- Address policy and legal questions to allow the forging of the new partnerships and collaborative activities that are essential to CAN's mandate.
- Determine the appropriate application of CAN's funding mechanisms.
- Identify aspects and dimensions of the developmental process that are ripe for improvement, through the application of specific innovative technologies and new approaches.
- Determine the specific details of FDA's role in CAN activities and the mechanisms for coordinating FDA input as part of NIH and FDA a new partnership to advance translational medicine and regulatory science.
- Establish a 24-member multidisciplinary Cures Acceleration Network Review Board.

While it is not possible to promise that all CAN projects will ultimately result in a successful treatment, NIH expects to achieve a ratio of 1.5 to 2 successes for every ten projects pursued, which would improve upon the current success rate. Given the number of diseases for which treatments are needed, we anticipate that the CAN program could make major contributions to improving health, saving lives, and lowering healthcare costs associated with many serious human disorders and conditions that currently lack effective therapies and pose major burdens for individuals, their families, and society.

SRO-4.4 By 2011, identify or study additional genes involved in communication disorders in humans and animal models. (Outcome)

FY	Target	Result
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.	Scientists successfully mapped a new locus on chromosome 9q34.3 and identified a new gene (TPRN) important for hearing. (Target Met)
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
Khan SY, Riazuddin S, Shahzad M, Ahmed N, Zafar AU, Rehman AU, Morell RJ,Griffith AJ, Ahmed ZM, Riazuddin S, Friedman TB. DFNB79: reincarnation of a nonsyndromic deafness locus on chromosome 9q34.3. Eur J Hum Genet. 2010 Jan;18(1):125-9. http://www.ncbi.nlm.nih.gov/pubmed/19603065 Rehman AU, Morell RJ, Belyantseva IA, Khan SY, Boger ET, Shahzad M, Ahmed ZM, Riazuddin S, Khan SN, Riazuddin S, Friedman TB. Targeted capture and next-generation sequencing identifies C9orf75, encoding taperin, as the mutated gene in nonsyndromic deafness DFNB79. Am J Hum Genet. 2010 Mar 12;86(3):378-88. http://www.ncbi.nlm.nih.gov/pubmed/20170899

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Scientists mapped a novel deafness locus, and identified a novel gene for nonsyndromic deafness. (Nonsyndromic deafness is hearing loss or deafness that is inherited and is not associated with other inherited clinical characteristics. Different types of nonsyndromic deafness are named according to their inheritance patterns.) A novel deafness locus, on chromosome 9q343, was mapped for nonsyndromic deafness DFNB79. Mutations of a novel deafness gene, C9orf75 (renamed TPRN; TPRN encodes taperin), were revealed to be responsible for nonsyndromic deafness DFNB79. This research is one of the first to use the combination of enriched genomic DNA from the DFNB79 locus and next generation sequencing (massively parallel sequencing) to identify a human disease gene. In inner ear hair cells, taperin is localized to a region at the base of stereocilia (tiny hairlike projections jutting from the top of cells in bundles that help transform sound energy into electrical energy). The exact function of taperin is being pursued using genetic, biochemical, molecular biological and cell biological techniques.

The goal of this project is to identify novel genes whose mutation is responsible for inherited human communication disorders and to determine the function of their corresponding proteins. Hearing loss is an important component of the NIH's research portfolio in inherited human communication disorders. When an individual inherits a mutated gene that is involved in hearing loss, the way that hearing loss presents itself varies from individual to individual. NIH researchers have focused on a systematic and comprehensive genetic approach to the identification of genes necessary for inner ear function. Once the gene of interest is identified, they use the tools of molecular and cell biology and mouse genetics to determine how the gene is regulated and how it functions. This work begins by identifying families known to have inherited hearing loss, and track down the region of the

chromosome that contains the causative genes. If a mutated gene causes hearing loss, then the function of that gene is necessary for hearing.

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 researchers are actively working to understand the genes responsible for human communication disorders. The 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 there is a compelling need for research to address the problem. For example, according to 2007 data from the CDC National Center on Health Statistics, approximately 36 million American adults report some degree of hearing loss. But hearing loss also affects young people. The CDC estimates that two to three out of 1,000 babies born in the U.S. each year have a detectable hearing loss, which can affect their speech, language, social, and cognitive development. The CDC also estimates that by the first grade, roughly five percent of children have noticeable speech disorders, including stuttering. Decades of research have determined that approximately 50-60 percent of cases of severe to profound childhood hearing impairment are hereditary or genetic, and scientists have identified over 100 genetic regions associated with non-syndromic hereditary hearing impairment (NSHI).

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, 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 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 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.

NIH-supported scientists have identified additional genes involved in communication disorders in humans and animal models. Once the genes that cause communication disorders are identified, scientists still have a lot of unanswered questions to explore, including understanding the precise cause of communication disorders due to mutations, detailed analyses of the expression pattern in cell types that are critical to communication, and biochemical characterization of the gene's protein product.

SRO-4.5 By 2011, identify genetic and environmental factors which predispose to three complex diseases. (Outcome)

FY	Target	Result
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.	Genome-wide association studies identified variation in the TERT gene and in the CHRNA5 nicotine receptor as related to lung cancer. (Target Met)
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;85:679-91 http://www.ncbi.nlm.nih.gov/pubmed/19836008

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Genome-wide association studies of lung cancer have been completed and published. Variation in the *TERT* gene was associated with risk of adenocarcinoma of the lung but not with other histologic types, suggesting a type-specific predisposing role that was consistent in smokers and non-smokers. Variation in the *CHRNA5* nicotine receptor gene was associated with all lung cancer types but appeared stronger in smokers in more recent decades, suggesting a possible role for increased nitrosamine content in cigarette smoke, the major environmental predisposing factor for lung cancer.

BACKGROUND

With the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, NIH 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) to examine these interactions at the level of the individual.

The GEI had 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 are placed in NIH databases and can be accessed by NIH-approved users.

The genetics component includes a genome-wide association program called GENEVA (Gene Environment Association Studies).

The aims of GENEVA are to:

- Identify genetic variants related to common, complex diseases
- Identify variations in gene-trait associations related to environmental exposures
- Address potential pathways to disparities in health outcomes

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 of 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.

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)

FY	Target	Result
2012	Complete need analysis surveys in underserved areas and based on these identified needs develop at least one feasibility test of technology to facilitate patient-controlled, secure image sharing between medical centers and a clinic operating in an underserved community. *(Baseline):* Regional group of three medical centers and about 40 outlying clinics has been established. Initial survey of needs among providers is complete and needs assessment among patients is at advanced planning stage. Token based patient controlled image exchange system is in early planning stage.	N/A
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.)	Researchers demonstrated a patient-controlled, secure, storage system-diagnostic infrastructure that will support exchange of medical image information between medical facilities. (Target Met)

Data Source and Validation
Award Summary of Contracts to the Radiological Society of North America: http://www.recovery.gov/Transparency/RecipientReportedData/pages/RecipientProjectSummary508.aspx?AwardIdSur=94401&AwardType=Contracts

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. The purpose of this project is to develop an Internet-based network for patient-controlled medical image sharing built upon the Integrating the Healthcare Enterprise (IHE) and Cross Document Sharing profile (XDS). At the Radiological Society of North America's (RSNA) 2010 Annual Meeting, researchers demonstrated a patient-controlled, secure, storage system-diagnostic infrastructure that will support the exchange of medical image information between medical facilities. This demonstration showed how participating institutions are empowering their patients to manage access to their medical imaging exams for consultations and retain them as part of a personal health record in a secure environment. The RSNA demonstration allowed users to acquire images and reports and send them to a "Clearinghouse" where they can later be retrieved for storage in a personal health record (PHR) system. Once the exams are stored in their PHR, users can archive these studies for future access, invite others to view their imaging study or selected studies, and/or download the images/report to the local device.

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 included the creation of jobs for a research program that can realistically accomplish the majority of its goals in two years and that, if successful, could 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 represent a range of clinical settings from the "high-tech" medical center to the "low-tech" rural clinic. The third project is research to develop a demonstration project for imaging sharing across established medical centers. This project is also actively developing 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.

SRO-4.7 (RA) By 2011, evaluate at least one novel animal model of type 1 diabetes. (Outcome)

FY	Target	Result
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.	NOD-scid IL2rγnull embryonic stem cells were generated. (Target Met)

Data Source and Validation
Beta Cell Biology Consortium - Diabetic Stem Cell Modeling of Human Disease: http://www.betacell.org/resources/data/research/DIAMOND/

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NOD-scid IL2rγnull embryonic stem cells were generated. Embryonic stem (ES) cell lines were derived from three subtypes of non-obese diabetic (NOD) mice. Embryos were harvested at 3.5 days post conception from each subtype, and expanded immature, undifferentiated cells (called blast cells) were cultured on a layer of "feeder cells"—mouse fibroblasts which provide a supportive environment by producing nutrients and growth factors—for 8-10 days primarily using standard mouse ES cell culture medium. After 8-10 days, clusters of blast cells were mechanically separated and plated onto new feeder layers in standard mouse ES cell culture medium. After 2 days, the emergent ES cell lines were expanded prior to freezing. In some cases, a special medium was used for derivation and expansion. These ES cell lines are a critical resource to enable researchers to 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 counter-parts. Thus, this research will lead to better understanding of the molecular mechanisms underlying the events leading to type 1 diabetes.

BACKGROUND

Type 1 diabetes 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 1 diabetes. 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 seventh 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 1 diabetes 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), two Recovery Act-supported projects are producing two key components required to reconstruct components of human type 1 diabetes in the mouse: 1) one project is producing human induced pluripotent stem cells (iPS) derived from type 1 diabetes patients; and 2) the other project is producing 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 counterparts. 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.

SRO-4.8 (RA) By 2011, develop and/or test at least one strategy for improving end-of-life care or palliative care. (Outcome)

FY	Target	Result
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.	A national Palliative Care Research Cooperative was supported to conduct innovative research to improve end-of-life and/or palliative care. (Target Met)

Data Source and Validation
Leblanc, T., J. Kutner, et al. (2010). "Developing the evidence base for palliative care: formation of the palliative care research cooperative and its first trial." Hosp Pract (Minneap) 38(4): 137-143. http://www.ncbi.nlm.nih.gov/pubmed/20890063

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. One strategy was identified for conducting innovative research to improve end-of-life and/or palliative care. A group of NIH-supported scientists is establish a unique, collaborative network in palliative care research. This group, the Palliative Care Research Cooperative (PCRC), is creating a national infrastructure for the conduct of high-quality, multi-disciplinary, clinical trials in palliative care. The PCRC will bring together experienced, multidisciplinary investigators from multiple institutions to facilitate innovative, high-impact, clinically useful palliative care research to inform practice and health policy. In addition, the PCRC will serve as a venue for recruiting new investigators and new expertise into the palliative care research community. A robust and feasible implementation plan based on measurable metrics of success and effectiveness of the collaborative is being developed. To demonstrate the value of the collaborative in terms of research productivity, the PCRC plans to design, conduct, and disseminate a multi-site clinical trial that will study the use of statins for co-morbid conditions in patients who are near death. The findings from this trial could provide vitally important information for clinicians caring for patients at the end-of-life. The PCRC provides one example of a strategy for overcoming some of the challenges associated with conducting research with individuals with life-limiting conditions, and could lead to significant improvements in the evidence base for end-of-life and palliative care.

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

In addition to supporting the PCRC, NIH funds other research efforts that examine 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.

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)

FY	Target	Result
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.	The study protocol has been developed and the sequencing of participants in the well-phenotyped cohorts has begun. (Target Met)

Data Source and Validation
National Heart, Lung, and Blood Institute program contact: Dr. Deborah Applebaum-Bowden, applebad@nhlbi.nih.gov

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. The study protocol was developed and exome (the coding portion of the genome) sequencing of participants in the well-phenotyped cohorts began. Representatives of the two sequencing centers and three cohort consortia met by conference call on a weekly basis to establish the goals for the project, plan for the necessary infrastructure, and determine the project design. The group established two phases for the protocol. The five groups finalized the phenotypes or outcomes to be included in Phase I at the in-person meeting in December, 2009. The projects included for Phase I sequencing are early onset myocardial infarction, cystic fibrosis, chronic obstructive pulmonary disease, pulmonary arterial hypertension, high body mass index with or without Type 2 diabetes, and LDL cholesterol levels. Each of the project teams set the specifics for sample inclusion, identified the appropriate samples from the various cohorts and had the samples sent to the sequencing centers. By the end of May, 2010, about 2500 samples from participants in the well-phenotyped cohorts passed the quality control criteria and entered into the pipeline for exome sequencing.

The phenotypes or outcomes to be included in Phase II were decided in May, 2010. The projects include blood pressure, stroke, asthma, acute lung injuries, additional cohorts for chronic obstructive pulmonary disease, cystic fibrosis, and a set of extensively phenotyped reference samples. Each project team determined the specifics for sample inclusion, identified the samples from the various cohorts, and arranged for shipment of the selected samples. By the end of the fiscal year, about 3000 samples for Phase II were received by the sequencing centers for quality control assessment and entry into the exome sequencing pipelines.

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 requires 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

Recovery Act funds have been used 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 7,000 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 is supporting DNA sequencing of the well-phenotyped cohorts for the identification of disease causing variants and understanding biological pathways. The cohorts being 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), as well as several cohorts with various lung diseases. By initiating the sequencing of the genomes of over 7,000 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 leading to an improved understanding of disease and biological processes.

SRO-4.10 (RA) By 2011, accelerate progress toward identifying relevant genomic alterations in 10 tumor types. (Outcome)

FY	Target	Result
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.	NIH began the identification of genomic alterations in an additional 8 tumor types. (Target Met)

Data Source and Validation

Deus, H.F., Veiga, D.F., Freire, P.R., Weinstein, J.N., Mills, G.B. and Almeida, J.S. (2010) Exposing the cancer genome atlas as a SPARQL endpoint. *J Biomed Inform*. 2010 Sep 23. (Epub ahead of print) http://www.ncbi.nlm.nih.gov/pubmed/20851208

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Cooper, L., Kong, J., Gutman, D., Wang, F., Cholleti, S., Pan, T., Widener, P., Sharma, A., Mikkelsen, T., Flanders, A., et al. (2010) An integrative approach for in silico glioma research. *IEEE Trans Biomed Eng*. 2010 Jul 23. (Epub ahead of print) http://www.ncbi.nlm.nih.gov/pubmed/20656651

TCGA has been mentioned multiple times in the news and through other avenues. Those links are available here and through our website: http://tcga.cancer.gov/media/news_overview.asp

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH began identifying genomic alterations in additional tumor types by adding new samples the TCGA pipeline, developing characterization laboratories and transitioning to second generation sequencing. Since the beginning of 2010, when the first samples of the expansion phase were contracted, more than 3000 cases have entered the TCGA pipeline, and TCGA currently maintains a pipeline of approximately 170 cases per month. Specifically, these samples have allowed for studies and dissemination of data on breast ductal carcinoma, breast lobular carcinoma, colon adenocarcinoma, rectal adenocarcinoma, lung squamous carcinoma, lung adenocarcinoma, acute myeloid leukemia and clear cell renal carcinoma. Data on the copy number

alterations, gene and miRNA expression, methylation/epigenomic profiles, single nucleotide polymorphisms and whole-exome—and some whole genome data—were made available for more than 600 non-pilot project cases during FY 2010. These data are accessible on the TCGA Data Portal or the associated TCGA-Project page available via dbGaP. Because TCGA is considered a community resource, all these data are being used without restriction by qualified researchers. The data were made immediately available via the web portal.

With these comprehensive datasets available on so many individual cases and on a wide number of tumor types, this enables the community to use the data in the portal and identify specific changes that are linked to specific clinical outcomes to improve patient care. The comprehensive nature of the data allows investigators to, for the first time, make direct comparisons of the different data types within and between patient samples.

During the pilot, only program glioblastoma multiforme and ovarian cancer data were available. While the pilot program demonstrated a "proof of principle" that a network was able to be developed and achieve comprehensive characterization, part of the FY2010 goals were to establish the next phase of the program, including centers to perform the additional characterization. This required establishing multiple new core laboratories to perform biospecimen processing and characterization. Additionally, the transition to second generation sequencing was completed in FY2010- shifting from 601 genes targeted in the first generation, to the entire exome or whole genomes by the end of FY2010.

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.

The Cancer Genome Atlas (TCGA) Phase II marked an expansion of TCGA to twenty additional tumor types beyond those studied in the pilot and involved a restructuring that applied three key "lessons learned" during the TCGA Pilot project. To ensure that the results generated from the Characterization and Sequencing Centers could be interpreted from a variety of technology platforms, the centers chose to use utilize high quality molecular analytes; perform experiments utilizing strict standardized protocols; and deposit the results in structured formats. The goal of TCGA, Phase II is to comprehensively characterize 500 cases of at least 20 tumor types, or 20,000 samples, over the next 5 years. This expansion began in FY 2010 with the goal of getting at least 8 tumor types into the pipeline above and beyond the initial 2 that were explored during the pilot.

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 NIH 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. Recovery Act support made 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 allows TCGA to include many major tumor types such as: lung, breast, kidney or colon tumors.

The Recovery Act has supported the technological innovation required by TCGA, which lays 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 is accelerating 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 results in many new jobs and allows the continued support of current staff. The measure also expedites the completion of a number of pilot-phase projects, and selected sites were required to hire individuals at all levels of the research and development continuum.

The measure supports 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 is being 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 is also further developing databases, enhancing analytical and data visualization tools, and making the data available to the research community. The data generated by the Network is a resource available to all biomedical researchers to stimulate further research leading to the development of diagnostic tools and novel drug therapies.

SRO-4.11 (RA) By 2011, analyze oral cancer genomes using high throughput methods to develop a blueprint of genetic alterations. (Outcome)

FY	Target	Result
2012	Analyze and annotate the genome sequences of 94 samples taken from oral and tongue cancers and compare with matched normal human tissue (total of 188 samples). *(Baseline):* No squamous cell specimens from oral cancers have been subjected to whole exome sequencing.	N/A
2011	Complete initial screening of 300 tissue samples from existing biorepositories to refer for secondary, quality control screening to ensure sufficient quality and quantity of cancer and normal tissue for genomic analysis. *Previous target:* *Analyze 124 additional samples and validate and integrate data to complete blueprint of oral cancer genome.* *(Baseline):* 137 samples have been screened.	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.	137 tissue samples were subjected to initial screening and only 53 of these passed the quality control screen, Thirty-three specimens have been subjected to sequencing studies. (Target Not Met)

Data Source and Validation
Annual progress reports.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Not Met. The researchers screened 137 tissue samples. However, only 53 samples passed the quality control screen, meaning they were suitable for genomic analysis in terms of variables such as histological confirmation and sufficient quality and quantity of tumor and matched, normal DNA. Considerable effort was devoted during the first months of these projects to ensuring that specimens selected from their banked repositories were suitable for genomic analysis. A two-stage screening process was instituted such that specimens ultimately analyzed would meet specific criteria, such as the following:

- confirmation by head and neck pathologists that the samples had > 70 % tumor nuclei and <30% necrosis
- de-identification of samples
- sufficient DNA for amplification
- matching of primary tumors and normal samples from same patient.

These screening protocols produced a 30-40% yield; that is, fewer than 40% of the samples previously indentified from the banked specimens were referred for genomic analysis. The development and implementation of the quality control screens and the lower than expected yield meant that the originally defined performance target was not met. Investigators revised their initial goals such that 94 oral cancer tissue samples matched with 94 samples of normal tissue taken from the same patients are now expected. Researchers are also changing the sequencing technique at one laboratory to use whole exome sequencing as the primary technique. The targets have been adjusted to reflect these technological improvements in genomic analysis.

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.

Under the Recovery Act, 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 are comprehensive genomic analyses that could advance the field of oral cancer research. This work is 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.

As the projects have progressed, the development and implementation of quality control measures for screening of the banked specimens and the decision to use whole exome sequencing (that is, re-sequencing all genes instead of focusing on the 6000 cancer-related genes originally planned in one project) allowed for a more accurate prediction of scientific productivity over the next two years. Recognizing that more time will be required than originally planned because of the quality control screening methods, the measure has been extended to FY 2012, at no cost to the government. The reduction in the number of samples to be analyzed in one project is not expected to reduce the scientific impact of the project; indeed, use of the whole exome sequencing method is an unbiased approach that holds the potential of being considerably more informative than the original, focused gene approach.

SRO-4.12 (RA) By 2011, demonstrate the feasibility of a new therapeutic strategy in a preclinical model of a neurological disease. (Outcome)

FY	Target	Result
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.	Completed the preclinical optimization of a gene therapy for spinal muscular atrophy (SMA), a neurodegenerative disease. (Target Met)

Data Source and Validation
Burghes, RC2 - NS064328: Delivery of therapeutic genes in motor neuron disease. Foust et al., Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. Nature Biotechnology 28:271-6 2010. http://www.nature.com/nbt/journal/v28/n3/full/nbt.1610.html Bevan et al., Early heart failure in the SMNdelta7 model of spinal muscular atrophy and correction by postnatal scAAV-SMN delivery. Human Molecular Genetics 19:3895-3905 2010. http://www.ncbi.nlm.nih.gov/pubmed/20639395 Davidson RC1- NS068280: RNA interference therapy for Huntington's disease studies in non-human primates. Progress Report (for period 9/30/2009 – 8/31/2010) available from the NINDS Office of Science Policy and Planning. Thomas R21 – NS062165: Activators of NRF2/ARE pathway as therapeutic target for Parkinson's disease. Progress Report (for period 6/01/2009 –5/31/2010) available from the NINDS Office of Science Policy and Planning. Farese - RC1 - NS068697 Enhancing progranulin expression – a therapy for frontotemporal dementia. Progress Report (for period 9/30/2009 – 8/31/2010) available from the NINDS Office of Science Policy and Planning Gomez-Pinilla, RC1 - NS068473: Broadly protective drug for TBI. Progress Report (for period 9/30/2009 – 8/31/2010) available from the NINDS Office of Science Policy and Planning; Sharma S., Ying Z., and Gomez-Pinilla F. A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. Experimental Neurology 226:191-99 2010. http://www.ncbi.nlm.nih.gov/pubmed/20816821 Contact: Cara Allen, NINDS Office of Science Policy and Planning. Email: allencar@ninds.nih.gov; Tel: 301-496-9271

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met with the preclinical optimization of a new treatment regimen for spinal muscular atrophy (SMA). SMA is a neurodegenerative disease that affects motor neurons, which are the nerve cells in the brain and spinal cord that activate muscles in the body. The gene therapy strategy used a modified virus (scAAV9 - adeno associated virus 9) to deliver the gene for SMN (survival of motor neuron) protein, which is deficient in SMA, to motor neurons. The treatment rescued motor function, neuromuscular physiology, and lifespan in a mouse model of SMN when the therapy was delivered on the first day after birth. Treatment on postnatal day five resulted in partial correction, and postnatal day 10 delivery had little effect, suggesting that there is developmental period in which this therapy has optimal benefit. Another series of experiments demonstrated that scAAV9 SMN delivery can correct early heart failure in a mouse model of severe SMA. Notably, the scAAV9 vector also

effectively delivered the therapeutic gene into motor neurons in a newborn monkey (cynomolgus macaque). This demonstration that the scAAV9 can traverse the blood-brain barrier in a non-human primate reinforces the clinical potential of this therapeutic approach for SMA. The blood-brain barrier is a natural protective barrier that excludes many potentially therapeutic agents from the brain and spinal cord.

Advances or Other Highlights

RNAi (RNA interference) is a therapeutic strategy that can specifically silence a harmful gene. RNAi is a promising therapeutic strategy for Huntington's disease and for many other genetic disorders in which disease results from harm caused by a mutated gene product rather than from the lack of a necessary protein. However, developing RNAi agents that are potent and also safe has been a challenge. By prioritizing safety early in the development of RNAi agents, investigators have found two exciting new therapeutic candidates that appear to be both safe and potent in silencing the Huntington's gene based on testing in cell culture, mice, and non-human primates. More extensive testing and development is underway.

Prior research had implicated oxidative damage and inflammation as key aspects of the underlying disease process in Parkinson's disease. The Nrf2/ARE signaling pathway, which regulates antioxidant and anti-inflammatory defenses, is a potential target for therapeutics. Research has now demonstrated that a set of experimental drug analogs (TP-224 MA, TP-319 EA, and TP 500 TFEA) protect against oxidative damage produced by MPTP, a toxin that mimics many aspects of Parkinson's disease, in a short-term mouse model. TP-319 EA showed the greatest potency in these tests, although TP-500 TFEA was most effective in traversing the blood-brain barrier. Research is underway to determine which of these potential drugs is most potent in a genetic mouse model of Parkinson's disease and to further characterize the neuroprotective effects of these compounds on a variety of measures of brain anatomy and biochemistry.

Frontotemporal dementia (FTD) is a devastating neurodegenerative disease. The identification of gene mutations that can cause FTD led to the inference that the disease may reflect deficiency of the protein progranulin. Screening in human blood cells that are progranulin deficient has now identified several drugs already approved by the FDA for other purposes that increase the expression of progranulin by up to five fold. The drugs fall into three different pharmacological classes of action, suggesting the possibility of combination therapies. Researchers have generated induced pluripotent stem cells from skin cells of FTD patients and differentiated brain cells from these stem cells that will be used in further testing of these drugs, as will mice with FTD causing mutations. Drug screening will also be extended beyond the FDA approved drug set to include novel drugs.

Traumatic Brain Injury (TBI) triggers a series of molecular and cellular changes that compromise nerve cell function, resulting in a wide spectrum of behavioral problems. Researchers have found that compound CNB-001, which is a derivative of the natural product curcumin, has potential to restore nerve cell function and behavioral deficits following TBI. Experiments in a controlled (fluid percussion) rat model of TBI demonstrated that CNB-001 had beneficial effects on several biochemical measures of nerve cell membrane integrity and on the performance of rats in a spatial learning task. Experiments are continuing to evaluate the effects of CNB-001 on other behavioral tasks.

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 supported 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 supporting 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.

TARGET CONTEXT AND CONDITIONS

Four of the Recovery Act projects aimed to optimize their treatment regimens in the first year. The investigators working on the spinal cord injury project proposed to define 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 is exploring the ideal time window for treatment. For one of the epilepsy drug development projects, the first year target was 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.

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)

FY	Target	Result
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.	The final analysis showed that there was no significant difference between the atorvastatin group and placebo group in preventing the progression of atherosclerosis in pediatric lupus patients. (Target Met)
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)

Data Source and Validation
Duke Medicine News and Communications press release, Atlanta, GA, November 7, 2010: "Statins Don't Prove Useful for General Pediatric Lupus Population." http://www.dukehealth.org/health_library/news/statins-don-t-prove-useful-for-general-pediatric-lupus-population

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met and the measure was Achieved. NIH researchers completed the data analysis and determined that statins did not make a statistically significant difference in the primary outcome of clinical efficacy. The difference in the primary outcome, progression of mean-mean common carotid intima-media thickness (CIMT), was not significant between the atorvastatin and placebo treated groups (yearly progression rates 0.0010 vs 0.0024, P-value=0.24). While the results do not demonstrate compelling evidence to support treatment with statins in children and adolescents with lupus as a group for the prevention of atherosclerosis, the study does provide information concerning routine use of statins when there is no significant clinical benefit.

Measure

A study, known as the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) trial examined the effect of statins in reducing vascular measures associated with the development of atherosclerosis in pediatric lupus patients. The double-blind, placebo-controlled clinical trial had an initial goal to recruit 280 participants from 20 centers in the Childhood Arthritis and Rheumatology Research Alliance (CARRA). To coordinate this large network effectively, clinical sites sent weekly reports to the Clinical Trials Manager and monthly calls were conducted to coordinate efforts between the sites. Interim analysis of the data revealed that repeated measurements of fat buildup in the blood vessels varied less than researchers had expected. This greater precision predicted a smaller standard error for statistical analyses. Hence, the investigators were able to decrease the sample size from

280 to 220. Participant retention and compliance through the 36-month study period were enhanced through coordinated strategies among the centers, such as holiday cards, newsletters, and a compensation plan.

In conclusion, the primary endpoint for clinical efficacy of statins did not achieve a statistically significant difference. The results do not demonstrate compelling evidence to support treatment with statins in children and adolescents with lupus as a group for the prevention of atherosclerosis. Other factors in individual cases may be reasons for statin treatment. However, the study reveals that there is no significant clinical benefit from the routine use of statins.

BACKGROUND

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.

Disease Burden

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.

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)

FY	Target	Result
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.	Three imaging methods were compared, including FDG-PET, FLT-PET, and DCE-MRI. The 3 methods could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy. (Target Met)
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)

Data Source and Validation

NCI grants CCNE U54 CA119367, ICMIC P50 CA114747 supported the work in this paper: 18F-FDG uptake in lung, breast, and colon cancers: molecular biology correlates and disease characterization.Jadvar H, Alavi A, Gambhir SS. J Nucl Med. 2009 Nov;50(11):1820-7. http://www.ncbi.nlm.nih.gov/pubmed/19837767

NCI Grant numbers R01-CA-131044, R01-CA-115296, and T32 CA009535 supported this work Image-guided sentinel lymph node mapping and nanotechnology-based nodal treatment in lung cancer using invisible near-infrared fluorescent light. Khullar O, Frangioni JV, Grinstaff M, Colson YL. Semin Thorac Cardiovasc Surg. 2009 Winter;21(4):309-15. http://www.ncbi.nlm.nih.gov/pubmed/20226343

This work was supported by a contract from the Cancer Imaging Program. Instrumentation factors affecting variance and bias of quantifying tracer uptake with PET/CThttp://online.medphys.org/resource/1/mphya6/v37/i11/p6035_s1
public resources of lung PET CT images: https://wiki.nci.nih.gov/display/CIP/RIDER

This is a currently issued grant. Principal Investigators: Robert Gatenby, MD and Robert Gillies, Ph.D., Institution: H. Lee Moffitt Cancer Center, Grant: 1U01 CA143062-01, Title: Radiomics of NSCLC,
http://projectreporter.nih.gov/project_info_description.cfm?aid=7777025&icde=6086960Project Period: 3/9/2010 – 2/28/2015

The FLT vs FDG trial is posted to clinicaltrials.gov http://www.clinicaltrials.gov/ct2/show/NCT00963807.

The trial that has completed accrual and in follow-up is posted:
http://www.clinicaltrials.gov/ct2/show/NCT00083083?term=6668&rank=4 and http://www.acrin.org/TabID/155/Default.aspx

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and the measure was Achieved. Three imaging methods (FDG-PET, FLT-PET, and DCE-MRI) were compared and the new scans have increased sensitivity over computed tomography (CT) scans. These scans may offer improved methods for assessing lung cancer therapy, however additional testing is needed before the scans can be implemented on a wide scale. The trial has successfully been expanded to a multicenter trial so that the additional testing can be conducted.

During the course of this measure, NIH researchers have conducted clinical trials and test-retest reproducibility, and developed the necessary electronic infrastructure and consensus standards. Some of these activities were lung cancer specific, exemplified by the trials and by specific collections in the Imaging Archive, such as the RIDER collections that include patient lung CT and PET images showing response to therapy. Others are more generally applicable to all molecular imaging, such as collections of MRI, PET, and CT phantom imaging to compare and contrast reproducibility. During this time period, sufficient evidence was developed by the lung cancer community that enabled CMS to reimburse for PET scans for determining initial treatment strategy for small cell lung cancer, as well as for non-small cell and for subsequent treatment strategy for non-small cell.

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.

SRO-5.8 By 2012, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies. (Outcome)

FY	Target	Result
2012	Device to measure hot flashes developed and tested in clinical studies is improved compared to other devices. *(Baseline):* Number of subjects enrolled in FY11 and total number for study TBD	N/A
2011	Complete 90% of planned study subject accrual and continue quantitative data collection. *[Previous Target]:* Complete 80% of planned study subject accrual and continue quantitative data collection. *(Baseline):* (FY10) Number of subjects enrolled in FY10 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)	141 women have been successfully enrolled in the trial (78% of target enrollment). (Target Exceeded)
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)

Data Source and Validation
The study progress report can be obtained from the National Center for Complementary and Alternative Medicine's Office of Policy, Planning and Evaluation at 301-451-8876.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and Exceeded. A total of 141 women successfully enrolled into the trial to date (78% of target enrollment). 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 NIH 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 40%. As a result of reaching 78% enrollment this fiscal year, the FY 2011 target has been adjusted to completing 90% of planned enrollment. This trial will be fully

enrolled when 180 women have been successfully recruited. It is likely that the trial will be fully enrolled ahead of schedule.

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 that 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. The meeting participants recommended that once device development was complete, clinical studies should 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 are needed. 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 was not 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 duration time 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 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.

SRO-5.9 By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations. (Outcome)

FY	Target	Result
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.	The role of genetic factors was established in Type 2 diabetes, prostate cancer, and hypertension, for which health discrepancies are noted between populations. (Target Met)
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)

Data Source and Validation
Speliotes EK et al.. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010 Oct 10. http://www.nature.com/ng/journal/v42/n11/full/ng.686.html Heid IM et al.. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010 Oct 10. http://www.nature.com/ng/journal/v42/n11/abs/ng.685.html Teslovich TM, Musunuru K, Smith AV et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 466, 707-713 (5 August 2010). http://www.nature.com/nature/journal/v466/n7307/abs/nature09270.html Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, Zeggini E, Huth C, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nature Genetics. 42:579-589, 2010. http://www.nature.com/ng/journal/v42/n7/abs/ng.609.html Stitzel ML et al. Global epigenomic analysis of primary human pancreatic islets provides insights into type 2 diabetes susceptibility loci. Cell Metabolism. 2010 Nov 3;12(5):443-55. http://www.cell.com/cell-metabolism/fulltext/S1550-4131(10)00405-5 Prokunina-Olsson L et al. Refining the prostate cancer genetic association within the JAZF1 gene on chromosome 7p15.2. Cancer Epidemiol Biomarkers Prev. 2010 May;19(5):1349-55. Epub 2010 Apr 20. http://cebp.aacrjournals.org/content/19/5/1349.full.pdf

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and the measure was Achieved. The role of genetic factors was established for three major diseases for which health disparities are noted between populations: Type 2 diabetes, prostate cancer, and hypertension.

Type 2 diabetes (T2D) is a major cause of morbidity and mortality worldwide. The FUSION (Finland-United States Investigation of NIDDM Genetics) study has performed follow-up genotyping based on T2D meta-analysis results from various study groups with whole genome scan data and imputed data. During the last 5 years, researchers have contributed to the identification of 38 loci associated with increased risk for T2D. Furthermore, a large number of novel variants have been identified for lipids, height, body mass index, waist-hip ratio, and metabolic traits. Researchers are working towards understanding the biological dysfunction associated with these variants and how they contribute to T2D.

The NIH's Cancer Genetic Markers of Susceptibility (CGEMS) team performed a genome-wide association study of 550,000 SNPs (single nucleotide polymorphisms, or small genetic variations that can occur within DNA sequences) in 1,172 individuals with prostate cancer (484 with nonaggressive prostate cancer, Gleason o7 and stage A/B; 688 with aggressive prostate cancer, Gleason Z7 and/or stage C/D) and 1,157 “control” individuals who did not develop prostate cancer during the same time period in the Prostate, Lung, Colorectal, and Ovary (PLCO) Screening Trial. A strong genetic association with prostate cancer susceptibility from the genome-wide scan was found at human chromosome 8q24 (at the SNP rs6983267) and was followed up with immediate replication in four other populations to validate the finding. This variant is associated with a population attributable risk of prostate cancer of 21% in men of European ancestry.

The Family Blood Pressure Program (FBPP) has carried out extensive linkage analyses (studies of genetic polymorphisms in multiple family members to identify markers co-inherited with a mutation) using various novel strategies and analyses and followed up on many of the linkage peaks with genome-wide association studies. A major emphasis of this phase of the FBPP has been on the role of gene variation on inter-individual variation in the brain, heart, and kidney complications of hypertension. Recent advances in genome-wide association studies are identifying novel candidate genes for hypertension, coronary heart disease, cerebrovascular disease, and kidney

disease. The FBPP is actively investigating the role of these genes in the complications of hypertension. For example, FBPP is asking whether the recently identified gene for coronary heart disease on chromosome 9 is association with left ventricular hypertrophy (thickening of the heart's lower left chamber) and heart failure among hypertensive patients. Ancillary studies to follow-up on and validate the results generated by the FBPP have been initiated, including the comprehensive mapping of a blood pressure quantitative trait locus (a chromosomal region associated with blood pressure)on chromosome 17, which uses the FBPP data for replication.

Measure

NIH supported three areas of research in which important genetic factors related to disease emerged. The following programs met, and sometimes exceeded, all their respective targets each year and successfully identified genetic factors that contributed to diseases. In addition to furthering genetic and scientific knowledge these studies also give insight into health disparities among populations. Together, the following studies successfully achieved the overall goal on time.

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.

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 was 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.

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, it is important to note that NIH pursues many more than three areas of disease research.

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, relied on 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, with type 2 diabetes (noninsulin-dependent diabetes mellitus, or NIDDM) as the most common form and occurring 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. Ultimately, these studies provided great insights into the genetic factors in diseases for which health disparities are noted.

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, funds research to identify genetic factors across the genome that play a role in three major diseases for which health disparities are noted. 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.

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 provided 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 were 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 was 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.

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)

FY	Target	Result
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	Conducted year 4 follow-up clinical exams and data collection on approximately 90% of the cohort, and chemical analysis for biomarkers were also performed. (Target Met)
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
Biro, etal."Pubertal Assessment Method and Baseline Characteristics in a Mixed Longitudinal Study of Girls." Pediatrics 2010; 126:e583-.e589 Wolff et al "Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls." Environ Health Perspect 2010; 118:1039–1046

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH researchers conducted follow-up clinical exams and collected data on approximately 90 % of the study cohort. Analysis of the cohort of approximately 1200 girls has revealed that female puberty begins earlier than expected. As compared to reports from 30 years earlier, 17.9% of Breast Cancer Environmental Research Centers (BCERC)participants at age 8 were at breast stage >2 among white participants contrasted to 10.5% from an authoritative Pediatric Research in Office Settings (PROS) study. Among black BCERC participants 37.0% were breast stage >2 contrasted to 36.6% (not a significant difference) in PROS.

The BCERC also reported on the association of biomarkers isolated from urine with breast and pubic hair development. Early appearance of these reproductive traits is considered an established risk factor for future breast cancer. The strongest finding was attenuation by enterolactone exposure of the BMI association with breast development. By determining the initial appearance of breasts and pubic hair, the investigators were able to show

that common exposures, such as phthalates that are found in plastics, and dietary components, like soy, can affect pubertal onset in a predicable way. Although the associations are small the effects could affect a significant proportion of the population because the exposures are very common in everyday life and by the level found in the girls was relatively high.

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.

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)

FY	Target	Result
2012	Test at least two behavior-based strategies that manage at least one candidate symptom and improve quality of life and health outcomes. *(Baseline):* Ongoing studies are exploring behavioral strategies for symptom management.	N/A
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.	Assessments identified a that an intervention for caregivers of individuals with Alzheimer's disease improved health outcomes, including sleep quality, and that another intervention reduced pain and improved cardiovascular fitness in patients receiving cancer therapy. (Target Met)
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
Elliott AF, Burgio LD, DeCoster J. (2010) "Enhancing caregiver health: findings from the Resources for Enhancing Alzheimer's Caregiver Health II Intervention." Journal of the American Geriatrics Society.**58**: 30-37. http://www.ncbi.nlm.nih.gov/pubmed/20122038 Griffith, K., J. Wenzel, et al. (2009). "Impact of a walking intervention on cardiorespiratory fitness, self-reported physical function, and pain in patients undergoing treatment for solid tumors." Cancer 115(20): 4874-84. http://www.ncbi.nlm.nih.gov/pubmed/19637345

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Researchers completed two studies that assessed the impact on health outcomes of behavior-based symptom management strategies, targeting symptoms that included pain, sleep quality, and/or fatigue. In one study, scientists focused on mitigating the adverse effects on individuals who provide informal care for family members or friends with Alzheimer's disease (AD), including poor sleep quality. Individuals with AD often display progressive cognitive decline and unpredictable behaviors. More than 70% of the 4.5 million individuals in the U.S. with AD live at home, with a spouse, other family member, or friend serving as an informal caregiver. The constant demands of providing care for someone with AD can take a toll on the mental and physical

health of the caregiver. The Resources for Enhancing Alzheimer's Caregiver Health (REACH) program was developed to assist AD caregivers. The REACH program taught caregivers about AD, along with strategies to help them manage troublesome behaviors of the care recipients. It also emphasized ways for caregivers to manage stress, maintain their social support groups, and enhance their own health and self-care activities. In a multisite study involving almost 500 AD caregivers, those who received the REACH intervention reported better physical, emotional, and overall health compared to those who received a packet of basic AD educational materials. In addition, the REACH caregivers had lower scores for depression, which contributed to reducing their sense of caregiving burden, and reported better sleep quality. These findings indicate that the REACH program, by providing information about both AD and self-care, helped AD caregivers maintain their own physical, emotional, and mental well-being.

In another study, scientists examined a behavioral intervention to reduce pain and increase cardiorespiratory fitness in cancer patients receiving chemotherapy or radiation therapy. This randomized clinical trial included 126 patients with breast, prostate, or other cancers that were randomized to a home-based walking intervention or usual care (control group). The intervention was an individualized exercise prescription for a brisk 20- to 30-minutes walk followed by 5 minutes of slower walking, 5 times per week. Pain and peak oxygen uptake (VO_2) were measured prior to chemotherapy or radiation and then after all treatment was completed. A validated self-assessment tool measured pain while cardiorespiratory fitness was measured by VO_2. Intervention patients were also telephoned bi-weekly by a nurse to assess walking progress, answer questions, and offer support. Results indicated that increased exercise dose was associated with decreased pain in the intervention group compared to the control group. When prostate cancer patients were compared to non-prostate cancer patients, prostate patients significantly increased their VO_2 by the end of their cancer treatment. It was speculated that prostate cancer patients may have improved more because prostate cancer treatment is often limited to radiation, which has fewer side effects than chemotherapy. These findings indicate that behavioral therapy may be effective in decreasing pain and improving or maintaining cardiovascular fitness in patients receiving cancer therapy. Further work may be needed to refine the intervention, especially for older patients and those receiving chemotherapy.

Ongoing research continues to develop and test strategies for managing symptoms to improve quality of life and health outcomes. The two studies discussed here are initial steps in developing effective behavioral strategies to reduce symptom burden caused by symptoms such as pain, poor sleep, and anxiety. 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 continue to systematically identify and test the effectiveness of behavioral methods for improving symptom management. Initial efforts focused on identifying candidate symptoms appropriate for assessment in studies of behavior-based symptom management strategies: pain, insomnia, and fatigue. For the last two years, behavioral strategies designed to manage these candidate symptoms have been assessed for their ability to impact patient quality of life and health outcomes. Measuring the effectiveness of these strategies continues to include assessments such as patients' abilities to perform activities of daily living, or patients' pain status. During the initial years of this goal, the current state of research into using behavioral methods to manage symptoms and improve quality of life was investigated. Following these initial assessments of quality of life, further study has and will continue to 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 include measurements of not only quality of life, but also factors such as longevity, chronic disease morbidity, and physical and mental functional status.

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)

FY	Target	Result
2012	Test one additional compound in animal models of extinction of drug seeking behavior and confirm in replication studies the effectiveness of compounds reported to date *(Baseline):* TBD based on compounds tested in 2010, 2011	N/A
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	Two compounds were tested in animal models of relapse, i.e., reinstatement of drug seeking behavior: D-serine enhanced the extinction of cocaine reinforced behavior and modafini enhanced extinction of methamphetamine reinforced behavior. (Target Met)
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
Kelamangalath L, Wagner JJ. D-serine treatment reduces cocaine-primed reinstatement in rats following extended access to cocaine self-administration. Neuroscience.2010 Sep 1;169(3):1127-35. Epub 2010 Jun 10. http://www.ncbi.nlm.nih.gov/pubmed/20541592 Reichel, CM, See, RE. Modafinil effects on reinstatement of methamphetamine seeking in a rat model of relapse. Psychopharmacology, 2010, 210: 337-346. http://www.ncbi.nlm.nih.gov/pubmed/20352413

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH researchers demonstrated the efficacy of two compounds to enhance the extinction of drug seeking in rats – D-serine and modafinil. In one study, researchers tested D-serine, a glycine agonist, for its ability to enhance extinction of cocaine-seeking behavior. D-serine was administered either before or immediately following extinction sessions--in which rats learn that their responses no longer result in cocaine administration. D-serine enhanced the ability of extinction training to reduce cocaine-primed reinstatement of drug-seeking behavior in rats that were previously given long periods of access to cocaine (thought to model dependence in humans). These results suggest that D-serine can act to enhance the consolidation of extinction learning and is therefore a promising adjunctive agent along with behavioral therapy for the treatment of cocaine addiction.

In the second study, researchers tested the effects of modafinil on extinction of methamphetamine reinforced responding. Modafinil is approved for the treatment of narcolepsy and chronic sleepiness during the waking hours, and has cognitive enhancing properties. Previous research has suggested it might be useful in the treatment of

psychostimulant addiction. The study showed that modafinil attenuated methamphetamine-primed as well as cue-induced reinstatement of responding for methamphetamine.

Extinction (or the unlearning) of conditioned responses is important for preventing relapse to drug addiction. This is because conditioned cues—the people, places or things associated with the drug experience--are frequently the triggers of relapse. In fact, these cues can be so powerful that a person may not even be aware of their occurrence, and yet the person experiences 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 2009 there were an estimated 21.8 million persons aged 12 or older (8.7 percent of that population) meeting criteria for substance abuse or dependence. [1] Substance abuse and dependence frequently co-occur with anxiety disorders, which are 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 2009, the number of persons needing treatment for an illicit drug or alcohol use problem was 23.5 million, and only 2.6million of them received treatment at a specialty facility based on results from 2009 NSDUH findings. [1] In 2008, there were 2.5 million adults with serious mental illness associated with substance dependence or abuse, and of these less than half received mental health treatment or substance use treatment at a specialty facility.

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.

SRO-5.13 By 2015, establish and evaluate a process to prioritize compounds that have not yet been adequately tested for more in-depth toxicological evaluation. (Outcome)

FY	Target	Result
2012	Test 10,000 compound main library in 50 qHTS and test 50 compounds in mid-throughput assays. *(Baseline):* Results from FY10 research	N/A
2011	Identify an additional 3,000 compounds to the library for testing, complete compound analytical analysis, and test 50 compounds in mid-throughput assays. *Previous target:* *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.	7,000 compounds were selected and collected as an establishment of the compound library. A subset of this library, "the 1408 library compound library," has screened an additional 20 qHTS assays. 50 compounds were identified for testing in 50 mid-throughput assays but testing was not conducted and was rescheduled for 2011. (Target Not Met)

Data Source and Validation
Review of the Biomolecular Screening Branch http://ntp.niehs.nih.gov/go/36083

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Not Met. Seven thousand compounds were selected and collected to establish the compound library. However, the mid-throughput assays were delayed. The Food and Drug Administration (FDA) recently became a partner to this project joining the National Toxicology Program, the NIH Chemical Genomics Center, and the U.S. EPA. Consequently, a decision was made to expand the number of compounds in the library to 10,000 to accommodate the needs and interests of other Federal agencies and organizations. The increased size of the library and a computational decision to test each compound in 14 different concentrations 3x in a single run necessitated the acquisition of a new robotics facility at the NIH Chemical Genomics Center, with delivery scheduled for February/March, 2011, which is a significant reason why the 50 mid-throughput assays were not conducted.

The expansion of this program increases the breadth of experience in human diseases and in animal models of human disease, as well as in toxicity pathway analysis and computational toxicology. By increasing the overall compound library the data is expected to be more robust, which should reduce any research gaps. Consequently, the expansion data will ultimately generate data that will be more useful to the scientific and regulatory community to use in the protection of human health and the environment. A subset of this library, the NTP "1408 compound library," was screened in 20 additional qHTS assays for effects on endpoints relevant to human disease, such as mitochondria, hERG, and various nuclear receptors. During 2010, a 50 compound subset of the library was scheduled to have been screened in 50 mid-throughput assays. The compounds were identified and obtained but testing was not initiated due to delays by EPA in establishing their testing contracts and providing these compounds for testing as part of the EPA ToxCast Phase II screening effort (NTP funds were provided via an Interagency Agreement to the EPA for the testing of these 50 compounds). Screening was rescheduled for 2011; this will not delay any future activities.

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.

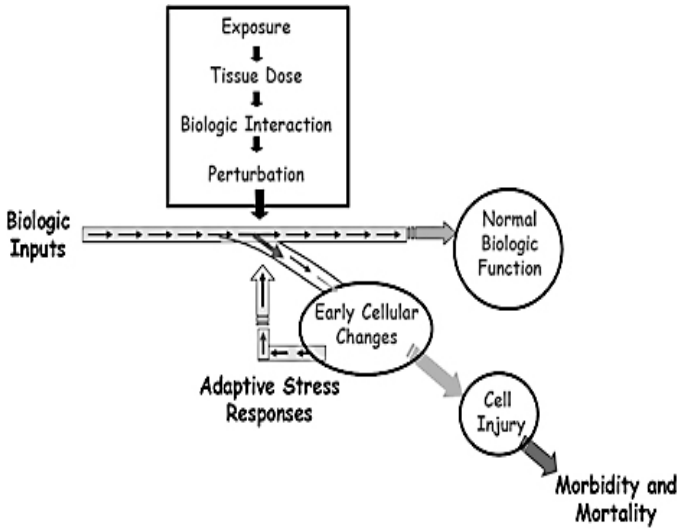

Figure 1 - From: "Toxicity Testing in the 21st Century, a Vision and Strategy" (NRC, 2007)

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 10000 compounds tested in quantitative high throughput screens (qHTS) and on at least 50 compounds tested in 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 will be tested in at least 500 mid-throughput assays that can provide more in-depth toxicological analysis.

SRO-5.14 By 2013, reduce tobacco prevalence among youth by preventing initiation and increasing rates of cessation. (Outcome)

FY	Target	Result
2012	Based on results of preliminary analysis, implement evidence-based behavioral cessation programs, and continue to assess the efficacy of cessation medicines in low income youth and adult populations. *(Baseline):* Completed 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.	N/A
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.	NIH has developed and tested smokeless tobacco use prevention interventions for youth and smoking cessation interventions in low income populations. These studies are ongoing. (Target Met)
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 Jon O. Ebbert, Herbert H. Severson, Ivana T. Croghan, Brian G. Danaher, Darrell R. Schroeder, A pilot study of mailed nicotine lozenges with assisted self-help for the treatment of smokeless tobacco users, Addictive Behaviors, May 2010: 522-525 http://www.ncbi.nlm.nih.gov/pubmed/20060229 Varenicline for Smokeless Tobacco Use http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7568685 Jon O. Ebbert, Ivana T. Croghan, Frederick North, Darrell R. Schroeder, A pilot study to assess smokeless tobacco use reduction with varenicline, Nicotine Tob Res 2010 Oct;12(10):1037-40. http://www.ncbi.nlm.nih.gov/pubmed/20724382 High Dose Nicotine Patch Therapy for Smokeless Tobacco Use http://cancercontrol.cancer.gov/grants/abstract.asp?ApplID=7689089

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH has developed and tested smokeless tobacco use prevention interventions for youth and smoking cessation interventions in low income populations. These studies are ongoing.

Notable advances in this area of research include a comparative effectiveness study, a clinical trial that featured counseling, and research on alternative methods of smoking tobacco.

In the comparative effectiveness study testing five different smoking-cessation aids, researchers found that a combination of the nicotine patch plus the nicotine lozenge was most effective at increasing smoking abstinence. All patients, including those in the placebo groups, received intensive smoking-cessation counseling. In addition, the placebo groups all achieved an unusually high rate of success in quitting, perhaps due to the intensive counseling.

In the large clinical trial that featured counseling, it was shown that telephone-based counseling that included motivational interviewing and cognitive behavioral approaches helps older teens quit smoking. The trial was the first to demonstrate a prolonged effect—defined in the trial as lasting at least 6 months—on smoking cessation among adolescent smokers. This finding is consistent with the recommendation in the U.S. Public Health Service's 2008 Clinical Practice Guidelines, which indicate that counseling can be an effective treatment to help youth quit smoking.

Another recent study found that waterpipe tobacco smoking, commonly known as hookah smoking, is associated with greater exposure to carbon monoxide (CO), similar nicotine levels, and "dramatically more smoke exposure" than cigarette use. The study involved 31 adults who were each tested after smoking one cigarette and after a 45-minute waterpipe smoking session.

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.

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)

FY	Target	Result
2012	Complete goal of identifying the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans. *(Baseline):* Data from GWAS for AMD and Glaucoma has led to gene discovery and animal model generation.	N/A
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	Researchers elucidated mechanisms of AMD neovascularization by exploring the biological roles of newly identified genetic variants of growth factors, complement components, SERPING1, CCR3, and HTRA1. (Target Met)
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)

Data Source and Validation
Target performance Chen Y, Bedell M, & Zhang K. Age-related Macular Degeneration: Genetic and Environmental Factors of Disease. *Molecular Interventions*. (2010); 10 (5): 271-281. http://www.ncbi.nlm.nih.gov/pubmed/21045241 Lee AY, Kulkarni M, et al. The effect of genetic variants of *SERPING1* on the risk of neovascular age-related macular degeneration. *Br J Ophthlalmol*. (2010); 94: 915-917. http://www.ncbi.nlm.nih.gov/pubmed/20606025 Yang Z, Tong Z, et al. Genetic and functional dissection of *HTRA1* and *LOC387715* in age-related macular degeneration. *PLoS Genetics* (2010); 6(2): e1000836. http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000836 Hou X, Kumar A, et al. PDGF-CC blockade inhibits pathological angiogenesis by action on multiple cellular and molecular targets. *PNAS* (2010); 107 (27): 12216-12221. http://www.ncbi.nlm.nih.gov/pubmed/20566880 Qazi Y, Maddula S, Ambati B. Mediators of Ocular Angiogenesis. *Journal of Genetics*. (2009 Dec); 88 (4): 495-515. http://www.ncbi.nlm.nih.gov/pubmed/20090210 Mason, AB& Hoh J. CCR3: Shedding New Light on a Dark Problem? *J Molecular Cell Bio* (2009 Oct); 1 (1): 17-19. http://www.ncbi.nlm.nih.gov/pubmed/19684049 **Other Highlights** Neale B, Fagerness J, et al. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (*LIPC*). *PNAS* (2010); 107 (16): 7395-7400. http://www.ncbi.nlm.nih.gov/pubmed/20385826 Chen W, Stambolian D, et al. Genetic Variants near *TIMP3* and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. *PNAS* (2010); 107 (16): 7401-7406. http://www.ncbi.nlm.nih.gov/pubmed/20385819 International AMD Genetics Consortium for Meta-Analysis NEI Ocular Genetics Program Director: Hemin Chin, 301-451-2020

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Researchers elucidated roles of newly identified key factors controlling choroidal neovascularization in AMD. These studies explored genetic variants of multiple factors including components of the complement system, SERPING1, growth factors, and HTRA1. NIH also expanded the Comparison of AMD Treatment Trials (CATT) to understand the pharmacogenetics of responses to anti-VEGF therapy.

CATT is a head-to-head comparative effectiveness study looking at relative safety, effectiveness, and dose responses of two similar drugs for CNV, Lucentis and Avastin, alone and in combination with other therapies. Both drugs work by blocking signaling activity of VEGF. Although these drugs have revolutionized the treatment of wet AMD, it is not clear why some patients respond better than others. To explore genetic factors impacting this variable response, a field known as pharmacogenetics, NIH expanded the CATT study to collect blood samples from participants to determine if certain patterns of genes control the clinical response to these anti-VEGF drugs; results from pharmacogenetic studies are expected next year.

Early stages of AMD are marked by deposits, called drusen, that accumulate beneath the retina. Drusen increase the risk of CNV, but the mechanism is not yet fully appreciated. In a landmark 2005 genetics discovery, the inflammatory molecules of the complement system were found to be a major risk factor for AMD. It was later shown that complement components c3 and c5 accumulated in drusen of AMD patients and were inducing VEGF expression in human tissue and in animal models. New research demonstrated that removing c3 or c5 reduced VEGF expression and CNV in an animal model of advanced AMD. Furthermore, *SERPING1* is a key regulator of the classic complement pathway. In a study of 556 patients and 256 controls, NIH funded scientists found that

genetic variants of *SERPING1* were associated with CNV risk, independent of other known genetic risk factors in the complement pathway. Some patients had a risk allele that increased likelihood of CNV, while others exhibited a protective allele.

Previous genetics studies had identified the ARMS2 locus as an AMD susceptibility region on human chromosome 10, but this region contains three genes, any of which could be contributing to AMD. An NIH group collaborating with a Chinese group used genetic tools to functionally and genetically dissect this region in Caucasian and Chinese populations. They pinpointed *HTRA1* for its strong role causing wet AMD. In AMD patients, excessive HTRA1 accumulates in drusen. HTRA1 is a serine protease that breaks down extracellular matrix, a meshwork of proteins and other molecules that attach to the outside of cells and regulate cell function in their larger environment. It is also inhibits a protein known as transforming growth factor (TGF) beta, which is involved in extracellular matrix formation and blood vessel formation. Both HTRA1 and TGF-beta may be used as molecular targets in treating CNV. Members of the Matrix Metalloproteinase (MMP) family have also been implicated in CNV (also see "other highlights" below). MMP proteins are stimulated by VEGF and degrade the extracellular matrix.

In addition to VEGF, recent progress has pointed to other growth factors involved in CNV. NIH scientists reported a new form of Platelet Derived Growth Factor (PDGF-CC). Blocking PDGF-CC by neutralizing the protein with antibodies, interfering with the RNA message, or genetic deletion suppresses CNV in animal models. Further exploration of the PDGF-CC pathway revealed glycogen synthase kinase-3 beta, a molecular target that may be modulated to regulate CNV. Fibroblastic Growth Factors (FGF) are a family of molecules involved in eye development and blood vessel growth; elevated levels of FGF have been observed in CNV. Pigment Epithelium Derived Factor (PEDF) works in opposition to VEGF to control CNV. A human genetic variant of PEDF (Met72Thr) was recently linked to wet AMD. Other growth factors (CTGF, TGF, Angiopoietin) have also been studied for their role in the VEGF pathway.

Advances or Other Highlights

A major genetics breakthrough identified genes in the cholesterol pathway contribute to AMD. Two major Genome Wide Association Studies (GWAS) were completed in 2010, leading to the identification of many new genes associated with AMD. Importantly, these studies pointed to a molecular pathway potentially involved with AMD, giving scientists a new biochemical handle for therapeutic interventions. GWAS requires collecting DNA from a large numbers of patients to discover significant genetic association for rare variants or genes that make small contributions to complex diseases. Two complementary NIH teams combined their data to scan the genomes of over 18,000 people. In addition to genes uncovered in previous studies, the teams identified two genes previously associated with high-density lipoprotein cholesterol (HDL) levels in the blood: hepatic lipase gene (LIPC) and cholesterylester transfer protein (CETP). Weaker associations were discovered for two other genes involved in cholesterol pathway: ATP-binding cassette transporter (ABCA1) and lipoprotein lipase (LPL). More research is needed to confirm these findings, but together these genes suggest a previously unknown role for cholesterol regulation in AMD susceptibility. HDLs are among a family of lipoproteins that transport essential fats, such as cholesterol, through the bloodstream. It is believed that early stages of AMD are affected by accumulation of oxidation products of cholesterol and other lipids in the retinal pigment epithelium, a layer of cells in the back of the eye. However, the relationship between HDL cholesterol in the blood and AMD is still unclear. The studies also identified a new strong association on chromosome 22, near a gene called metalloproteinase inhibitor 3 (TIMP3). Mutations in TIMP3 had been known to cause Sorsby's fundus dystrophy, a rare, inherited early-onset form of macular degeneration.

Multiple research teams around the world have been collecting data from a large number of AMD patients around the world for genetic studies. To unify these international efforts into a single well-coordinated collaboration, the NIH hosted the first meeting of the International AMD Genetics Consortium for Meta-Analysis on June 15, 2010. Fourteen teams met or participated via videoconference to discuss progress, data sharing, phenotype definitions, meta-analysis procedures, data replication, and future publication plans. The Consortium created two working groups—data analysis and phenotype—and established a plan for meta-analysis for AMD GWAS.

BACKGROUND

Age-related macular degeneration (AMD) and glaucoma are complex eye diseases that predominantly affect people later in life. 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. Glaucoma is a group of eye disorders sharing a distinct type of optic nerve damage that can lead to blindness. Both AMD and glaucoma result from a combination of genetic and environmental factors

Prevalence/Incidence

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. 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. 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.

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. In a major breakthrough using these data in GWAS, 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. Two other genes were linked with the observed progression to advanced (or 'wet') 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.

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.

Early stage age-related Macular Degeneration (AMD) can develop into two forms of advanced AMD, but the genes and factors determining which form develops are only beginning to be understood. Geographic atrophy, the hallmark of 'dry' AMD accounts for 80 to 90 percent of advanced disease. However, 90 percent of patients with severe central vision loss suffer from choroidal neovascularization (CNV)—'wet' AMD, which occurs when abnormal blood vessels start to grow in the choroid tissue under the light-sensing retina. These new blood vessels tend to be very fragile and often leak blood and fluid. The blood and fluid raise the macula, the central part of the retina, from its normal place at the back of the eye causing damage and loss of central vision. To treat neovascular AMD, ophthalmologists either use laser light to destroy or seal off new blood vessels to prevent leakage, surgery or, more recently, drugs that block Vascular Endothelial Growth Factor (VEGF). VEGF is a regulator protein that stimulates sprouting of abnormal blood vessels. The Comparison of AMD Treatments Trial (CATT) is comparing different VEGF-blocking drugs head-to-head and in combination therapy. However, not all patients respond to these treatments, so scientists are exploring other genes that regulate ocular angiogenesis in the hopes of finding new avenues for therapy.

A protein in the chemokine receptor family, CCR3, was discovered in 2009 by NIH scientists for its essential role in choroidal neovascularization in AMD. Usually associated with allergic responses, CCR3 is known to be expressed in white blood cells, eosinophils, which migrate to sites of inflammation. But in AMD patients and in animal models, CCR3 expression of was also found choroidal cells in the eye, acting like a switch to stimulate CNV. This advance may usher a new era in the management of CNV, using CCR3 for early diagnosis of CNV as well as a gateway for treatment.

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)

FY	Target	Result
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 BARI 2D, ACCORD, Look Ahead, and FAVORIT trials.	N/A
2010	Report findings of the primary results of the BARI 2D Trial. *(Baseline):* (FY08) Investigators have collected data on interventions to reduce CVD morbidity in patients with type 2 diabetes.	The primary results of the BARI 2D study showed that neither prompt revascularization vs. delayed revascularization nor insulin sensitization vs. insulin provision was superior in terms of mortality. (Target Met)
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's 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)
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)

Data Source and Validation
A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease. New England Journal of Medicine. Vol 360: 2503-2515. 2009. http://content.nejm.org/cgi/content/short/360/24/2503 On-Demand Video of Press Conference Coverage at American Diabetes Association 2009: http://www.medpagetoday.com/MeetingCoverage/ADA/14524 Circulation, Volume 120, 22 Dec 2009 (related abstracts on pp 2550-2558, 2529-2540) http://circ.ahajournals.org/content/vol120/18_MeetingAbstracts/ Journal of the American College of Cardiology, Volume 55, Issue 10, Supplement 1, 9 March 2010. Relevant abstracts are on A49. E462, A128.E1198, A128.E1195, A156. E1462, A156.E1464, A127.E1193 http://content.onlinejacc.org/content/vol55/10_MeetingAbstracts/ American Diabetes Association Annual Meeting – June 2010 – BARI 2D presentation http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=79343

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. The BARI 2D study showed that neither prompt revascularization vs. delayed revascularization nor insulin sensitization vs. insulin provision was superior in terms of mortality.

The BARI 2D study randomized 2368 patients with type 2 diabetes and heart disease to either prompt revascularization and intensive medical therapy (IMT) or IMT alone with delayed or no revascularization. A second randomization compared insulin-sensitization to insulin-provision therapy. The primary endpoints in all cases were mortality and a composite endpoint that consists of death, myocardial infarction (MI, commonly known as heart attack), or stroke. No significant differences in outcome were observed between groups in either of the randomizations.

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 by 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 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 USRDS, 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 Data and Safety Monitoring Board. 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.

SRO-6.4 By 2015, 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)

FY	Target	Result
2012	Investigate the role of mucus gel formation in healthy controls and asthma patients. *(Baseline):* Little is known about the mechanisms of mucus formation in the airways.	N/A
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	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.	Histoblood group antigens were explored as susceptibility factors for asthma exacerbations.' O-secretor mucin glycan phenotype was identified as a risk factor for asthma exacerbations. (Target Met)
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)

Data Source and Validation
Anh L Innes, Kelly Wong McGrath, Ryan H Dougherty, Charles E McCulloch, Prescott G Woodruff, Max A Seibold, Kimberly S Okamoto, Kelsey J Ingmundson, Margaret C Solon, Stephen D Carrington, and John V Fahy **The H Antigen at Epithelial Surfaces is Associated with Susceptibility to Asthma Exacerbation** Am. J. Respir. Crit. Care Med., Aug 2010; doi:10.1164/rccm.201003-0488OC http://www.ncbi.nlm.nih.gov/pubmed/20732988

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The 2010 target was Met. Histoblood group antigens were explored as susceptibility factors for asthma exacerbations. The O-secretor mucin glycan phenotype was identified as a risk factor for asthma exacerbations in an initial case control study. Findings have been confirmed in a replicate study. This sheds new light on the pathophysiology of asthma exacerbations.

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 (AE, 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 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 met to share experiences, successes, and concerns, as well as to assess the state of the field.

Imaging modalities had not been used effectively to study the development of AE. Research directions 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.

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)

FY	Target	Result
2012	Complete enrollment into a comparative study of three non-nucleoside reverse transcriptase inhibitor (NNRTI)-sparing antiretroviral regimens for treatment-naïve HIV-1-infected individuals. *(Baseline):* Regimens containing Efavirenz are often recommended as a first line therapy for HIV-infected patients. However, for some people an EFV-containing regimen is undesirable, due to side effects, teratogenicity, pharmacokinetic (PK) interactions, or acquired NNRTI-resistant virus.	N/A
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	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.	Initiated the Promoting Maternal-Infant Survival Everywhere (PROMISE) study to examine strategies to prevent antepartum, intrapartum and postpartum (breastfeeding) transmission while promoting maternal and infant health worldwide. (Target Met)
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
NIAID Press Release: New Study Examines Best Ways to Prevent Mother-to-Child HIV Transmission and Preserve Maternal and Infant Health.http://www.niaid.nih.gov/news/newsreleases/2010/pages/promise.aspx ACTG Web site- https://actgnetwork.org/ MTN Web site- http://www.mtnstopshiv.org/ IMPAACT Web site - https://impaactgroup.org/

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH researchers initiated a large, multinational clinical trial called P1077, also known as the Promoting Maternal-Infant Survival Everywhere (PROMISE) study, to determine how best to reduce the risk of HIV transmission from infected pregnant women to their babies during pregnancy and breastfeeding while preserving the health of these children and their mothers. The study aims to enroll 7,950 HIV-infected women who are pregnant or have recently given birth and 5,950 HIV-exposed infants of these women from 18 countries whose levels of resources range from high to low. The International Maternal Pediatric Adolescent AIDS Clinical Trials network is conducting the study.

The PROMISE study has four distinct research components/protocols:

- The first component will examine which of two proven strategies is safer and more effective at preventing mother-to-child HIV transmission before and during delivery: giving HIV-infected pregnant women a three-antiretroviral-drug regimen beginning as early as 14 weeks of gestation, or giving them the antiretroviral drug zidovudine beginning as early as 14 weeks of pregnancy and a single dose of the antiretroviral drug nevirapine during labor. The regimen of zidovudine and nevirapine is currently the standard of care in many countries for women who do not yet require treatment for their HIV infection.
- The second component of the PROMISE study will compare the safety and efficacy of two methods of preventing mother-to-child HIV transmission during breastfeeding.
- The third component of the PROMISE study will examine the effects of short-term use of a three-antiretroviral-drug regimen during pregnancy and breastfeeding to prevent mother-to-child HIV transmission on the health of HIV-infected mothers who do not yet need treatment
- The last component of the PROMISE study involves protecting the health of HIV-exposed but uninfected infants. The study will determine whether continuing cotrimoxazole prophylaxis in HIV-exposed, uninfected infants from the time they stop breastfeeding through age 18 months decreases their risk of illness and death without causing side effects or generating bacterial resistance to cotrimoxizole. In resource-limited settings, it is standard to give the antibiotic cotrimoxazole once daily to infants exposed to HIV at birth until the infant has stopped breastfeeding and is known to be HIV-uninfected.

BACKGROUND

While there has been a decline in HIV/AIDS mortality as a result of the increased availability of antiretroviral treatment worldwide, new infections continue to impede efforts to curtail the epidemic. While progress continues to be made in lowering the number of new HIV infections, these infections still remain at unacceptably high levels in the US and throughout the world. In addition, while effective treatment strategies are allowing HIV-infected individuals to live longer than in the past, AIDS-related illnesses remain a significant cause of morbidity and premature mortality. Existing prevention methods such as education, counseling, and condom use are important in reducing the number of HIV infections, but thus far, have been unable to thwart the impact of the epidemic on their own or in combination. Therefore, new prevention methods and treatment strategies, as well as ways to eliminate HIV infection altogether will need to be developed in the coming years as they are still essential to successfully overcoming the epidemic.

Prevalence/Incidence

In 2008, 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 2008, 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 2008, while the number of children newly infected HIV (430,000) decreased by 18% in that same time frame.

In the United States, the most recent statistics from the Centers for Disease Control and Prevention revealed that from 2004 through 2007, the estimated number of newly diagnosed HIV/AIDS cases in the 34 states with confidential name-based HIV infection reporting increased 15%. This is most likely due to changes in state reporting regulations and an increase in HIV testing. In 2007, the estimated overall rate of newly diagnosed

HIV/AIDS infections in the 34 states was 21.1 per 100,000 people. African-Americans continue to face the greatest burden of HIV/AIDS. At 76.7 per 100,000, the rate of new HIV infections among African-Americans in the United States is seven times the rate among whites. In 2007, African-Americans accounted for 51% of all diagnosed cases of HIV/AIDS. Men who have sex with men (MSM) accounted for 53% of all diagnosed cases.

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, thereby weakening the social stability and threatening 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

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 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. In addition, behavior change interventions are also a very significant method of primary prevention of HIV infection and an integral component of any biomedical prevention strategy.

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 supported six 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.

NIH also supports research programs that will work with collaborative HIV/AIDS clinical trials 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 co-morbidities, 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.

Through the HPTN the NIH is currently conducting 11 studies that are evaluating different strategies for HIV prevention including the use of antiretroviral regimens for the prevention of mother to child transmission; community-level prevention interventions; treatment of injection drug users; pre-exposure prophylaxis; and a study of HIV incidence and study enrollment in targeted populations. Other initiatives are also being pursued to identify optimal prevention packages that could lead to clinical evaluation. Five studies being conducted through the MTN are evaluating the safety, acceptability and/or effectiveness of microbicides, while several other studies are in various stages of development. To complement and support these efforts, the NIH supports the evaluation of the safety and efficacy of topical microcides in non-human primates. It has also re-issued the Integrated Preclinical/Clinical Program for HIV Topical Mircrobicides, which encourages advanced development of new and pioneering microbicide candidates and combinations and fosters the translation of new microbicides/combinations from preclinical studies to pilot clinical studies. The Microbicide Innovation Program continues to support the identification and development of new microbicide approaches and targets through preclinical and basic research.

The ACTG and INSIGHT clinical trials networks focus primarily on treatments for HIV-infected adults and adolescents, while the IMPAACT network conducts studies aimed at optimizing the treatment of HIV-infected children, adolescents and pregnant women. IMPAACT also collaborates with the ATN to conduct HIV prevention studies in adolescents. Each of these 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 and for patients who have failed all available treatment options, for whom first line therapy is not a viable option, and/or for those or present with significant clinical problems as a result of AIDS disease, including co-infections such as tuberculosis, hepatitis and malaria. In FY09, 45 studies evaluating HIV therapeutics strategies were initiated or continued in adults at domestic and international sites supported by the NIH and 34 therapeutic studies were concluded or completed. In addition, 25 therapeutic studies addressing complications or co-infections of HIV were also initiated or continued, while 7 such studies were completed or concluded. Similarly, 25 studies were initiated or continued to evaluated HIV treatment regimens for infants, children, adolescents and/or pregnant women while 7 therapeutic studies for these populations were completed or concluded during FY09.

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)

FY	Target	Result
2012	Support clinical studies in at least one IGI system. *(Baseline):* "First-in-human" pilot studies have been initiated on image-guided interventions for treatment of prostate cancer, epilepsy, and prevention of hip fracture.	N/A
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.	New feasibility studies have begun on three IGI technologies for the diagnosis of skin and lymph node cancer and for ultrasound-based treatment of cardiac arrhythmias. One IGI system for prostate biopsy is being tested in human studies. (Target Met)
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
Clinical Evaluation of an Ultrasound Based Imaging System for Guiding Cardiac Ablation http://projectreporter.nih.gov/project_info_description.cfm?aid=8015869&icde=6162384 Progress report information can be obtained from John Haller, Ph.D., hallerj@mail.nih.gov Intra-operative Confocal Imaging to Guide MOHS Surgery http://projectreporter.nih.gov/project_info_description.cfm?aid=8015350&icde=6162438 Progress report information can be obtained from John Haller, Ph.D., hallerj@mail.nih.gov Intraoperative OCT for Determining Lymph Node Status and Staging Cancer http://projectreporter.nih.gov/project_info_description.cfm?aid=8015729&icde=6162489 Progress report information can be obtained from John Haller, Ph.D., hallerj@mail.nih.gov Preprint of manuscript submitted to IEEE Transactions on Biomedical Engineering - An MRI-Compatible Robotic System with Hybrid Tracking for MRI-Guided Prostate Intervention https://jshare.johnshopkins.edu/lwhitco1/papers/2010_APT_MRI_TBME_Preprint.pdf

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Three new feasibility studies have begun on IGI technologies for the diagnosis of skin and lymph node cancer and for ultrasound-based treatment of cardiac arrhythmias. One IGI system for prostate biopsy is being tested in human studies.

Numerous studies have demonstrated the efficacy of needle-based biopsy and therapy procedures in the diagnosis and treatment of prostate cancer. Present-day methods for real-time image-guided needle placement in the prostate provide limited placement accuracy and low imaging specificity to tissue abnormalities. Magnetic resonance imaging (MRI) is an attractive choice for image-guidance due to its high three-dimensional spatial resolution, high specificity to soft tissue abnormalities, real-time capability for monitoring needle placement and induced physiological changes, and its ability to show concurrent metabolic activity when combined with spectroscopy. The technical obstacles to real-time MR image guided needle access to the prostate include the high magnetic field, confined physical space of the MR scanner bore, the limited physical accessibility of the prostate, and practical requirements for patient comfort when positioned in the scanner. Researchers have developed a clinically qualified version of their actuated image-guided robotic system for MR image guided transrectal needle placement in the prostate, and are evaluating quantitatively the performance of the system in human subject clinical trials. This actuated robot promises several advantages over previous technologies including increased needle placement accuracy, reduced procedure time, improved patient comfort, and the (otherwise impossible) ability to perform needle insertions and therapeutic interventions inside the scanner bore.

One group of investigators is continuing their research to move from the laboratory to the clinic the technique they have already developed for image guided ablation therapy. This system can show the physician regions of the heart which have already been treated. Currently physicians have no means to examine these regions. In Phase I, the investigators successfully built the system and demonstrated its efficacy. In phase II they plan a series of clinical tests to demonstrate its utility for treating atrial arrhythmias in patients.

Confocal microscopy may enable screening and diagnosis of skin cancers such as melanomas and basal- and squamous-cell carcinomas, or may guide surgery of such cancers, directly and in real-time on the patient. The screening, diagnosis or surgical guidance may be noninvasive, with minimal need for biopsy, minimal pain and minimal expense. Confocal microscopy may also prove useful for noninvasively diagnosing and treating many other types of cancers such as oral, head-and-neck, breast and cervical cancers. The goal of this project is to translate a bench-top line-scanning confocal microscope into a clinical instrument for intra-operative imaging during Mohs surgery, and to test feasibility for detecting basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) margins on patients, using aluminum chloride as a contrast agent for staining nuclear morphology in reflectance. The motivation is to create a relatively simple, small and low-cost confocal microscope for real-time imaging in reflectance, to guide surgery in diverse settings. The proposed immediate application is intra-operative mapping of BCCs and SCCs to guide Mohs surgery. BCCs and SCCs occur with among the highest rates of incidence, with an estimated 1.3 million new cases diagnosed and an estimated 1 million surgeries performed every year in the USA alone. Surgery is guided by frozen pathology which is labor-intensive and time-consuming. Confocal microscopy images nuclear detail in vivo and thus may enable intra-operative mapping directly on the patient in real-time. Rapid examination of cancer margins may be performed on surgically exposed tissue in situ, to guide accurate and complete excision, while preserving surrounding normal tissue. The imaging may serve as an adjunct to pathology for guiding surgery, while saving labor and cost. Patients may benefit with more efficient procedures, less anesthesia and less time in the operating room. Preliminary results demonstrate the feasibility of detecting BCCs, with topically applied aluminum chloride to enhance cancer-to-normal tissue contrast, in surgically-exposed shave-biopsy wounds in situ on patients. Furthermore, a laboratory bench-top line-scanning confocal microscope demonstrates excellent imaging of nuclear and cellular detail in human skin in vivo.

The surgical treatment of solid tumors frequently involves the resection and post-operative histopathological assessment of sentinel and loco-regional lymph nodes to determine the extent to which the cancer may have spread. This information is also used to stage the disease. The stage of the disease determines the prognosis and dictates treatment strategies. Assessing lymph node status (whether each is normal, reactive, or contains metastatic disease) and staging the disease intraoperatively has significant opportunity to improve the treatment of cancer, and the use

of high-resolution real-time intraoperative imaging has the potential to guide interventions, rather than relying solely on post-operative histopathology. This project involves the clinical translation and investigation of intraoperative three-dimensional optical coherence tomography (3-D OCT) for assessing the micro-architecture of lymph nodes. In contrast to all other imaging techniques that either require resection, bisection, and disruption of lymph nodes, or offer insufficient resolution to visualize morphology in situ, 3-D OCT imaging can be performed through the intact capsule of surgically-exposed lymph nodes that can remain in situ. Through preliminary results, it has been demonstrated that 3-D OCT can differentiate between normal, reactive, and metastatic lymph nodes based on image biomarkers. The intraoperative assessment of lymph node status and the staging of cancer has the potential to update and direct the surgical intervention in real-time, to reduce or eliminate the need for the surgical removal of lymph nodes, to reduce costs, and most importantly, to reduce or eliminate the risks of lymphedema, a highly morbid and lifelong complication from the surgical treatment of many types of cancer.

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, the NIH supports 41 projects in the area of image-guided interventions. These include 7 cardiac and 4 neurosurgical interventions, as well as 14 image-guided interventions for the treatment of cancer.

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 was 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 continued to support technology development demonstrating the feasibility of new IGI technologies, and pilot tests in humans of one IGI system.

In FY 2010, three new feasibility studies have begun on IGI technologies for the diagnosis of skin and lymph node cancer and for ultrasound-based treatment of cardiac arrhythmias. One IGI system for prostate biopsy is being tested in human studies.

SRO-7.7 By 2011, assess community-based methods for facilitating cancer research and providing patients access to optimal cancer care. (Outcome)

FY	Target	Result
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	Begin implementation of the assessment of community-based research program components *(Baseline):* Program components are not in existence	Data from the 10 funded NCCCP hospitals was collected, analyzed, and compiled, including: case studies/site visits, cancer registry reports on adherence to evidence based practice, patient surveys, and a micro-cost survey. (Target Met)
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
The following reports can be found at: http://outcomes.cancer.gov/areas/qoc/ncccp/evaluationsolicitation/ • Comparative Case Study Report for NCI's Community Cancer Centers Program During the First and Second Years of Implementation • NCCCP Evaluation: Micro-cost Study Results from Contract Year 1 • National Cancer Institute Community Cancer Centers Pilot Program (NCCCP): Baseline Patient Survey Report

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH researchers collected, analyzed, and compiled data from the 10 NCCCP hospitals– from case studies, registry based reports of adherence to evidence based practice, patient surveys, and a micro-cost study. Case studies, conducted as site visits were completed, which included meetings with a wide variety of staff from key leaders to support staff. Sites reported cancer registry data on six clinical effectiveness measures for breast cancer diagnosis and treatment and colorectal cancer diagnosis and treatment. Patient surveys were also conducted to measure the impact of the NCCCP from the perspective of the patient. These assessments are assisting in the overall evaluation of site performance. A micro-cost study was also conducted to identify average and/or incremental costs associated with NCCCP activities, including NIH-funded and site supplemental costs. This assessment is assisting to determine the sustainability of the NCCCP.

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 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 developed 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.

SRO-7.8 (RA) By 2011, create genomic resources to identify rare genetic variants that contribute to primary open angle glaucoma. (Outcome)

FY	Target	Result
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.	The NEIGHBOR consortium conducted SNP-based GWAS on 2,507 glaucoma patients and 2,901 controls, far exceeding initial goals in the largest GWAS to date. (Target Met)
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
NEIGHBOR Program Director: Hemin Chin, PhD 5635 Fishers Lane Rockville, MD 301-451-2020 Hemin@NEI.NIH.GOV http://www.nei.nih.gov/anniversary/symposia/glaucoma_agenda.asp

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. The NEIGHBOR consortium conducted SNP-based GWAS for both POAG patients and the healthy controls. The total numbers of genetics samples NEIGHBOR sent to the Center for Inherited Disease Research (CIDR) for SNP-based genotyping exceeded the initial goals by 35 percent: 2,507 primary open-angle glaucoma (POAG) cases and 2,901 age- and gender-matched controls (initial goal 2,000 each). The lead statistical geneticists conducted the preliminary analysis of the data. Additional analyses of the results will be needed to confirm the contributions of candidate genes to POAG.

In December 2009, 14 NEIGHBOR consortium members met to review progress and to finalize collaboration details including establishing a memorandum of understanding, glaucoma phenotype definitions, data inclusion criteria, and data analysis and publication procedures and timelines. The consortium agreed to release all the GWAS data to the Database of Genotype and Phenotype (dbGaP) upon publication, and make the genetic resource available to the broad scientific community. The consortium expects to release the data in May 2011.

Genetics samples collected from clinical sites across the country were combined with samples collected from previous NIH studies (Advanced Glaucoma Intervention Study [AGIS], Collaborative Initial Glaucoma Treatment Study [CIGTS], Glaucoma Genetics Study [GLAUGEN], Nurses Health Study, Health Professionals Study, Women's Health Study). The phenotype ascertainments were harmonized, primarily using a physiological definition of glaucoma (based on testing visual field of patients and controls) and an anatomical definition (imaging the ratio of the optic cup to optic disc size). The coordinating centers performed quality control on genetic samples

before sending them to CIDR for SNP-based genotyping for the GWAS analysis, and for uniform phenotype classification.

Advances or Other Highlights

The NIH hosted a symposium on focusing on Glaucoma. Progress from the NEIGHBOR consortium was presented by consortium scientific leaders, including the design of the GWAS, sample collection, and statistical genetics. NIH computational bioinformaticists described preliminary efforts to conduct high-throughput targeted sequencing from a subset of 200 NEIGHBOR POAG case samples to discover rare genetic variants within exons and flanking intronic sequences that contribute to glaucoma.

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 a 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 created 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 supported and extended unique, timely scientific opportunities. The funds accelerated 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.

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)

FY	Target	Result
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	Four research teams initiated characterization studies of stem and progenitor cells. (Target Met)

Data Source and Validation

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Progress Report for 5 RC2 HL101606-02 submitted on July 7, 2010 - Program contact: Dr. John Thomas, thomasj@nhlbi.nih.gov

Generation of Transgene-Free Lung Disease-Specific Human iPS Cells Using a Single Excisable Lentiviral Stem Cell Cassette. Somers A, Jean JC, Sommer CA, Omari A, Ford CC, Mills JA, Ying L, Sommer AG, Jean JM, Smith BW, Lafyatis RA, Demierre MF, Weiss DJ, French DL, Gadue P, Murphy GJ, Mostoslavsky G, Kotton DN. *Stem Cells*. 2010 Aug 16. [Epub ahead of print] Abstract in pubmed: http://www.ncbi.nlm.nih.gov/pubmed/20715179

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2012 target was Met. Induced-pluripotent stem (iPS) cells were generated and compared with embryonic stem (ES) cell lines, revealing important differences in these two cellular models. iPS cell lines were derived from patients and characterization was initiated.

The four projects made the following progress:
Researchers generated induced-pluripotent stem (iPS) cell lines from healthy donors and from patients with blood disorders. These cell lines have potential as new cellular disease models and the characterization of these iPS cell lines was initiated. The generation of human iPS cell lines from blood cells offers advantages over fibroblasts; it is more convenient, less invasive, and requires less time.

Researchers analyzed the methylation status of embryonic stem (ES) cells and iPS cells. They are in the process of determining the gene expression profile of iPS cell lines, determining differences in large intergenic non-coding RNAs between ES cells and iPS cell lines, analyzing and comparing proteins and metabolites in ES cell and iPS cells, and comparing ES and iPS cellular disease models for fragile X syndrome-related gene 1.

Researchers have improved the protocol for generation of iPS cell lines -- increasing the efficiency ten-fold, iPS cell lines have been generated from normal control subjects and from Down syndrome patients, and an IRB protocol has been obtained for the collection and banking of additional tissue samples from patients with genetic diseases.

Researchers have successfully recruited 3 genotypes of individuals with 2 lung diseases (alpha-1 antitrypsin deficiency and cystic fibrosis) and 1 control group without lung disease. A novel reprogramming vector was used that permitted efficient reprogramming of disease specific somatic cells into iPS cells that are free of reprogramming transgenes. Over 90% of the iPS clones generated were reprogrammed with a single copy of the vector, are pluripotent, and are not dependent on the age of the donor.

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 supported the 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. Investigators are comparing cells derived from ES cells and iPS cells to each other and to tissue-derived progenitor cells. Investigators are also creating 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 the current understanding of stem cells, the NIH is supporting the following efforts:

- 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 address key gaps in our understanding of stem and progenitor cells. The studies begin to determine stem cell characteristics, mechanisms of differentiation, and characteristics of differentiated cells. The research addresses 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.

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)

FY	Target	Result
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.	Developed the infrastructure, software and hardware, for the Image Library database. Established submission pipeline. Populated the site with images and videos. Added Annotation fields. (Target Met)

Data Source and Validation
The Cell: An Image Library can be viewed at http://cellimagelibrary.org/

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH developed a database of accessible and searchable images illustrating cellular and molecular architecture, functional organization, and dynamic cell behaviors.

The first several months were used to start up the system. Activities focused on developing two software modules which allow uploading of images and videos in many formats, along with the capability of adding descriptors by the contributors or the annotation team. In this first year, the site was populated and became publically accessible. The database is searchable and grouped under several categories including: cell process, cell component, cell type, and organism. The investigators report that thousands of images have been committed from outside contributors. Now that the software is in place, populating the Library is a major focus. Several strategies were proposed to increase the rate of image flow.

A team of Annotators was recruited, and has been soliciting and contributing images and videos for the Library. The submission pipeline was established and images have populated the site on a daily basis. Images were deposited on the site and thousands more are in the in the process of being scanned for upload onto the site. Presently, the collection includes both the best known images of a particular cellular process as well as raw data images that traditionally has remained unpublished but may be of value to the research, education and general community. The Annotator Module received critical input from investigators and the Advisory Council of the American Society for Cell Biology and modifications in appearance and ease of use of the site already have been implemented.

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 Image Library has created 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. 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 met 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

The following steps were taken to create a comprehensive and publicly available library of cell images: 1) design and implement the electronic architecture needed for the Image Library; 2) populate the database of reviewed cell images which currently contains nearly 15,000 images; 3) assess the effectiveness of the preliminary database and incorporate feedback-based modifications continuously; Current objectives are to seek long-term support for the library and explore option for linking the library with other databases .

The 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 engages and benefits 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.

SRO-7.11 (RA) By 2012, gather sufficient data to support the development of a national standard for normal fetal growth. (Outcome)

FY	Target	Result
2012	Complete data collection to support the development of a national standard for normal fetal growth. *(Baseline):* Recruited at least 50% of the study participants needed.	N/A
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.	The study protocol has been expanded to recruit twin pregnancies, in addition to singleton pregnancies, to conduct a series of ultrasound exams, nutrition surveys, body measurements, and blood collection. (Target Met)

Data Source and Validation
RECOVERY - Assays of Biological Specimens in Support of the National Standard for Normal Fetal Growth Study https://www.fbo.gov/spg/HHS/NIH/NICHD/NIH-NICHD-DESPR-2010-26/listing.html "RECOVERY" The National Standard for Normal Fetal Growth: Clinical Centers https://www.fbo.gov/spg/HHS/NIH/NICHD/NIH-NICHD-DESPR-10-24/listing.html

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. The study protocol was expanded to recruit twin pregnancies, in addition to singleton pregnancies, to conduct a series of ultrasound exams, nutrition surveys, body measurements, and blood collection. Six new clinical sites and one laboratory were added to the study. Women will be recruited in the first trimester and followed through pregnancy. Each woman will receive six scheduled ultrasound exams. Women will be asked to donate blood samples at enrollment and at follow-up visits at 16-22 weeks, 24-28 weeks, and 34-37 weeks of gestation. After delivery, the newborn will be carefully measured to record birthweight, head circumference, and other body measurements.

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.

Support from the American Recovery and Reinvestment Act (ARRA) enabled researchers 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 were hired at a greater number of research sites. Additional staff included 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, researchers expanded the study protocol to include twin pregnancies, and will 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.

SRO-8.6 By 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES). (Outcome)

FY	Target	Result
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.	NHANES vision data released to public was used to estimate prevalence of diabetic retinopathy and is being analyzed to establish baselines for HHS Healthy People 2020 goals. (Target Met)
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
The Vision questionnaire data collected in the home interview is available here http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/quex07_08.htm The Vision Exam data collected in the Mobile Examination Center is available here http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/exam07_08.htm Vision baseline and goals in HHS Healthy People 2020 Initiative,: http://www.healthypeople.gov/hp2020/Objectives/TopicArea.aspx?id=48&TopicArea=Vision Zhang X, Saaddine J, et al. Prevalence of Diabetic Retinopathy in the United States 2005-2008. *JAMA*. (2010); 304(6):649-656 http://jama.ama-assn.org/cgi/content/abstract/304/6/649

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. The NHANES data has been collected and researchers used these data to conduct an analysis of diabetic retinopathy prevalence. NHANES Vision data from the 2007-2008 questionnaire and mobile examination centers were released to the public in September 2009. The Vision questionnaire data collected in the home interviews and the mobile examination center data are available online.

Epidemiologists from the NIH, the Centers for Disease Control and Prevention (CDC), and the Department of Health and Human Services have been analyzing these data and used them to evaluate progress towards the vision goals in Healthy People 2010 as well as in setting baseline data for the objectives in Healthy People 2020.

One initial analysis used the NHANES data from 2005-2008 to generate prevalence estimates for visual impairment due to diabetic retinopathy. Previous nationwide prevalence estimates for diabetic retinopathy were based on data collected 1988-1994, and there has been a documented increase in diabetes prevalence in the US. A collaborative analysis from CDC, NIH and academic epidemiologists estimated the US prevalence of diabetic retinopathy was 28.5 percent among persons aged 40 years and older with diabetes (representing 3.8 percent of the total US population), with vision-threatening diabetic retinopathy in 4.4 percent of persons with diabetes (0.6 percent of the total US population). After analyzing the data by gender, race, insulin-use and other risk factors, the investigators noted an especially high prevalence of diabetic retinopathy in ethnic minorities with diabetes (38.8 percent of non-Hispanic blacks and 34 percent of Mexican Americans compared to 26.4 percent of non-Hispanic whites). Given the increasing rates of obesity and decreasing levels of physical activity among the US population as a whole, the prevalence of diabetes in the US is expected to increase. In turn, the number of people at risk of losing their vision from diabetic retinopathy, particularly among racial/ethnic minorities, is expected to increase.

BACKGROUND

The NIH collaborated with the National Center for Health Statistics (NCHS) 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 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. Other causes of blindness, such as diabetic retinopathy are addressed in the survey. 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 were 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 facilitated a preliminary analysis of the raw survey data: verified the merging of individual responses into a secure, annotated database using unique survey participant identification numbers; checked for errors and inconsistencies; applied statistical weights based on sampling methodology; and, cross-validated data items across survey response categories. At the completion of this preliminary analysis in late 2009, NIH and other co-sponsoring agencies received the data for an additional quality control review of the consolidated data file and its related data documentation and had 60 calendar days to report any issues back to NHANES staff. Vision data and related documentation from the 2007-2008 NHANES survey were publicly released by NCHS in 2010 and used to develop national estimates of visual impairment.

SRO-8.7 By 2015, identify three (3) key factors influencing the scaling up of research-tested interventions across large networks of services systems such as primary care, specialty care and community practice. (Outcome)

FY	Target	Result
2012	Complete target by identifying three effective implementation strategies that enhance the uptake of research-tested interventions in service systems such as primary care, specialty care and community practice. *(Baseline):* (FY12) 5-7 studies underway to identify effective implementation strategies for research tested interventions	N/A
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	Three intervention studies that utilize implementation mechanisms, strategies, or techniques were identified to improve the uptake of effective interventions for mental health services, HIV and drug use disorders, and alcohol screening and treatment in healthcare or community settings. (Target Met)
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
Wang W, Saldana L, Brown CH, and Chamberlain P. Factors that influenced county system leaders to implement an evidence-based program: A baseline survey within a randomized controlled trial. *Implement Sci*. 2010 Oct 6;5:72. http://www.implementationscience.com/content/5/1/72

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH researchers identified at least three intervention studies that utilize implementation mechanisms, strategies, or techniques to improve the uptake of effective interventions in community settings. Several NIH studies have taken various approaches to examine factors that influence the development, implementation, and dissemination of evidence-based interventions, including scaling-up a mental health intervention in foster care; treating drug abuse and testing a continuum of care for HIV treatment in the criminal justice system; and implementing alcohol screening, intervention, and treatment in primary care. Highlights of ongoing studies are described below.

One study tests how well the Community Development Team (CDT) model is able to promote the adoption, implementation, and sustainability of an evidence-based intervention called Multidimensional Treatment Foster Care (MTFC) to decrease the prevalence of foster care placements in publicly-funded child services systems throughout the State of California and in selected counties of Ohio. CDTs are designed to impact the implementation process at different levels (e.g., county, system, organizational, practitioner, and consumer) through multi-county team meetings, expert consultation, peer-to-peer exchange, and individualized consultation. To examine the effectiveness of the CDT intervention, counties are randomly assigned to the (1) CDT plus Standard Implementation of MTFC condition, or to the (2) Standard Implementation of MTFC only condition. Analyses will examine group differences in the intervention outcomes (e.g., rates of adoption, implementation, and sustainability of MTFC), as well as the hypothesized moderating effects of fixed factors (e.g., poverty, urban/rural, being a Federal System of Care county, consumer advocacy, history of collaboration) and the mediating effects of dynamic factors (e.g., psychological and organizational climate; culture and attitudes toward evidence-based practices). Findings from a baseline survey indicate that the number of youth in foster care was the primary predictor of the system leader's decision to implement the intervention, and the system leader's perceptions of positive climate and organizational readiness for changes contributed to the number of days until consent to participate. The study will provide information that increases the understanding of "what it takes" to engage and support uptake, implementation, and sustainability of evidence-based programs in communities.

Another study focused on identifying and treating HIV and drug use disorders among high risk populations and for intervening to counter relapse-recidivism cycle. For example, the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) Initiative is a multisite research collaborative, launched in 2002, to develop and test evidence-based approaches for treating drug abuse and related conditions in the criminal offender population. Now in its second phase, CJ-DATS will test implementation strategies to foster treatment adoption and promote continuing care. In September 2010, the CJ-DATS research protocol to study the implementation of a continuum of care for HIV prevention and treatment for offenders infected with or at risk for HIV was approved. In FY 2011, CJ-DATS will begin execution of a research protocol to increase HIV testing and linkage to treatment following incarceration for individuals in the criminal justice system. NIDA also expects to hold a meeting of CJ-DATS investigators to discuss preliminary findings and protocol progress to date.

Researchers are also examining the effectiveness of an implementation model called the Practice Partner Research Network's Accelerating Alcohol Screening – Translating Research into Practice (AA-TRIP) in increasing the use of a Clinician's Guide to improve screening, brief intervention, and treatment (medical management and pharmacotherapy) in primary care. This study is also examining whether disease-specific outcomes are improved in patients with hypertension and diabetes as a result of improved screening, intervention, and treatment, as well as identifying identify barriers and facilitators to implementation of these practices in primary care. Examples of barriers and facilitators to screening, brief intervention, and medication use that have been identified include lack of familiarity with screening guidelines or medications (barrier) and educating and involving all staff (facilitator). In the next phase of the study, the investigators will conduct a "crossover intervention" in which the control sites become the intervention sites and the intervention sites become the control sites. Feedback from the first phase of intervention will be used to refine the AA-TRIP model for use in the newly designated intervention sites, and the newly designated control sites will be monitored to determine the sustainability of the effects of the previously administered AA-TRIP.

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. The ultimate end of this research is not simply to increase implementation at the individual practice level but to scale-up those changes across large systems, states and nations.

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.

SRO-8.8 By 2012, identify at least one candidate intervention that extends median lifespan in an animal model. (Outcome)

FY	Target	Result
2012	Identify one candidate intervention that extends median life span in an animal model. *(Baseline):* Testing of lifespan and other parameters will enable identification of candidate compounds.	N/A
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.	Phase II testing began on rapamycin and NDGA. (Target Met)
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
Interventions Testing Program: http://www.nia.nih.gov/ResearchInformation/ScientificResources/CompoundsInTesting.htm http://www.nia.nih.gov/ResearchInformation/ScientificResources/InterventionsTestingProgram.htm Information about the Phase I studies: Miller, R. A., Harrison, D., Astle, C. M., Baur, J. A., deCabo, R., Fernandez, E., Flurkey, K., Javors, M. A., Nelson, J. F., Pletcher, S., Sharp, Z. D., Sinclair, D., Starnes, J. W., Wilkinson, J. E., Nadon, N. L., Strong, R. (2010) Rapamycin, But Not Resveratrol or Simvastatin, Extends Lifespan of Genetically Heterogeneous Mice. J. Gerontology, Biological Sciences (available online before the journal goes to press, http://biomedgerontology.oxfordjournals.org/content/early/2010/10/25/gerona.glq178.full.html). 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.ncbi.nlm.nih.gov/pubmed/19587680 For information about the Phase II studies, contact Nancy L. Nadon, Ph.D., Nancy.Nadon@nih.gov

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Investigators initiated 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. Phase II testing of rapamycin will include a lifespan analysis to confirm the Phase I results as well as several studies designed to determine the effects of rapamycin on health span including:

- analysis of metabolism, including metabolic rate and insulin sensitivity;
- maintenance of function by hematopoietic stem cells (stem cells for renewing blood cells);
- blood chemistry parameters that reflect kidney function;
- histopathology of several organ systems (liver, kidney, lung, heart, pancreas, adrenal glands, skeletal muscle) to evaluate age-related structural changes;
- changes in locomotor activity and cognition;
- changes in body composition (percent fat versus percent lean);
- measurements of oxidative stress in DNA and proteins.

The mTOR signaling pathway, through which rapamycin is believed to work, will also be analyzed to measure age-related changes in the components of the signaling pathway and the effect of rapamycin on those changes.

Phase II testing of NDGA (nordihydroguaiaretic acid) also began in 2010. NDGA has antioxidant and anti-inflammatory activity. The Phase I testing demonstrated that NDGA extended median lifespan by 12% in male – but not female – mice, and that NDGA levels in the blood were much lower in female mice than in male mice. The Phase II study will test three doses in male mice but only the highest dose in female mice, dependent on the outcome of a pilot study to demonstrate that pharmacological blood levels can be achieved in females.

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. However, because of adverse side effects, rapamycin is not the ideal drug for extending lifespan in humans, and Phase I testing continues on several other compounds through the NIH Interventions Testing Program: acarbose, methylene blue, and 17-α-estradiol.

In addition, Phase I testing of fish oil will begin in December 2010. Epidemiological studies have indicated that fish oil supplementation may confer health benefits, including protection against heart disease, in humans. Results from short-lived mouse strains show that fish oil can robustly increase lifespan, with beneficial effects on pathways such as inflammation and oxidation that are thought to be involved in the regulation of aging.

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. An important activity in this area is the Intervention Testing Program 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. 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 2009, ITP researchers found that the drug rapamycin, used to help prevent rejection of transplanted organs in humans, extended life span in mice. Rapamycin is an inhibitor of the mTOR (mammalian target of rapamycin) pathway, which helps to regulate cell growth and proliferation. Because rapamycin powerfully suppresses the immune system, its utility in extending the human life span is probably limited. However, this research has more clearly identified the mTOR pathway as important for extending life span and may lead to the development of other compounds that target this pathway in ways that do not cause harmful side effects. Further testing on rapamycin is planned to confirm these results and elucidate the compound's effects on health span.

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

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).

Phase I testing will continue on three compounds that were selected in 2009: 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 shown 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. Preliminary data will be available for these compounds in 2012.

Phase II studies on rapamycin have begun in 2010 and includes a lifespan analysis to confirm the Phase I results as well as several studies designed to determine the effects of rapamycin on health span: analysis of metabolism, including metabolic rate and insulin sensitivity; maintenance of function by hematopoietic stem cells (stem cells for renewing blood cells); blood chemistry parameters that reflect kidney function; histopathology of several organ systems (liver, kidney, lung, heart, pancreas, adrenal glands, skeletal muscle) to evaluate age-related structural changes; changes in locomotor activity and cognition; changes in body composition (percent fat versus percent lean); and measurements of oxidative stress in DNA and proteins. The mTOR signaling pathway, through which rapamycin is believed to work, will also be analyzed to measure age-related changes in the components of the signaling pathway and the effect of rapamycin on those changes.

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)

FY	Target	Result
2012	Identify three pathogen and/or host factors. *(Baseline):* Two pathogen and/or host factors identified.	N/A
2011	Identify two pathogen and/or host factors. *(Baseline):* Infrastructure and capacity established to identify pathogen and/or host factors	N/A

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

Performance Results for the FY11 GPRA Performance Target will be reported in February, 2012.

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 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.

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)

FY	Target	Result
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.	NIH-supported research has generated a body of knowledge to demonstrate a capacity to reduce the total years lost to disability (YLDs) among persons in the United States with major depressive disorders by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences co-morbid illnesses including Alzheimer's Disease, cancer, and chronic obstructive pulmonary disease, and alcohol use. (Target Met)
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)

Data Source and Validation
Emslie GJ, et al. Treatment of Resistant Depression in Adolescents (TORDIA): Week 24 Outcomes. Am J Psychiatry 2010;167:782-791.doi: 10.1176/appi.ajp.2010.09040552 Arean PA, Raue P, Mackin RS, Kanellopoulos D, McCulloch C, and Alexopoulos GS. Problem- solving therapy and supportive therapy in older adults with major depression and executive dysfunction. Am J Psychiatry, 2010 Nov;167(11):1391-8. Epub 2010 Jun1 doi: 10.1176/appi.ajp.2010.09091327 Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, Counihan PJ, Kapoor WN, Schulberg HC, and Reynolds CF. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. JAMA. 2009 Nov 18; 302(19):2095-103. Epub 2009 Nov 16 http://jama.ama-assn.org/content/302/19/2095.abstract R01AA017477-02, BRENNAN, PENNY, Pain, Depression and Alcohol Use in Later Life R01AA016274-06, WILLIAMSON, DOUGLAS E, Affective & Neurobiological Predictors of Adolescent-Onset Alcohol Use Disorders R01AA018701-01A1, MC CARTY, CAROLYN A, The Role of Depression in the development of Alcohol Problems Among Adolescents R01AA020463-01A1, SATRE, DEREK D, Motivational Interviewing to Reduce Substance Use Among Depression Patients R01AA015385-06, SALLOUM, IHSAN M, Optimizing Pharmacotherapy for Bipolar Alcoholics R01AA016629-04, HODGE, CLYDE W, Behavioral and molecular mechanisms of ethanol-induced depression

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met and the measure was Achieved. NIH-supported research has generated a body of knowledge to demonstrate a capacity to reduce the total years lost to disability (YLDs) among persons in the United States with major depressive disorders by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences co-morbid illnesses including Alzheimer's Disease, cancer, and chronic obstructive pulmonary disease, and alcohol use.

Over the past eight years, NIH has successfully demonstrated achievement of several strategic targets through research focused on early detection, prevention, and treatment of chronic, recurrent, or treatment-resistant depression and depressive disorders co-morbid with other illnesses. Beginning in FY 2003, NIH identified a link between a specific gene-environment interaction related to high stress and vulnerability to depression. In FY 2004, NIH reported a strong correlation between vascular changes resulting in unique lesions in the brain and depression in the elderly. In FY 2005, NIH reported on progress made in identifying individual characteristics associated with differing response to pharmacological and behavioral treatment for depression. In FY 2006, NIH identified several new, effective strategies for long term depression care management and outcomes among the elderly via the Prevention of Suicide in Primary Care Elderly Trial (PROSPECT) and maintenance treatment studies. In FY 2007, NIH-supported research demonstrated the effectiveness of using combined treatments or multi-step treatment sequences for chronic or recurrent depression through the results of two large-scale clinical trial studies - Sequential Treatment Alternatives to Relieve Depression (STAR*D) and Treatment for Adolescent Depression Study (TADS). In FY 2008, NIH reported on advancements in imaging techniques, observational studies, and animal models to examine interactions between depression and other co-morbid disorders like Alzheimer's disease, cancer, and chronic obstructive pulmonary disease. In FY 2009, NIH reported significant progress made in demonstrating the effect of combination psychotherapy and pharmacological treatment of depression on an individual's improved functional capacity as it relates to social role function, work function, and employment. Now in the last reporting year of this measure, NIH-supported studies focused on developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and to improve the understanding of the mechanisms by which depression influences at least two co-morbid illnesses, such as post-stroke depression and alcohol use. A selection of studies is highlighted below.

Several NIH-funded studies developed and tested the effectiveness of specific treatments for recurrent and treatment-resistant depression among adolescents. For example, the Treatment for Adolescents with Depression

Study (TADS) demonstrated that for most adolescents with major depression, long-term, treatment leads to sustained remission and recovery. Other studies concentrated on examining treatment strategies to improve remission and reduce relapse rates. A multi-site clinical study called Treatment of Resistant Depression in Adolescents (TORDIA) examined treatment options for adolescents whose depression has not improved after one initial course trial of a selective serotonin reuptake inhibitor (SSRI) antidepressant treatment. Adolescents were randomly assigned to one of four interventions for 12 weeks: (1) switch to another SSRI-paroxetine (Paxil), citalopram (Celexa) or fluoxetine (Prozac); (2) switch to a different SSRI plus cognitive behavioral therapy (CBT) that emphasizes problem-solving and behavior change; (3) switch to venlafaxine (Effexor), another type of antidepressant; or (4) switch to venlafaxine plus CBT. Among those individuals who responded at week 12, the rate of and time to relapse for those assigned to receive psychotherapy were similar to those assigned to receive medication alone. The remission rate and time for individuals assigned to receive combination therapy were similar to the rate and time for those assigned to receive medication alone. The likelihood of remission was much higher and time to remission was faster among those individuals who showed clinical response by week 12. The findings demonstrate that early treatment effects are associated with greater likelihood of remission and recovery among adolescents with hard-to treat depression.

Another NIH study investigated whether problem solving therapy (PST) is an effective treatment in older patients with depression and executive dysfunction. Reduction of depressive symptom severity was comparable for the two treatment groups during the first 6 weeks of treatment, but at weeks 9 and 12, the problem-solving therapy group had a greater reduction in symptom severity, a greater response rate, and a greater remission rate than the supportive therapy group. These results suggest that problem-solving therapy is effective in reducing depressive symptoms and leading to treatment response and remission in a considerable number of older patients with major depression and executive dysfunction. The clinical value of this finding is that problem-solving therapy may be a treatment alternative in an older patient population likely to be resistant to pharmacotherapy.

Other research teams examined the functional impact of treatment of chronic, recurrent, or treatment resistant depression. One study assessed the long-term effects on total healthcare costs of the Improving Mood: Promoting Access to Collaborative Treatment (IMPACT) program for late life depression compared with usual care. Participants were randomly assigned to the IMPACT intervention or to usual primary care. The intervention participants had access to a depression care manager who provided education, behavioral activation, support of antidepressant medication management prescribed by their regular primary care provider, and problem solving treatment in primary care for up to 12 months. On average, the IMPACT participants had lower total healthcare costs than those in usual care. The IMPACT program is associated with a high probability of lower total healthcare costs during a 4-year period.

NIH examined the effects of alternative depression interventions in comparison to usual care. For example, one research team examined the effectiveness of telephone delivered collaborative care for post-coronary artery bypass graft (CABG) depression versus usual physician care. Participants with depression were randomly assigned to receive either eight months of care provided by nurses working with patients' primary care physicians or usual care in which physicians typically lack such collaborative nursing assistance. Based on the study results, compared with usual care, the telephone-delivered collaborative care for treatment of post-CABG depression resulted in greater improved mental health-related quality of life, physical functioning, and mood symptoms.

Other studies have developed treatment models to improve quality of life and outcomes among individuals with co-morbid impairments. The interventions include algorithmically derived treatment alternatives and collaborative care models, which use a team approach to ensure treatment adherence and to monitor symptom response and side effects. The Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) evaluated the impact of a care management intervention on suicide ideation and depression in older primary care patients over 24 months. According to the PROSPECT findings, those receiving the collaborative care intervention had a higher likelihood of receiving antidepressants and/or psychotherapy and had a greater decline in suicide ideation than the comparison group. In addition, treatment response occurred earlier on average in the intervention group and a greater number of individuals with major depression in that group achieved remission. The study results suggest that sustained collaborative care maintains high utilization of depression treatment, reduces suicidal ideation, and improves the outcomes of major depression.

NIH also developed preventive intervention algorithms to alter the risk of developing depression, known to occur with some frequency in conjunction with other illnesses. One research team conducted a study to assess the efficacy of antidepressant pharmacotherapy and psychotherapy in preventing post stroke depression. Patients were randomly assigned to receive one of three interventions: the antidepressant medication escitalopram, pill placebo, or psychological problem-solving therapy (PST). Individuals who received either escitalopram or PST were less likely to develop depression than those in the placebo group. The results thus suggested that the use of an antidepressant or problem solving therapy can decrease the number of depression cases among non-depressed individuals over the first year following a stroke.

NIH supported studies focused on improving the understanding of the relationships between alcohol use disorders (AUDs) and co-morbid depressive disorders in various population subgroups and on developing behavioral and pharmacotherapy interventions for dually diagnosed patients. Such studies included those that explored the interplay between pain, depression, and alcohol use in midlife/senior adults and those that examined how risk for depression influences the development of AUDs during adolescence. Other treatment studies for AUDs and co-morbid depressive disorders 1) tested the effectiveness of a specific brief intervention during screening to reduce hazardous drinking outcomes in outpatients being treated for depression; 2) explored drug combinations in treating patients with co-morbid alcohol dependence and bipolar disorder; and 3) investigated therapeutic mechanisms of alcohol-induced depression during abstinence.

In summary, NIH has developed a knowledge base about a number of evidence-based treatments that, if fully implemented, could result in a significant reduction in the total years lost to disability (YLDs) among persons in the United States with major depressive disorders. This knowledge base includes new strategies of intervention early in the life course, such as the treatment of adolescents with depressive disorders, and later in life, when depression is frequently associated with co-morbid illnesses and other impairments, and is known to significantly impact disability among older adults.

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, and 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 undertook 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 was 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 involved 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 was conducted to examine treatment strategies tailored for specific populations, such as racial and ethnic minorities and the elderly. NIH also invested 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 allowed 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 sharpened 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.

SRO-9.2 By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities. (Efficiency) (Outcome)

FY	Target	Result
2012	Complete 75% of patient recruitment for testing an educational intervention and a secondary stroke prevention program in underserved, African American, urban communities. *(Baseline):* Databases, study materials and protocols are in place or at final stages of development.	N/A
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	Established a framework for the pilot stroke prevention program for the Alaska Native population. (Target Met)
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)

Data Source and Validation
U01NS048069, Alaska Native Stroke Registry, Progress Report U54NS057405, Stroke Disparities Program, Program Advisory Committee Quarterly Report *Enhancing Participation of Underrepresented Groups in Biomarker Research* (PI Dorothy Edwards), R01 subproject 5617 of University of Wisconsin P60 Center of Excellence in Health Disparities Research, funded by NCMHD [P60MD003428 (5617)] Sharif DP, Mathews K, Williams MM, Hoffsuemmer J, Ememobong M, Edwards DF. More Than Tuskegee: Understanding Mistrust about Research Participation. Journal of Health Care for the Poor and Underserved. 2010 Aug: 21(3):879-97. Progress and quarterly reports available from NINDS Office of Science Policy and Planning. Contact: Cara Allen, allencar@ninds.nih.gov, 301-496-9271

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Comprehensive assessment of the stroke epidemiology, vascular risk factors, cultural understandings of vascular health and lifestyle, and structural barriers to risk reduction strategies has informed the development of a community level prevention intervention pilot program that aims to reduce the burden of stroke in the Alaska Native population. To develop this targeted behavioral stroke prevention intervention, NIH-supported researchers used information from the Alaska Native Stroke Registry (ANSR) project, a population based study that aims to better understand the epidemiology of stroke in Alaska Natives.

The behavioral stroke prevention intervention pilot that has been developed incorporates:
(1) values and cultural elements that are widely held by the Alaska Native community - the program uses storytelling as a vehicle for learning and complex family-friend dynamics that are common as social support structures in the Alaska Native rural and remote communities;
(2) scientific rigor with academic and Alaska Native health leadership partnerships which have been integral to the development of the pilot intervention, and (3) targets of effective self-management of blood pressure and medication adherence which were informed by the prior epidemiological research investments in the Alaska Native community.

The program has been successful in developing critical infrastructure for the implementation of a community based participatory research system (CBPR). CBPR methodology was used so that the design targets issues impeding vascular wellness in the Alaska Native population. CBPR was also used to strengthen partnerships with multiple levels of the community and the community health leadership which will be critical to the implementation *as well as the long-term sustainability* of the intervention. The infrastructure building that has been completed during the past year includes:

1. *Principal Investigators (PIs):* The program is now formally under multiple PIs which includes a nationally recognized stroke behavioral interventionalist who has worked in multi-ethnic communities, and a member of the leadership of the Center for Alaska Native Health Research (CANHR) who is a behavioral interventionalist in the Alaska Native population.
2. *Expansion of the Program Advisory Committee (PAC):* The PIs have added a noted interventionalist and researcher in multiple native populations including Alaska Natives, Hawaiian Islanders, and Native Americans.
3. *Expansion of the Scientific Advisory Committee (SAC):* The PIs have expanded the SAC to include community representatives and other researchers with Alaska Native expertise. The SAC has been important in providing extensive guidance on the tone, cultural competence, and health literacy of the survey instrument. These survey instruments are currently under review by the multi-layered institutional review board.
4. *Outreach:* Significant outreach to the community has also occurred through in-person meetings with stakeholders in rural Alaskan communities and a relationship has been established with the CANHR, which has extensive research experience in rural communities. CANHR is also sharing information regarding vascular

disease risk and health beliefs which are invaluable to the ANSR program.

These efforts demonstrate the involvement of the Alaska Native community at every level of intervention development, as well as the commitment of local and national stakeholders to designing and implementing an effective stroke risk reduction strategy for the Alaska Native community.

Based on the knowledge gained from the infrastructure expansion efforts and epidemiological research conducted in this project, as well as significant infrastructure support by NIH, the framework for a pilot intervention has been developed and is being vetted through the community leaders and the program's scientific and program advisory committees.

Advances or Other Highlights

Alaska Native Stroke Registry

Recently, the epidemiology research conducted as part of the ANSR project has resulted in one manuscript on stroke incidence that is currently in Alaska Native peer review. Also, an abstract from that work has been accepted for the 2011 International Stroke Conference. Other products include the development of a new, comprehensive survey instrument that includes vascular risk measures, medication adherence, social health networks, community social organization utilization, health-illness beliefs, explanatory models of disease, health locus of control, and barriers to physical activity. A secondary analysis of the CANHR data that describes the epidemiology of hypertension among the Yupik peoples of the Yukon-Kuskokwim (YK) delta is being reviewed and drafted in a manuscript.

Stroke Disparities Program

This multi-component program has continued to implement interventions in the African-American community by targeting acute stroke treatment delivery (ASPIRE), secondary prevention (PROTECT DC), and studying intracerebral hemorrhage (DECIPHER). The ASPIRE program has completed the pilot intervention in Ward 7 of Washington, DC and began the larger intervention in metropolitan DC in September 2010. PROTECT DC has enrolled 152 participants with an exceptionally high retention rate. DECIPHER has completed 81% of enrollment. The success of enrollment in DECIPHER led directly to the development of the project Enhancing Participation of Underrepresented Groups in Biomarker Research which is supported by NIH. These programs have collectively presented at several major conferences and have resulted in numerous manuscripts. For example, data from these projects contributed to a study that examined barriers to medical research among African Americans, and identified mistrust of the healthcare system as the primary barrier. The results of this analysis will help investigators better address issues with poor participation among African American communities, and indicate that efforts to increase participation should incorporate strategies to reduce mistrust.

Stroke Warning Information and Faster Treatment (SWIFT)

The SWIFT study, part of the NIH-supported Specialized Program of Translational Research in Acute Stroke (SPOTRIAS), have completed testing of the effects of a culturally sensitive educational intervention on knowledge retention and on time to arrive to the Emergency Department after a stroke. The outcome and results of the intervention are currently under review.

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, 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-supported 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-supported 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).

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)

FY	Target	Result
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.	Maintained the BIRN and disseminated imaging and clinical information to support the development of analytical software tools. (Target Met)
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)
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)

Data Source and Validation
NIH MRI Study of Normal Brain Development (https://nihpd.crbs.ucsd.edu/nihpd/info/index.html) Fonov V, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL; Brain Development Cooperative Group. Unbiased average age-appropriate atlases for pediatric studies. Neuroimage. 2011 Jan 1;54(1):313-27. Epub 2010 Jul 23.(http://www.ncbi.nlm.nih.gov/pubmed/20656036)

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. Data that includes repeated anatomic magnetic resonance imaging scans, and clinical information collected from over 500 children continue to be available to the scientific community. Diffusion tensor imaging (DTI) and magnetic resonance spectroscopy data are also available. There will be over 800 datasets of DTI information available. The DTI data is a particularly ambitious component of the overall project because it is the first time researchers have applied the new technology to collect the data on a longitudinal scale. The amount of correction needed for each dataset was extensive. Each dataset contains several individual scan "slices" and each "slice" was manually corrected for artifacts.

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.

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)

FY	Target	Result
2012	Begin hearing testing on asymptomatic children who test positive for CMV infection. *(Baseline):* (FY11) NIH-supported scientists successfully enrolled children who tested positive for CMV infection in the study.	N/A
2011	Enroll children who tested positive for CMV infection in the follow-up study to monitor hearing function. *(Baseline):* (FY10) 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.	Scientists determined that 0.45 percent of enrolled children have congenital CMV infection. (Target Met)
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)

Data Source and Validation
Boppana SB, Ross SA, Novak Z, Shimamura M, Tolan RW Jr, Palmer AL, Ahmed A, Michaels MG, Sánchez PJ, Bernstein DI, Britt WJ, Fowler KB; National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA. 2010 Apr 14;303(14):1375-82. http://www.ncbi.nlm.nih.gov/pubmed/20388893 Related press release: http://www.nih.gov/news/health/apr2010/nidcd-13.htm

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Scientists screened 20,448 newborns and determined that 92 (0.45%) had congenital CMV infection. This data was collected from a study that compared the effectiveness of two methods for screening newborns for CMV infection.

Advances or Other Highlights

Scientists not only determined the percentage of newborns who had CMV infection, but they were able to determine that tests using the dried blood spots typically collected from newborns using a traditional "heel stick"

method are not effective as a screening tool for newborn CMV infection. In order to be included as part of a screening test, the minimum sensitivity should be at least 95 percent. The investigators' findings indicate that dried blood spot tests (using the polymerase chain reaction, or PCR) will only detect 30-40 percent of babies with CMV infection. More than half of the babies who are infected with CMV would be missed.

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 the CMV and Hearing Multicenter Screening (CHIMES) Study to research 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.

SRO-9.5 By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia. (Outcome)

FY	Target	Result
2012	Continue recruitment to 899 subjects. *(Baseline):* 611 subjects recruited in FY 2011.	N/A
2011	Continue recruitment to 611 subjects. *[Previous Target]:* Continue recruitment to 914 subjects. *(Baseline):* 323 subjects enrolled in FY2010.	N/A
2010	Continue recruitment to 476 subjects. *[Previous Target]:* Achieve cumulative enrollment of 1776 subjects. *(Baseline):* (FY09) Achieve cumulative enrollment of 38 subjects.	Achieved cumulative enrolment of 244 subjects. (Target Not Met)
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
DCC LOTT monthly performance report. http://clinicaltrials.gov/ct2/show/NCT00692198?term=LOTT&rank=1 National Heart, Lung, and Blood Institute program contact: Dr. Antonello Punturieri, punturieria@mail.nih.gov

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2012 target was Not Met. The Long-Term Oxygen Treatment Trial (LOTT) has achieved cumulative enrolment of 244 subjects (about 51% of the targeted enrollment of 476).

The LOTT trial is designed to test 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. Currently, Medicare reimburses for oxygen therapy in patients with severe hypoxemia (for which there is scientific evidence of benefit) but not in patients with moderate disease, and the benefits and potential harm of oxygen treatment for such patients are unknown. Recruitment in the trial has been much more difficult than expected. The study protocol was revised in 2009 to broaden inclusion criteria to encompass patients who need oxygen after moderate exercise in addition to patients who need oxygen at rest. Implementation of the revised protocol is now ongoing at all of the sites. Patient recruitment has continued to be more difficult than expected since patients (potential participants) falsely believe that they need oxygen—they often believe that if a doctor has prescribed oxygen, they cannot stop even if they do not have the recommended resting blood levels for oxygen according to

Medicare standards. Many potential participants are thus unwilling to risk being randomized to the group that will not receive oxygen therapy.

BACKGROUND

Chronic obstructive pulmonary disease, or 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 based on the inclusion of patients that need oxygen after moderate exercise in addition to those that need oxygen at rest, resulting in 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 Data and Safety Monitoring Board, the NIH has approved the protocol modifications, and implementation of the revised protocol is now ongoing at all of the sites.

The LOTT researchers at 14 clinical centers across the United States plan to study approximately 1100 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 includes training of staff, subject screening and recruitment, interventions, and follow-up with data collection and monitoring.

Patient recruitment for the trial began in 2008. Most of the trial centers obtained approval for the revised study protocol in the Spring of 2010. Participants are randomized to receive or not to receive supplemental oxygen for approximately a minimum of one year and up to 4.5 years. Patient recruitment has continued to be more difficult than expected because patients (potential participants) falsely believe that they need oxygen—they often believe that if they have been prescribed oxygen, they cannot stop even if they do not have the recommended resting blood levels for oxygen according to CMS standards. (CMS reimburses for oxygen therapy in patients with severe hypoxemia, for which there is scientific evidence of benefit, but not in patients with moderate disease, and the benefits and potential harm of oxygen treatment for such patients are unknown.) Many potential participants are thus unwilling to risk being randomized to the group that will not receive oxygen therapy. Another factor contibuting to slow recruitment is the diffuse false beleief among practitioners that oxygen supplementation is always good for a patient. LOTT is trying to address this precise question.

As a result, the 2011 target has been adjusted to account for this challenge in patient recruitment. 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

The new knowledge generated by NIH-funded research cannot benefit human health unless the information is communicated in ways that are useful to the public, practitioners, policymakers, researchers, and others who will use the information. 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 – both in the U.S. and abroad – to clinicians, public health systems, health organizations, and the general public. Equally important is the transfer of 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.

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 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 ICs collect, disseminate, and exchange information on biological science, medicine, and health. One of the Institutes, the National Library of Medicine (NLM), is the world's largest medical library and works closely with the other ICs to ensure the effective communication of research results.

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)

FY	Target	Result
2012	Conduct 23 SIDS risk reduction activities for African Americans caregivers and health providers serving African Americans across all of the nine health districts in Mississippi. *(Baseline):* There are no known statewide efforts in Mississippi to disseminate African American-focused SIDS risk reduction materials.	N/A
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.	Presentations on SIDS risk reduction were presented at four national meetings for health professionals who can spread the Back to Sleep message to African American parents, caregivers, and health care providers. (Target Exceeded)
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)
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)

Data Source and Validation
Conference evaluation forms and reports. To obtain a summary of the information shared from the conference organizers, please contact Shavon Artis at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at 301-435-3459.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met and Exceeded. The NIH successfully submitted abstracts and presented at the following four national conferences: Centers for Disease Control and Prevention's Health Communications Conference, Association of Maternal and Child Health Programs Annual Conference, National Association of Boards of Pharmacy Annual Meeting, and the NIH Clinical Center Annual Symposium for Pharmacists. Each of these conferences afforded the NIH the opportunity to present on the Back to Sleep Campaign and its culturally-specific materials for African Americans. In each conference session, between 350 and 500 people were in attendance. Approximately 2,000 health professionals were reached overall. The presentations highlighted what it takes to develop a successful campaign with tailored materials, what a culturally sensitive message should incorporate, and how to best convey safe sleep recommendations to African American communities. Barriers and challenges were addressed and many of the session attendees were interested in how they could order the campaign's African American outreach materials and distribute to their patients/clients. The audience included physicians, nurses, case workers, community health workers, social workers, and pharmacists. The pharmacists were a non-traditional segment of health professionals to reach out to, but their impact on disseminating the message is unique. Pharmacists play a vital role in educating patients who are parents, caregivers, and family members about SIDS risk-reduction strategies. In a time where there is limited access to health care and in remote, rural areas, often times, pharmacists may be the only health professional a patient comes in contact with and who they ask many of their health questions. So, pharmacists are an under-utilized profession for disseminating safe sleep message that NIH is working to improve on through provider-led and learner-led continuing education sessions.

Conference evaluations confirmed that the presentations were effective in increasing knowledge about the SIDS risk reduction and that the health professionals found the information very useful. Many stated that they felt more comfortable discussing the safe sleep message with their patients and clients after hearing the presentation.

Advances or Other Highlights

Earlier this year, the NIH completed development of the online module for the Nurses' Continuing Education Program on Sudden Infant Death Syndrome (SIDS) Risk Reduction. Over 10, 500 nurses have successfully completed the continuing education program since it began in 2007, either using the provider-led curriculum, print format, or the online module. Many of the nurses who have received continuing education credits are also using the program to train other nurses in hospitals across the country.

The NIH also collaborated with a nonprofit organization to open an Information Resource Center in Jackson, Mississippi. The center featured health information materials from many of NIH’s 27 Institutes and Centers and includes information on vision health, cancer, heart disease, dental care, diabetes, and many other health topics in addition to the materials on SIDS. It provided an excellent vehicle to disseminate accurate, up-to-date SIDS and other health information to Mississippi residents, many of whom are African American.

Efficiency

Originally, it was planned to only develop and present SIDS risk reduction presentations at two conferences. However, the opportunity presented itself to present at two additional conferences. This expanded the number of health professionals we could reach, and enabled NIH to reach different types of health professionals such as advocacy health professionals and pharmacists. This afforded the Back to Sleep message to be disseminated to a broad range of health professionals who can spread the safe sleep message.

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 2006 SIDS rate is 0.55/1,000 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 one 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 is collaborating on this campaign with other sponsors, including professional groups, advocacy organizations, and government agencies.

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 professional and advocacy organizations with strong ties to African American communities 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 three organizations. The leaders of the 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 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 continues to support scientific research to examine trends in infant care practices and environmental and cultural influences on the diffusion of public health recommendations in a nationally representative sample that includes both minority and non-minority mothers. 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.

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)

FY	Target	Result
2010	Reduce cataloging time by 7 minutes per title and realize an additional savings of 0.10 FTE. *(Baseline):* (FY09) 95 minutes per title	The time to catalog an item has been reduced by 7 minutes per title, from 95 minutes to 88 minutes, and a savings of 0.10 FTE has been realized. (Target Met)
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 FY11 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 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met and the measure was Achieved. The number of minutes to catalog an item has been reduced by 7 minutes, from 95 minutes to 88 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 0.3 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.

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)

FY	Target	Result
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.	Sharing from already-conducted scientific studies of warfarin (Coumadin) anti-coagulation, through knowledge base PharmGKB was feasible and other consortia have used this data-sharing model. (Target Met)
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 GAP (Global Alliance for Pharmacogenomics Research) collaborative studies underway, see http://www.nigms.nih.gov/Initiatives/PGRN/GAP/Studies.htm(under first set of studies). Pharmacogenomics Knowledge Base (PharmGKB), see http://www.pharmgkb.org/views/loadConsortia.action. RIKEN Center for Genomic Medicine (CGM) collaborations, see http://www.pharmgkb.org/views/loadConsortia.action(under fourth set of studies). Excerpt from the July 2010 PGRN Retreat report (http://www.pharmgkb.org/network/14680140.pdf).

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and the measure was Achieved. Pharmacogenomics Knowledge Base (PharmGKB) supports pharmacogenetic data sharing consortia like the International Warfarin Pharmacogenetics Consortium (IWPC), which is devoted to pooling genotype and phenotype data relevant to the anticoagulant warfarin.

IWPC uses clinical and pharmacological data to determine proper warfarin dosage. Currently, the “outliers” or “extremes” of dosing, those not fitted well by the developed algorithm, are being examined in a genome association study to discover new genetic factors. The results are just becoming available and analysis is underway. Additionally, because this data-sharing consortium worked well, other consortia were started similar to this data-sharing model.

Measure

The mission PharmGKB is to collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response. Efforts began in 2007 with 13 participating groups who agreed upon the headings for depositing data. This group began standardizing datasets in PharmGKB in preparation for a meta-analysis of the

data. The meta-analysis was used to construct an algorithm for warfarin dosing. This activity has become a model for data-sharing.

PharmGKB is a publicly available Internet research tool developed with funding from NIH and is part of the NIH Pharmacogenomics Research Network (PGRN), a nationwide collaborative research consortium. The PharmGKB database is a central repository for genetic, genomic, molecular and cellular phenotype data and clinical information about people who have participated in pharmacogenomics research studies. The data includes, but is not limited to, clinical and basic pharmacokinetic and pharmacogenomic research in the cardiovascular, pulmonary, cancer, pathways, metabolic and transporter domains.

Advances or Other Highlights

Developing collaborative interactions is one of the broad goals of the Pharmacogenomics Research Network and PharmGKB. Meeting set goals have led to the following successes since 2006:

The RIKEN Center for Genomic Medicine collaboration is now in place to address pharmacogenomic questions in genome-wide association studies. To date, 18 studies with over 16,000 samples have been initiated, and the first analyses are being reported. The structure of the collaboration is an important model for building future relationships (now formalized as the PGRN-CGM network resource).

- The International Warfarin Pharmacogenetics Consortium (IWPC) group has been instrumental in developing genotype-based algorithms for warfarin dosing across multiple ethnicities. This consortium is a model for information sharing, where critical questions can be answered with a data-driven approach. The Pharmacogenomics Knowledge Base (PharmGKB) played a key role as a *neutral convener*.

- The PGRN statistics groups' annual workshops were very valuable to share study results and to compare analytic approaches (now formalized as the P-STAR network resource).

- The PGRN has successfully facilitated multiple network-authored papers in high-profile areas such as the utility of pharmacogenomics testing.

- The network has sponsored multiple scientific symposia on pharmacogenetics, along with stakeholder scientific organizations at joint conferences (e.g., CSHL and AHA meetings), and at their own stand-alone open scientific meetings.

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 three years, up to 13 international groups shared existing data sets via PharmGKB.

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.

PharmGKB data has yielded a possible algorithm for warfarin dosing based upon genotype. This has helped to establish a data-sharing procedure. It supports the incorporation of pharmacogenetic information for 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. Due to the success of PharmGKB's efforts, 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 success of PharmGKB illustrates how effectively sharing basic pharmacogenetic results and preparing to translate those results into clinical practice (for anticoagulation) can improve health outcomes. 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 then began on analyzing differences among the various treatment and research protocols and standardizing the datasets. In FY 2009, NIH grantees began a meta-analysis using standardized data. FY 2010, the meta-analysis has helped researchers develop a dosing algorithm based on the existing datasets which can be used to establish initial dosing levels in clinical trials. The success of this target, has established the feasibility of sharing data from scientific studies to develop personalized treatments for testing in clinical trials.

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)

FY	Target	Result
2012	Incorporate at least one new social networking technology as a modality for NIH stakeholders to obtain information on new grants initiatives, policies and/or processes *(Baseline):* minimal use of social networking technologies	N/A
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.	NIH identified that existing grants process resources were primarily text based, and developed eight new multimedia outlets including online seminars and videos, podcasts, and twitter feeds. (Target Met)
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
Seminars, presentations and feeds are compiled at www.grants.nih.gov including: Office of Laboratory Animal Welfare – Education Resources – Seminar Recordings and Reference Material http://grants.nih.gov/grants/olaw/educational_resources.htm All About Grants Podcast http://grants.nih.gov/podcasts/All_About_Grants/index.htm Enhancing Peer Review at NIH – Training and Communications – Videos and Supporting Materials http://enhancing-peer-review.nih.gov/training_communication.html#videos NIH for Funding Twitter Feed http://twitter.com/NIHforFunding

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was met. An initial assessment of the pre-existing, centrally-maintained web-based resources was conducted to determine the breadth of media formats and number of resources available to NIH grants applicants and grantees. It was determined that the existing resources were extensively available as text-based guidance, with the exception of two instructional videos. Additional instructional videos were identified in the eRA Virtual school repository maintained by electronic research administration. NIH has expanded the number of centrally maintained multi-media outlets focused on grants to include two new quarterly on-line seminar series on issues related to animal research, three video presentations on changes to the peer review process, a new podcast series entitled "All About Grants", and two twitter feeds on funding opportunities and the stem cell registry.

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.

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)

FY	Target	Result
2012	Partner with a minimum of 2 regional groups dedicated to women-owned or socially and economically disadvantaged small businesses to enable knowledge transfer, increase awareness, and increase access to SBIR/STTR opportunities *(Baseline):* 0 partnerships over past several years	N/A
2011	Utilize new on-line technologies to provide a 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	NIH conducted and/or participated in three outreach activities in 2010 at regional or national conferences. (Target Met)

Data Source and Validation
NIH-sponsored webinar on the NIH SBIR/STTR Program, http://center.ncet2.org/index.php?option=com_joomla_lms&Itemid=53&task=course_guest&id=12 Kentucky Innovation and Entrepreneurship Conference, http://ksef.kstc.com/?300 NIH-sponsored 12th Annual NIH SBIR/STTR Conference, http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-096.html

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was met. NIH staff participated in three outreach events and successfully increased awareness of the NIH SBIR and STTR programs among woman-owned and socially & economically disadvantaged small businesses. Various outreach activities targeting this segment of the small business research population were conducted including:

NIH-sponsored webinar on the NIH SBIR/STTR Program, March 2010:
Approximately 1000 people attended an NIH-sponsored webinar that targeted women-owned and minority and disadvantaged small companies to learn about the SBIR and STTR programs and how to submit an application.

NIH SBIR/STTR presentation at a Kentucky Innovation and Entrepreneurship Conference, Lexington, KY, April 2010:
NIH gave a presentation to about 40 woman entrepreneurs about the funding opportunities that are available through the NIH SBIR and STTR programs and how women scientists may access these funds in a session entitled "Women in Science: The Leaky Pipeline"

NIH-sponsored 12th Annual NIH SBIR/STTR Conference, Raleigh, NC, June 2010:
As part of NIH's annual SBIR/STTR conference, the NIH hosted a luncheon session entitled "Women in Business: From the Trenches". A panel of experienced business women and entrepreneurs shared their business insights and experiences with a group of approximately 130 women entrepreneurs. The panel members offered first-hand advice on how to navigate the challenging financial environment and the world of business. They shared how they have translated health-related research ideas into tangible successes and gave tips on how to network effectively and how to win over investors. Of the ten participants who responded to NIH's request for feedback on the conference, 80% indicated that the interactive format was effective, 60% felt the content/subject matter was useful, and 70% felt the session should be offered at future NIH SBIR/STTR conferences.

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.

CTR-10 By 2014, expand the scope of the Hazardous Substances Data Bank to include 14 nanomaterials. (Outcome)

FY	Target	Result
2012	Augment the Hazardous Substances Data Bank with comprehensive records for 4 nanomaterials and review initial database specifications. *(Baseline):* New database specifications to begin storing data on nanomaterials.	N/A
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

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

Performance Results for the FY11 GPRA Performance Target will be reported in February, 2012.

BACKGROUND

The Hazardous Substances Data Bank (HSDB) is a toxicology data file produced by the NIH, 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
Emergency Medical Treatment
Animal Toxicity Studies
Metabolism/ Pharmacokinetics
Pharmacology
Environmental Fate & Exposure
Environmental Standards & Regulations
Chemical/Physical Properties
Chemical Safety & Handling
Manufacturing/User Information
Laboratory Methods
Special References
Synonyms and Identifiers

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 powder 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 therefore 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

The productivity of biomedical research depends on the talent and dedication of the scientific workforce. To strengthen the Nation's research capacity, broaden the research base, and inspire current and future generations of researchers, NIH supports many innovative training programs and funding mechanisms that foster scientific creativity and exploration. Also fundamental to the success of biomedical research is the availability and accessibility of essential research tools, cutting-edge technologies, adequate facilities, information repositories, and related services. Such research resources are at the core of research and innovation, as they often set the boundaries for what scientific questions can be investigated. NIH plays a significant role in providing researchers with the tools they need to uncover the causes and courses of disease and to develop new methods of diagnosis, treatment, and prevention.

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)

FY	Target	Result
2012	N ≥ 12% *(Baseline):* 10%	N/A
2011	N ≥ 12% *(Baseline):* 10%	N/A
2010	N ≥ 12% *(Baseline):* 10%	Award rate to comparison group reached 12%. (Target Met)
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)

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: Jennifer Sutton Program Policy and Evaluation Officer Office of Extramural Programs (301) 435-2686

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. At least 12% more NIH Kirschstein-NRSA predoctoral trainees and fellows remained in research relative to two comparison groups of Ph.D.s. In contrast to other doctoral students at the same institutions 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 1989 through 1999 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 Kirschstein-NRSA funding are compared to those not trained under NIH Kirschstein-NRSA funding. In FY 2010, NIH predoctoral trainees and fellows were 12% more likely to remain active in biomedical research than non-NIH trainees and fellows; this result met 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 Kirschstein-NRSA Trainees and Fellows	30.0% (6,500/21,652)	17. 6% (3,815/21,652)
Comparison Group A	11.2% (8,294/74,229)	5.2% (3,835/74,229)
Comparison Group B	5.2% (1,165/22,426)	2.0% (440/22,426)

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 89 new or updated research education, research training, and career development funding opportunity announcements in FY 2010. 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 nearly 1,600 individuals in FY 2010. 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.

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)

FY	Target	Result
2012	N ≥ 12% *(Baseline):* 10%	N/A
2011	N ≥ 12% *(Baseline):* 12%	N/A
2010	N ≥ 12% *(Baseline):* 12%	Award rate to comparison group reached 14% and exceeded the target by at least 2%. (Target Met)
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)

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: Jennifer Sutton Program Policy and Evaluation Officer Office of Extramural Programs (301) 435-2686

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. At least 14% more NIH postdoctoral fellows receiving research training through the Kirschstein-NRSA program remained in research relative to comparison groups. In contrast to postdoctoral fellows that applied for, but did not receive Kirschstein-NRSA research fellowship support during the same time period, NRSA postdoctoral fellows from 1989 through 1999 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 Kirschstein-NRSA funding are compared to those not trained under NIH Kirschstein-NRSA funding. In FY 2010, NIH postdoctoral fellows were 13.7% 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 Kirschstein-NRSA Fellows	45.5% (4477/9836)	30.6% (3006/9836)
Other Postdoctoral Fellows	28.6% (3150/11,209)	16.9% (1851/11209)

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 89 new or updated research education, training, and career development funding opportunity announcements in FY 2010. 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 2010, NIH made more than 200 career transition awards to newly independent scientists and more than 50 New Innovator awards to exceptionally creative and promising new investigators.

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.

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)

FY	Target	Result
2012	(Development [Dev]) Initiate development of planned business modules to build capacity and functionality of the NIH Business System. * No Development activity for FY12	N/A
2012	(Integration [Int]) Complete integration activities for full functionality and usability of priority modules for successful development efforts within 3 years of initiated development. * Planned - Service and Supply Activities Fund Module [Dev.2011/Dep.2012] * Planned - Oracle 12i Upgrade [Dev.2011/Dep.2013]	N/A
2012	(Deployment [Dep]) Conduct priority deployment activities to enable user accessibility and skill development within 2 years from the onset of integration. * Planned - Service and Supply Activities Fund Module [Int.2012/Mat.2012] *(Baseline):* Initiation of deployment for modules that have moved out of the integration phase	N/A
2012	(Maintenance [Mat]) Maintain deployed business modules. * Planned - Service and Supply Activities Fund Module [Dep.2012] * Planned - NIH Grants Interface Module (ERA) [Dep.2011] *(Baseline):* Commencement of support for business modules.	N/A
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.2012]	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. * No Integration activity for FY11	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

FY	Target	Result
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]	Initiated development of planned business module, NIH Grants Interface Module (Target Not Met)
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]	Completed integration activities for NIH Grants Interface Module (Target Met)
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]	Conducted priority deployment activities for GovTrip Phase II Travel Module (Target Met)
2010	(Maintenance [Mat]) Maintain deployed business modules. * Planned - GovTrip and Phase II (Pilot) Travel Module [Dep.2010]	Maintained post deployment support for GovTrip and Phase II (Pilot) Travel Module (Target Met)
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)
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)

FY	Target	Result
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
NBS Point of Contact: Brian Frantz, 301-451-1913 or frantzb@mail.nih.gov Repository on Sharepoint at http://sps.nbs.nih.gov/default.aspx...

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

DEVELOPMENT

The FY 2010 Development target was Not Met.

NIH Grants Interface Module (eRa)

The Financial System Integration (FSI) is the first part of the Healthier Financial Management Initiative (HFMI) project utilized by the National Institutes of Health (NIH) effecting financial management and control. In order to leverage the latest application integration technology utilized at NIH, a Web Services architecture was implemented to integrate the eRA IMPACII Grants system with NIH's Business System (NBS). Features of this implementation include real-time funds control, as well as asynchronous processing of Commitments and Obligations to the NBS General Ledger. The Requirements Analysis, Design, and Development phases were conducted from April 2010 through August 2010. In addition to the integration of the eRA-IMPACII system with NBS, NIH executed the option of integrating DHHS Program Support Center's (PSC) Payment Management System (PMS) with NIH's Business System to align all Grant activity (commitments, obligations and expenditures) with the financial system. This implementation has leveraged existing file based data transfer methods to support 2 transactional Interfaces: Outbound Obligation Extract to PMS and Inbound Expenditure Processing to NBS.

Oracle 12i Upgrade

Office of Management and Budget (OMB) Policy Memorandum M-10-26: *Immediate Review of Financial Systems IT Projects* has impacted a number of planned activities for NBS that were planned to begin in FY 2010 and continue during FY 2011. This OMB Policy guidance required all CFO Act agencies to immediately halt the issuance of new task orders or new procurements for all financial system projects pending review and approval from OMB. As an Operating Division of the DHHS, NIH submitted a consolidated review package along with

DHHS' other enterprise resource programs (Unified Financial Management System (UFMS) and Healthcare Integrated General Ledger System (HIGLAS)) that are currently under review by OMB. The OMB review cycle impacts the following initiatives: NBS transition/upgrade to Oracle R12, the Common Government-wide Accounting Classification (CGAC) structure, the transition to Treasury GTAS initiatives.

INTEGRATION
The FY 2010 Integration target was Met.

NIH Grants Interface Module (eRa)
The Integration Testing and User Acceptance Testing (UAT) cycles heavily involved NBS staff, members from the Office of Financial management (OFM), individuals within the Office of Extramural Research (OER), and PSC's Department of Payment Management. Integration Testing covered a vast majority of the integrated business scenarios owned by NIH's Grants Community and Financial Management Community. 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.

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, extensive training materials and sessions were conducted with key personnel identified by senior management. Business owners from the Budget & Finance areas were also briefed on the workforce impacts resulting from the delivery of the FSI project, community participation for UAT, results from test cycles, and expected downtime cutover dates.

DEPLOYMENT
The FY 2010 Deployment target was Met.

GovTrip Phase II Travel Module
In June, 2010, the GovTrip 2.0 upgrade was deployed to all GovTrip customers. NIH conducted GovTrip 2.0 hands-on training for IC Help Points of Contact and Computer Based Training modules for all staff.

MAINTENANCE
The FY 2010 Maintenance target was Met. Maintenance of deployed business modules has been met with full user support which includes: NBS Operations and Maintenance (O&M) 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.

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 O&M 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 2010 the NBS saw a 20% reduction in the number of user call assistance tickets from FY 2009. 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 (PMO) is implementing an enterprise PMO model to ensure that the NBS Program's project portfolio is managed in accordance with its governance construct and proceeds based on project management plans aligned with NIH and NBS organizational objectives. The intent is to provide consistent guidance to NBS Program staff and enable sustainable, reliable, and business-driven program management support to project leads.

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 shift.

Since the initial deployment of NBS travel (GELCO), DHHS' goal of deploying one e-Travel system throughout the Department has been mandated. NIH deployment of the mandated e-Travel system, GovTrip solution, which addressed NIH mission-critical travel requirements was fully deployed across the NIH in January 2010.

American Recovery and Reinvestment Act (ARRA) of 2009 funding permitted the NIH to accelerate enhancements and new functionality to specifically remedy long standing Information Technology (IT) General Access Controls (GAC) security concerns, financial audit deficiencies and better meet NIH's critical business needs. ARRA initiatives implemented during FY 2010 included Oracle Governance, Risk and Compliance (GRC) Controls that remediated NBS deficiencies for IT GAC through Access and Preventive Controls. GRC Controls also allowed the NBS to further remedy audit deficiencies around the tracking of NBS functional configurations. Additionally, in FY 2010 development and testing was completed for the NIH Extramural Research Administrations IMPAC II/NBS integration via web services, NBS systemic funds control, DHHS Program Support Center (PSC) Payment Management System (PMS) integration with the NBS for NIH grant payments, and the Management Account System/Common Account Numbering (MAS/CAN) Retirement allowing NIH to migrate to one set of accounting books. Each of these enhancements were implemented to begin Q1 FY 2011. In Q1 FY 2011, NBS/Defense

Financial Accounting System (DFAS) Payroll integration and Oracle Projects Phase I (Reimbursable/Interagency Agreements) will commence and be implemented in Q3 FY 2011 (June 2011) and Q1 2012 (October 2011) respectively. FY 2010 development and implementation efforts for the mandated Internal Revenue Code (IRC) Section 3402 – (T) – Vendor Pay Withholding was delayed based on a congressionally mandated start date revision of Calendar Year (CY) 2012 instead of CY 2011. IRC Section 3402 – (T) activity is projected to start in late FY 2011 for a CY 2012 (January 2012) implementation.

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

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)

FY	Target	Result
2012	Continue conversion of business processes: 98% of business processes being done electronically by FY 2012. *(Baseline):* (FY11) TBD% of business processes being done electronically.	N/A
2011	Continue conversion of business processes: 95% of business processes being done electronically by FY 2011. *(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.	Approximately 89% of all grant business transactions are currently being done electronically and the Electronic Tracking and Analysis module was added to eRA. (Target Met)
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)
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)

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 @ Phone: 301-594-9747

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH processed approximately 89% of all grant business transactions electronically. eRA's efforts were successful, even with the added effort, and direction of the ARRA projects. eRA deployed the Electronic Tracking and Analysis process to its suite of applications. In addition, efforts are underway for the electronic processing of Administrative Supplements (Type 3s) and the electronic processing of Change of Institution (Type 7s).

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 interest (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.

CBRR-6.1 By 2011, construct or renovate 153 biomedical research facilities in order to build the capacity to conduct the proposed research. (Output)

FY	Target	Result
2011	Complete 1 facility *(Baseline):* Number of projects completed: (FY10) TBD	N/A
2010	Complete 12 facilities *(Baseline):* Number of projects completed: (FY09) TBD	All 12 construction grants were completed either early or on time. (Target Met)
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 were granted extensions 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)

Data Source and Validation
The completion dates are located in the NCRR Construction Grants Management System. For more information please contact Patricia Newman at (301) 435-0864. Information regarding a specific grant may be found using the NIH Reporter database.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. All 12 construction grants to support the construction or renovation of biomedical research infrastructures 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.

BACKGROUND

The NIH's 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.

CBRR-6.2 By 2015 complete construction/commissioning of 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)

FY	Target	Result
2012	Conduct design development *(Baseline):* Number of biocontainment facilities completed: (FY11) TBD	N/A
2011	Conduct project programming and environmental review *Previous Target:* *Complete 0 biocontainment facilities.* *(Baseline):* Number of biocontainment facilities completed: (FY10) TBD	N/A
2010	Complete 1 facility *(Baseline):* Number of biocontainment facilities completed: (FY09) 13	NIH completed construction of three (3) extramural biocontainment facilities. (Target Met)
2009	Complete 7 facilities *(Baseline):* Number of biocontainment facilities completed: (FY08) 6	*Revised Results* NIH completed construction of three (3) extramural biocontainment facilities. (Target Not Met) *Previous Results* 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	*Revised Results* NIH completed construction of six (6) extramural biocontainment facilities. All six of the biocontainment facilities were met either early or on-time. (Target Met) *Previous Results* NIH completed construction of four (4) extramural biocontainment facilities. (Target Met)
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 locted in the NIAID BUZZSAW database. For more information, please contact the NIAID Office of Strategic Planning and Evaluation Branch @ 301-443-9941.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH completed construction of three 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. The facilities are part of the following universities: University of Tennessee (Memphis), Tulane University, and George Mason University.

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 the Extramural Biocontainment Facilities Construction 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 purpose of the Extramural Biocontainment Facilities Construction Program 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.

Due to external issues beyond NIH's control, the Hawaii facility is not expected to be completed before 2015; therefore the measure is being extended to 2015. Environmental and budgetary issues at the University of Hawaii have delayed the onset of construction. Specifically, the measure extension results from the grantee being unable to obtain matching funds from the state legislature as originally planned, and changes in the planned construction site. Additionally, due to a transcription error, University of Tennessee was mistakenly reported as completed in FY 2008; however, this facility was not completed until FY 2010. While the University of Pittsburgh was completed and reported in FY 2007, this facility was inadvertently reported again as completed in FY 2009. Tulane University and George Mason University were both completed in FY 2010. To date, 14 of the 15 biocontainment facilities are complete.

CBRR-7 By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research. (Output)

FY	Target	Result
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	100% of the 572 expiring grants eligible for renewal or recompetition were reviewed. (Target Met)
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)

Data Source and Validation
ARIS is an internal management database. For more information, please contact Robert W. Eisinger, Ph.D. or Wendy Wertheimer at (301) 496-0357. The annual Trans-NIH Plan for HIV-Related Research is available at http://www.oar.nih.gov/strategicplan/.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and the measure was Achieved. OAR utilized the enhanced AIDS Research Information System (ARIS) to efficiently conduct a trans-NIH portfolio analysis of 100 percent of the 572 grants eligible for renewal or recompetition. ARIS is 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. This portfolio analysis was conducted in concert with the ICs and a panel of outside experts.

In FY 2010, the highest priorities for AIDS research were: 1) prevention of the acquisition and transmission of HIV, including research on microbicides, vaccines, and behavioral and social science interventions; and 2) prevention and treatment of HIV-associated comorbidities, coinfections, and comortality. Approximately 19 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 AIDS 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.

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.

Measure

This process now has been implemented as an integral part of the annual trans-NIH strategic planning and budget processes to enhance OAR'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. For example, several years ago many grants were awarded to address basic research related to a number of then-common opportunistic infections. Over the past few years, with the advent of antiretroviral regimens, which have extended the lives of HIV-infected individuals, these infections are no longer common in these patients. Thus this area of basic research, while scientifically important, is now deemed of lower priority for AIDS-designated funding. As the epidemic evolves, and as science progresses both in advances to treat and prevent HIV disease, it is anticipated that this annual review will provide an ongoing mechanism to reassess the allocation of AIDS-specific dollars to reflect these changes.

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.

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.

CBRR-8 By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management. (Output)

FY	Target	Result
2012	Ensure that 100% of trainee appointment forms are processed electronically *(Baseline):* (FY11) TBD 0% processed electronically	N/A
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	Introduced a policy requiring all appointment forms to be processed electronically as of January 2011, and implemented essential xTrain system improvements and training. (Target Met)
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
Notice in NIH Guide for Grants and Contracts announcing the required use of xTrain in January 2011 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-072.html xTrain performance results were calculated using reports from NIH's internal IMPAC II information management system. For more information, contact: Jennifer Sutton Extramural Program Policy and Evaluation Officer Office of Extramural Programs (301) 435-2686

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Over the past year, Electronic Research Administration (eRA) staff improved the xTrain system by expanding the range of activities for which appointments may be submitted, introducing batch processing for appointments, modifying the system to permit all program directors in multi-PD/PI training grants to submit appointments, and implementing a reminder system to notify users when a termination notice is due. In addition, NIH issued a notice in its Guide for Grants and Contracts announcing the required use of xTrain in January 2011, and enlisted the assistance of various internal and external groups in increasing communications about the system and the mandate for its use, developed web-based training for users outside of the NIH, and completed a user guide for internal users.

Together, these steps contributed to increased use of the system. In FY 2010, universities submitted 1,432 research training, education, and career development appointments electronically, representing 26.1% of the 5,480 FY 2010 appointments processed.

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 continuing efforts since then, the program has maintained progress towards the achievement of its annual objectives.

BACKGROUND

The 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 growth in the number of institutions using xTrain, the percentage of appointments submitted electronically fell short of projections for FY 2009. As a result, the FY 2010 target was adjusted to address issues of system usability, functionality, capacity, user training, and outreach, and NIH announced plans to begin requiring institutions to use xTrain to submit appointments for training grants and other training-related activities as of January 2011. With multiple improvements to the system in FY 2010, along with increased outreach and training, the percentage of appointments submitted electronically by year-end was 26.1 percent, more than double the previous year. NIH anticipates that it is now back on track to meet its targets for processing training appointments electronically in FYs 2011 and 2012.

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)

FY	Target	Result
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	Achieved an average annual cost of $36,703 per grant. (Target Met)
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)

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 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH achieved an average annual cost of $36,703 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.

CBRR-10 By 2015, 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)

FY	Target	Result
2012	Deposit chemical structure and biological data for 175 new small molecule probes in PubChem *(Baseline):* The Molecular Libraries Program has an inventory of 68 small molecule probes at the end of the pilot phase of the program.	N/A
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.	98 new high-throughput assays were added to the MLP Portfolio. (Target Exceeded)
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 Program: http://mli.nih.gov/mli/mlp-overview/ Notice of Opportunity for Fast Track Entry of Assay Projects for High Throughput Screening into the NIH Roadmap Molecular Libraries Probe Production Centers Network http://grants.nih.gov/grants/guide/notice-files/NOT-RM-09-011.html **Identification of Metabotropic Glutamate Receptor Subtype 5 Potentiators Using Virtual High-Throughput Screening.** Mueller R, Rodriguez AL, Dawson ES, Butkiewicz M, Nguyen TT, Oleszkiewicz S, Bleckmann A, Weaver CD, Lindsley CW, Conn PJ, Meiler J. *ACS Chem Neurosci.* 2010 Apr 21;1(4):288-305. Epub 2010 Jan 28. http://www.ncbi.nlm.nih.gov/pubmed/20414370 **Synthesis and SAR of novel, 4-(phenylsulfamoyl)phenylacetamide mGlu4 positive allosteric modulators (PAMs) identified by functional high-throughput screening (HTS).** Engers DW, Gentry PR, Williams R, Bolinger JD, Weaver CD, Menon UN, Conn PJ, Lindsley CW, Niswender CM, Hopkins CR. *Bioorg Med Chem Lett.* 2010 Sep 1;20(17):5175-8. Epub 2010 Jul 8. http://www.ncbi.nlm.nih.gov/pubmed/20667732 **Chronic active B-cell-receptor signalling in diffuse large Bcell lymphoma.** Davis, R.E., Ngo, V.N., Lenz, G., Tolar, P., Young, R.M., Romesser, P.B., Kohlhammer, H., Lamy, L., Zhao, H., Yang, Y., Xu,W., Shaffer, A.L., Wright, G., Xiao, W., Powell, J., Jiang, J-, Thomas, C.J., Rosenwald, A., Ott, G., Muller-Hermelink, H.K., Gascoyne, R.D., Connors, J.M., Johnson, N.A., Rimsza, L.M., Campo, E., Jaffe, E.S., Wilson, W.H., Delabie, J., Smeland, E.B., Fisher, R.I., Braziel, R.M., Tubbs, R.R., Cook, J.R., Weisenburger, D.D., Chan, W.C., Pierce, S.K., Staudt, L.M.*Nature*, 2010, 463(7277):88-92. http://www.ncbi.nlm.nih.gov/pubmed/20054396 **HTS-driven discovery of new chemotypes with West Nile Virus inhibitory activity.** Chung, D.H., Jonsson, C.B., Maddox, C., McKellip, S.N., Moore, B.P., Heli, M., White, E.L., Ananthan, S., Li, Q., Feng, S., Rasmussen, L. *Molecules*, 2010, 15(3): 1690-1704. http://www.ncbi.nlm.nih.gov/pubmed/20336008 **A Novel and Specific NADPH Oxidase-1 (Nox1) Small-Molecule Inhibitor Blocks the Formation of Functional Invadopodia in Human Colon Cancer Cells.** Gianni D, Taulet N, Zhang H, Dermardirossian C, Kister J, Martinez L, Roush WR, Brown SJ, Bokoch GM, Rosen H. *ACS Chem Biol.* 2010 Oct 15;5(10):981-93. http://www.ncbi.nlm.nih.gov/pubmed/20715845 **Synthesis and characterization of iodinated tetrahydroquinolines targeting the G protein-coupled estrogen receptor GPR30.** Ramesh, C., Nayak, T.K., Burai, R., Dennis, M.K., Hathaway, H.J., Sklar, L.A., Prossnitz, E.R., Arterburn, J.B. *Journal of Medicinal Chemistry*, 2010, 53:1004-1014. http://www.ncbi.nlm.nih.gov/pubmed/20041667 **Identification of known drugs that act as inhibitors of NF-κB signaling and their mechanism of action.** Miller, S.C., Huang, R., Sakamuru, S., Shukla, S.J., Attene-Ramos, M.S. Shinn, P., Van Leer, D., Leister, W., Austin, C.P., Xia, M. *Biochem Pharmacol*, 2010, 79:1272-1280. http://www.ncbi.nlm.nih.gov/pubmed/20067776

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met and Exceeded. The Molecular Libraries Program (MLP) Portfolio added 98 new high-throughput assays. The metrics for new HTS assays, new chemistry projects, and deposition of HTS assays in PubChem have been met. To date, the MLP selected 490 high-throughput screening (HTS) assays for entry into the Molecular Libraries Probe Production Centers Network (MLPCN) production pipeline in the program. The assay portfolio represents a wide range of biology related to various disease areas:

- cancer (28%)
- allergy and infectious diseases (24%)
- neuroscience (18%)
- general medical sciences (12%)
- diabetes/metabolic/endocrine (8%)
- heart/lung/blood (6%)
- other (4%)

The HTS assay campaigns undertaken to date have led to more than 181 chemistry projects and generated 169

small molecule probes. The scientific process of generating probes is not linear and depends on the difficulty of the target and underlying biology. Based on the track record for probes generated in FY2010, the program is on track to achieve the FY2011 target. The seven probes submitted during the fourth quarter of FY2010 are applicable to understanding disease mechanisms in the areas of neurological disorders, diabetes/metabolic/endocrine disorders, and cancer. The MLP has made the results of 117 HTS assays screened against 300,000 compounds in the central MLSMR freely available to researchers through PubChem, along with detailed information on the probes developed though the screening process.

Efficiency

The MLP generated a Fast Track mechanism for HTS assays to enter the program. The Fast Track mechanism has increased the efficiency by which novel assays enter into the MLP. This has led to an increase in the number of assays established in the Portfolio per year; hence, the MLP exceeded the FY2010 target.

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.

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)

FY	Target	Result
2010	350 shared instrumentation grants awarded with sample shared usage. *(Baseline):* 350 ARRA SIG Awards	Three hundred and seventy-four (374) shared instrumentation grant awards were made to domestic public and nonprofit institutions. (Target Exceeded)
2009	84 shared instrumentation grants awarded with sample shared usage. *(Baseline):* 84 ARRA 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 is located in the NIH research Portfolio Online reporting Tool (RePORT) at http://RePORT.nih.gov.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and the Measure was Achieved. The NIH awarded three hundred and seventy-four (374) shared instrumentation grants to domestic public and nonprofit institutions. They types of instruments that were supported include: magnetic resonance systems, confocal microscopes, mass spectrometers, and protein x-ray crystallography systems. These instruments will support over a thousand researchers. It is anticipated that these awards will stimulate the economy and in turn create or maintain jobs in America by allowing researchers to continue to acquire critical instruments for scientific research projects.

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 aligned 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.

CBRR-12 (Priority Goal) By 2012, reduce the fully loaded cost of sequencing a human genome to $15,000. (Efficiency) (Outcome)

FY	Target	Result
2012	Reduce the fully-loaded cost of sequencing a human genome to $15,000. *(Baseline):* Fully-loaded cost of sequencing a human genome is $25,000.	N/A
2011	Reduce the fully-loaded cost of sequencing a human genome to $25,000. *(Baseline):* Fully-loaded cost of sequencing a human genome is $31,125.	N/A
2010	New sequencing machines in routine production at centers. *(Baseline):* Fully-loaded cost of sequencing a human genome is $50,000.	New sequencing machines are in routine production at centers and are on track to meet sequencing targets. (Target Met)

Data Source and Validation
Kris Wetterstrand, M.S. Office of the Director National Human Genome Research Institute, NIH Phone: 301-435-5543 Email: **wettersk@mail.nih.gov**

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. Sequencing workflows at NIH's large-scale sequencing centers are stable. This is also reflected in the performance of cost measures, which decreased across all centers in comparison to last quarter.

BACKGROUND

DNA sequencing has enabled the production of the human reference genome sequence, has enabled much more powerful approaches to the study of normal and disease-associated genetic variation in the human population, and has become a core technology in contemporary biomedical research with many different applications. Sequencing the human genome would not have been possible without major reductions in the cost of DNA sequencing during the decade of the 1990's. The continued rapid decline in sequencing cost and increased flexibility of next-generation technology obtained during the past decade has allowed many new uses for sequencing technology. One of the new uses is termed re-sequencing. Re-sequencing is one way that sequencing is applied to find the differences among people. To reach the ultimate goal of a comprehensive understanding of genetic variation in populations and human disease, the costs of genome sequencing must continue to decrease.

Rationale

Despite an exceptional record of improvement, genome sequencing is still too expensive to be applied as widely as necessary to achieve a full understanding of common disease and to realize personalized medicine. To understand the genetic bases of common, complex diseases such as cancer, diabetes, heart disease, and Alzheimer's, it will be necessary to sequence the genomes of many thousands, or even tens of thousands, of people per study to understand the genomic variants that contribute to these disorders. In the next few years, NIH aims to continue reducing sequencing costs and increasingly enable more studies to be conducted. The intent of DNA sequencing is ultimately to achieve personalized genomic medicine. Medical decision-making on an individualized basis will require obtaining genome sequence information as a routine part of clinical care. The cost point where this will become more routinely feasible is probably about ~$1,000.

The best current estimate of the true cost of genomic DNA sequencing comes from data from the NIH large-scale sequencing program. This program supports cooperative agreements with three academic institutions and carefully monitors the costs of genome sequencing on a quarterly basis. Although vendors of DNA sequencing instruments or services publicly describe their costs of generating a human genomic sequence as $10,000 or even less, these figures generally represent only the cost of the actual supplies used in the sequencing process. At least one private sequencing service provider offers a similarly low price, but it remains to be seen whether this is sustainable (use of private capital to offset current costs cannot be ruled out). However, the total costs (rather than price) must be the focus of the reduction. These total costs are referred to as "fully loaded costs", i.e., what it actually takes to produce useful data, including reagents, personnel, reasonable instrument amortization, facilities and other overhead costs, and computational analysis.

At the beginning of FY 2010, the cost to generate a complete human genome sequence at the necessary quality (being able to identify genetic variations with high confidence) was approximately $50,000. NIH has previously described a goal to cut the total cost in half, to $25,000, by the end of 2011. NIH anticipated that this would be achieved by incremental contributions from many sources in the sequencing process, resulting in increased efficiency in the utilization of reagents, increased data output per fixed-cost run of the DNA sequencing instruments due to technology improvements, and continued reductions in computational expenses. Similar incremental changes have been the basis for cost reductions in the past. Notably, since submitting the initial 2011 goal, significantly improved "short read" platforms have been introduced. Although this disrupted the previous cycle of incremental development, as new platforms are stabilized in production and incremental development begins again, these platforms appear likely to quickly afford at least the two-fold cost decrease projected by the end of 2011. For the end of 2012, NIH proposes a further decrease in cost of sequencing a human genome about 40%, to $15,000. As before, incremental improvements in the latest platforms are expected to enable this decrease. However, it is possible that introduction of yet another disruptive platform will occur.

One significant caveat in all of these estimates is that they assume a certain quality needed to constitute a "human genome sequence". Explicitly, the quality is adequate when it allows investigators to understand the variations in the individual genome that occur at a certain frequency (usually 1% or less) with enough accuracy and coverage. Not all platforms achieve this in the same way (although current short read technologies usually require 25 to 30-fold redundancy). Moreover, as more and more knowledge accumulates about human variation, it may be possible to achieve the same confidence in understanding variation in a single human genome with less effort (that is, one will be able to understand individual differences with much less data). This will also effectively decrease the cost in the long run.

TARGET CONTEXT AND CONDITIONS

The reduction of sequencing costs will be enabled through the NIH-funded large-scale DNA sequencing centers that are engaged in medical sequencing to discover disease-related genomic changes. A key activity of these centers, which complements and enables a high rate of data production, implements newly emerging technologies in a real-world setting to achieve the highest efficiency of DNA sequence production. The centers bring outstanding expertise to the practical challenges of producing high-volume, high-quality sequence data, and constitute a critical resource that feeds essential information back to the commercial vendors. Thus, technologies developed by private companies that received early support from NIH were rapidly commercialized in an iterative process that relied heavily on feedback from the experienced users at the sequencing centers. That feedback, in addition to basic research discoveries whose origins were supported by an NIH technology development program, is the feedstock for continued ambitious cost reductions that are exemplified by this goal, and that likely will occur as commercial vendors refine and optimize sequencing systems. In fact, since the time that this goal was initially proposed, one of the major sequencing platform vendors announced a technical improvement that would result in a two-fold improvement in throughput per machine run. It will take roughly six months to a year to bring these new machines into large-scale production and to understand their stable costs and performance over time.

NIH recognizes that all of its efforts involve some degree of uncertainty because of the risk inherent in the nature of scientific discovery. NIH promotes ambitious goals because achieving each holds great promise to address a critical need and improve the health of the Nation. Efforts that are ambitious and/or involve uncertainty will, by

nature, be difficult: The pathway to discovery may not be linear -- indeed the history of sequencing cost reduction is not -- and the building blocks needed to make a scientific breakthrough still have to be determined. Recent advances in genomic sequencing technologies have gone hand-in-hand with parallel achievements in nucleotide chemistry, fluorescence detection, microfluidics, algorithm development and computational processing, and other enabling scientific areas. The key challenges are to extract the most efficient operation of current technologies and to stimulate the new field-altering leaps that will be necessary to continue to drive down the cost of human genome sequencing. Sustaining a pool of qualified geneticists and technology experts is critical.

Achievement of the measure requires support for technology and process enhancements in NIH's large-scale sequencing centers, enhancements that will then propagate to the research community by publications and collaborative ventures, and is dependent on secondary effects of NIH activities in medical sequencing. The incremental advances in economics that are needed to achieve the goal will be driven primarily by gaining experience obtained from using the new technologies to their best advantage. Also, the expanded uses of genomic sequencing that will be enabled with the consequent market forces will result in a steady decline in costs from competition, as has been amply demonstrated over the past few years. In the area of basic research, large NIH projects for advancing methods, pushing down costs, and demonstrating the value of comprehensive genomic analysis are ongoing. There are also new opportunities in clinical applications, in areas such as pharmacogenomics and genetic screening for predisposition to a multitude of diseases, which likely will move rapidly toward routine clinical applications as prices drop. Trans-NIH activities have been productive and will continue to help guide the applications of human genomic sequencing in biomedical research. The feedback circuit of supply and demand for DNA sequencing, and competition in the marketplace, together with routine incremental cost improvements, will lead to achievement of the 2012 cost goal.

The $15,000 cost target is derived from public and non-public information obtained from DNA sequencing vendors and the large-scale sequencing center staffs about current costs and what additional science would be enabled by a two-fold cost reduction. The primary instruments that will be in use in the centers in 2011 are now being delivered. With the competitive forces and expanding market described above, these vendors have incentive to keep costs fixed while increasing capabilities and, therefore, achievement of a 50% reduction in the cost of human genome sequencing for biomedical research and early clinical applications can be anticipated. However, the costs of human genome sequencing are not solely determined by the performance of instrumentation. A critical point here is that costs at very high throughput centers are optimized for efficiency, much like in a production factory. This is different than, for example, a laboratory using a single research instrument, where costs will be higher. High-throughput work requires highly standardized methods, robust laboratory information management systems, and other features not present in a small lab. In addition, it requires modifying methods and software provided by the machine vendor (for example, to operate many machines in parallel), and it involves optimizing reagent use. For these reasons, approximately $10 million per year of large-scale sequencing center grant funds are designated for technology and methods development. This NIH support for both investigating DNA sequencing instrumentation and process development from laboratory management systems through computational analysis is critical for the continued decline in human genome sequencing costs and for achieving this goal. Moreover, the information gained at the high throughput centers is communicated back to the vendors who use it to make methodological and technical improvements.

Quarterly reports from the large scale sequencing centers are being used to monitor the cost decreases of a fully loaded genome, and ensure that the centers are on their way to meet the goal. Every quarter, NIH receives a report from each of the three large-scale sequencing centers funded, which includes detailed information about data production, quality and cost. NIH staff evaluate these reports together with the external scientific consultants to the large-scale sequencing program (the consultant committee is constituted as described in the original solicitation for centers).

These data are analyzed to identify cost, throughput and quality trends and deviations from those trends that could be a symptom of a production problem in order to identify points for management attention. Trends are also compared between competing large-scale sequencing centers. Trends and projections are used for planning new sequencing projects as additional capacity opens, recognizing opportunities for more projects and new kinds of projects that become possible with increased value for science. The scientific consultants to the program

periodically ask for modifications of the progress report based on what they believe will be most useful in monitoring progress.

It must be stated explicitly that there is a risk of not reaching the 2012 goal. Although costs are expected to decrease, even with no further disruptive technologies, it is much more difficult to predict specific timelines more than 12 months ahead of time. It is easy to appreciate this when one considers that improvements have been occurring historically on an exponential curve over the long term (for example, three orders of magnitude in the last five years). On such a curve, even a small delay can have significant effects on achievement of a specific goal by any specific time.

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

NIH recognizes human capital as one of the most important resources of the agency. A highly qualified workforce, operating within a positive environment that provides employees with the tools needed to be successful, is critical for an organization to effectively and efficiently perform its mission. Thus, NIH integrates human capital considerations in planning and decision-making to achieve optimal results. In particular, continuous improvements are being sought in areas such as human capital planning and organizational alignment, workforce management, recruitment and retention, career development, performance measurement, results orientation, and succession planning. The strategic management of human capital is a cornerstone in NIH's ongoing effort to enhance organizational capacity and maximize performance.

SMHC-4 By 2012, ensure NIH reports tracked commercial functions and cost savings from completed commercial services studies efficiently and on time. (Efficiency) (Output)

FY	Target	Result
2012	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
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.	FAIR Act inventory and Post-Competition Accountability were completed and submitted to HHS (Target Met)
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)

Data Source and Validation
Katy Perry, Competitive Sourcing Manager and Director, Division of Management Support, OMA/OM/NIH Contact number: 301-496-4606 Debra Wade, FAIR Act inventory coordinator, Division of Management Support, OMA/OM/NIH Contact number: 301-496-4606

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH completed and submitted FAIR act reports to HHS through the FAIR Act inventory. NIH tracked and reviewed the commercial functions and cost savings from completed commercial services quarterly. Eleven organizations completed their final period of performance and will not be included in additional post-competition accountability. Due to language in the Omnibus Appropriations Bill (H.R. 1105) that prohibits any competition that could result in outsourcing, NIH has not completed any further competitions that could be tracked through Post-Competition Accountability reporting,

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 language within the 2009 Omnibus Appropriations Act, Agencies have been directed to discontinue competitive sourcing reviews until further guidance. The language further states Agencies are required to continue with the FAIR Act Inventory and post-competition reporting. NIH has revised the measure 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

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 effectively deliver health and human services via effective human capital management strategies.

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 language in the Omnibus Appropriations Act 2009, that prohibits A-76 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 is currently in maintenance mode and has completed the objective to provide improvements to the functional areas studied within NIH. Therefore, this measure will be ending by 2012.

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

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)

FY	Target	Result
2012	Determine pathway for upgrading Portal technology *(Baseline):* Quality management plan established.	N/A
2011	Upgrade the Portal technology to Oracle WebCenter Suite 10g platform and evaluate system performance *Previous target:* *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.	Conducted usability testing with HR and non-HR IC users. Monitored satisfaction and usage of portal community pages, portlets, and projects and improved the portal usability by implementing changes to the information architecture. Consulted with Content Managers to improve the HR content on the NIH Portal. (Target Met)
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)

Data Source and Validation
HR Portal User Guides - http://hr.od.nih.gov/hrintranet/portalguides.htm HR Professionals Community - http://hr.od.nih.gov/hrintranet/hrprofcommunity.htm Human Resources (HR) Community - http://hr.od.nih.gov/hrintranet/hrcommunity.htm

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH continuously monitored satisfaction and usage of human resources content on the NIH Portal against the established baseline. The NIH Office of Human Resources (OHR) held quarterly meetings with Content Managers to gather feedback 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 included:

HR Professionals Community

- Repurposed WRD Project for ProjectDocs Library and removed ETFC organizational Charts due to minimum usage. Revisited the need for other 8 OHR projects including OHR Knowledge Directory
- Updated OHR Organization Chart Portlet to reflect the current OHR organizational structure
- Created Emergence Preparedness and Survey Guidance community pages to support OHR business initiatives at tactical level
- Consolidated HR SAID Activities Summary to HR SAID Dashboard to enhance the usability
- Removed Metrics: CSD Dashboard based on the Content Manager's decision

Human Resources (HR) Community

- Created Hiring Resources for Managers community page to give HR hiring authorities and administrative officers the first hand information and tools to improve their hiring strategies and processes.
- Updated NIH Training Catalog to interface with new NIH Training Center web search
- Updated EBIS System into HR Systems and
- Improved Recruitment information for managers and highlighted new HR systems including the Employee Benefits Information System (EBIS)

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 FY2010, we revised and uploaded an additional 730 OHR documents.

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 FY10 October – December 2009	**2nd Q FY10 January – March 2010**	**3rd Q FY10 April – June 2010**	**4th Q FY10 July – September 2010**
Hits	22,435	24,133	23,612	30,134
Visits	16,941	18,607	18,128	23,012
Users	3,241	3,496	3,155	3,705

HR Professionals Community (Audience OHR Staff)

	1st Q FY10 October – December 2009	**2nd Q FY10 January – March 2010**	**3rd Q FY10 April – June 2010**	**4th Q FY10 July – September 2010**
Hits	17,497	18,434	18,420	21,530
Visits	11,335	12,119	11,897	14,334
Users	670	782	657	760

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 in several formats. Making the HR Community of the NIH Portal available to the NIH community gives 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 HR Systems, Analytics and Information Division (HRSAID), formerly 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 HRSAID 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 was successful in developing an HR Community on the NIH Portal. This has become the primary site for NIH HR information, systems and resources. The activity to identify HR critical elements and tools to monitor use and quality of the HR information was also realized. In 2005, HRSAID launched the HR Community area of the NIH Portal, trained users on accessing the Portal and the Community area, and marketed the Community's availability. HRSAID also eliminated, where feasible and appropriate, access to HR systems, information and resources through means other than the Portal.

In 2005, HRSAID established the HR critical elements to track various levels of usage and identified methods to measure the elements. For example, assuming usage of the HR Community site is one of the critical elements,

HRSAID worked with CIT to determine methods to greater quantify and define usage as distinct hits on the HR Community site. HRSAID 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 2006, HRSAID established baselines of the previously defined HR critical elements through the use of the Analytics Server which measures usage of the HR Community, HR tools and information on the NIH Portal. HRSAID also developed corrective strategies plan to improve the usability and quality of HR information on the HR Community site of the NIH Portal.

In 2007, new pages were added to the HR Community site, for use by HR Professionals, Clinical Center Employees, Senior Executives Services (SES) Members, and Administrators/Managers. In addition, new pages were added in the subject areas of Career Development and Training, 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.

In 2009, CIT changed the NIH Portal operation support to a fee based model. HRSAID combined 10 OHR projects into one OHR Knowledge Directory and consolidated Portal from 6 down to 2 communities for ease of use. In Human Resources (HR) Community, "Who are my HR Contacts" Portlet was revised to create more usable interfaces for both NIH and OHR staff. We improved Recruitment information for managers and highlighted new HR systems including the HR Classification and Recruitment Documents System. Interns and Fellows Community was eliminated and the content was migrated into portal projects. HR Metrics Community pages were moved within the HR Professionals community to facilitate the distribution of important internal OHR information.

In the beginning of FY2011, NIH will upgrade the NIH Portal technology from BEA Aqualogic User Interaction (ALUI) v 6.0 SP1 to an Oracle WebCenter Suite v10g platform. Once the software is upgraded, the Portal system is expected to be more reliable, and to have enhanced functionalities and better performance. This measure is being extended to FY2012 so that HRSAID can assess the upgraded NIH Portal and determine what improvements are needed to ensure that the NIH Portal can remain an effective tool supporting the HR community. The portal assessment will incorporate user feedback and usage data. This information will support the FY2012 overall evaluation of Portal technologies so that NIH can determine an appropriate upgrade pathway for the system. The extension of this measure doesn't require any additional budget or resources.

SMHC-6 Provide opportunities for enhanced leadership skills to meet the challenges of workforce management and/or individual advancements. (Ongoing) (Output)

FY	Target	Result
2012	Examine [EX] key area to enhance leadership skills * Study best practices in supervisory training for federal populations and conduct competency gap analysis at NIH to determine if there are better ways to implement basic mandatory training for all new and existing supervisors [IM 2013]	N/A
2012	Implement [IM] recommendation from prior year assessments * Create and implement an executive on-boarding program. [EX.2011/AS.2013]	N/A
2012	Assess [AS] results of implementation * Assess results from leadership development program for new supervisors and individual performers preparing for supervisory roles. [IM 2011]	N/A
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]	A study was done looking at best practices in supervisory development in the literature and in similar organizations. In addition, a committee was formed with cross-NIH membership to determine which base skills should be required of all new supervisors in a mandatory training. A draft policy was created and an SOW submitted to begin development of a course. (Target Exceeded)
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]	The first session of NIH Executive Leadership Program (ExLP) was developed, launched, and completed. 20 participants were selected via a competitive NIH-wide process. They attended sessions offered by Brookings, Washington University Olin Business School, and current and former NIH senior leaders. (Target Exceeded)

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 @ 301-443-7135 The Leadership Development for Supervisors program contact is Kristen Dunn-Thomason, Director, NIH Training Center, 301-443-7135, thomasok@mail.nih.gov. The website for the ExLP is http://trainingcenter.nih.gov/ExLP.html

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

Leadership Development for Supervisors

The FY2010 target was Met Efficiently. An examination was made 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. Best practices were determined via review of the literature and information gleaned from the previous year's leadership benchmarking visits. A leadership development program was piloted within an individual NIH office, and results from that pilot have begun to be analyzed. Basic new supervisor training was benchmarked against best practices as well as against practices across the Institutes and Centers of NIH. An NIH-wide committee was formed to examine the minimum topics for supervisory training at NIH. A list of the 25 most important topics was developed, and a Statement of Work was created to begin development of a course. In addition, focus groups were completed to examine components of an optional leadership development program to go beyond the required new supervisor training for individuals or offices who would like leadership development beyond any minimum requirements.

NIH Executive Leadership Program

The FY2010 target was Met Efficiently Investing in current and future leaders is a top priority at the NIH. In FY10 the information and consensus gathered from the FY09 study of leadership development was used to implement the NIH Executive Leadership Program (ExLP). This program targeted leaders likely to compete for senior executive roles within the next five years, as well as newly-appointed or current "Top 5" leaders throughout our organization.

NIH partnered with the leadership and academic institutions to deliver this six-month leadership experience. Key faculty for this program included accomplished professors and featured guest speakers such as members of Congress, political analysts, and policy experts. Through a competitive application process, a small group of NIH leaders were selected to participate in the program. This leadership program offers participants an opportunity to interact with NIH senior leadership via special events, panel discussions, lectures, and mentoring opportunities.

Key features included:

- 360 assessments
- Leadership coaching/establishing an Executive Development Plan
- Peer Advising
- Special events and activities with NIH senior executives
- Opportunities to participate/lead high-priority workgroups and committees

Topic themes included:

- Leading at the Top
- Executive Communications
- Policy Making on the Hill
- Leading in Networks
- Leading in the Public Sector

In 2010, twenty participants from twenty ICs (representing both NIH's scientific and administrative communities) successfully completed the program and are now among an elite group to be considered for future high-level special projects and assignments.

NIH is continuously assessing and evaluating the program to ensure alignment with established goals and expectations.

Efficiency

The FY 2010 examination of leadership development need for new supervisors and application of "best practice" lessons learned for was completed early, such that a pilot could begin ahead of schedule and an SOW for mandatory supervisory training could be released. The FY2010 implementation of a leadership development program to prepare high potential leaders for top 5 positions was also completed early, as the course was not only begun but also completed with beginning evaluation taking place within the FY.

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:

- 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 – The development of an implementation plan to act on the recommended leadership competencies and other programs.
- Assess – The ongoing process of assessing results of implemented plans.

SMHC-7 Address diverse workforce recruitment needs to ascertain highly qualified staff to conduct or support biomedical research. (Ongoing) (Output)

FY	Target	Result
2012	Examine [EX] key area to enhance recruitment *Develop corporate recruitment strategy to focus on diversity recruiting, student recruiting, and trans-NIH hiring. [IM. 2013/ AS. 2014]	N/A
2012	Implement [IM] key area to enhance recruitment *Implement re-engineering strategies for existing HR policies and procedures, to support the 80 day hiring timeline instituted by OPM.[EX 2011] [AS 2013]	N/A
2012	Assess [AS] results of implementation *Results from the use of Human Resources Classification and Recruitment Document System (HR CARDS). [IM 2011]	N/A
2011	Examine [EX] key area to enhance recruitment *Enhance assessment and re-engineering strategies for existing HR policies and procedures, to better support the 80 day Hiring timeline instituted by OPM. [IM. 2013/ AS. 2014]	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]	58 series, 86 titles, and 363 PDs in HR CARDS. The number of PDs in HR CARDS increased by 53%. (Target Met)
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]	Posted the standard operating procedure (SOP) for Shared Certificates, Drafted the SOP for Global Recruitment (GR). Briefed Branchs, ICs and other communities on the GR Process. Disseminate the NIH recruitment brand internally and externally through the Corporate Recruitment Unit. (Target Met)
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 recommendation 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: • **Global Recruitment and Sharing Certificates**: Cheryl Wild, Client Services Division/OHR/OD 301.451.4610 • **Position Description Library/HR CARDS**: Chris Parker, Client Services Division/OHR/OD 301.4514722 • **80 Day Hiring Timeline**: Joe Martin, Client Services Division/OHR/OD 301.594.9035 • **Corporate Recruitment Strategy**: Lori Thompson, Client Services Division/OHR/OD 301.594.2157

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

FY 2010 GPRA Target 1 **Incorporate PDs into the PD Library.**

The FY 2010 target was Met. The CSD HR Classification and Recruitment Document System (HR CARDS) had an initial 238 position descriptions, representing approximately 40 separate types of positions. An additional 125 PDs have been developed and added to the database, including 18 additional series. To-date there are 58 series, 86 titles, and 363 PDs in HR CARDS. The number of PDs in HR CARDS for FY10 fiscal year has increased by 53%. The HR-CARDS system was operational in advance of anticipated deadlines and in an extremely cost-effective manner. The Classification Unit (CU) of CSD has closely coordinated the development of HR-CARDS with HR-SAID and continues to further define and enhance the database system parameters; load, store, and add additional position descriptions and supporting documentation. Other efforts with HR-SAID include a joint presentation on HR CARDS to top NIH administrative and managerial staff and continue to hold periodic meetings and ad hoc conference calls to discuss updates and future enhancements to the HR-CARDS system. The impact of HR CARDS can be seen in five major areas: 1)HR CARDS' ready use as "preclassified and finalized" positions and other supporting documents (evaluation statements, job analyses, and FLSA determinations) has contributed materially to the expediting of recruitment requests; 2)HR CARDS documents are being used as templates to save time in the development of more individualized, tailored documents; 3) HR CARDS documents are serving as talking tools for HR Specialists in pre-recruitment meetings; 4)the content of HR CARDS serves as a learning resource for HR Specialists; and 5) the use of CARDS assures well documented and supported position descriptions.

FY 2010 GPRA Target 2 **Implementation of NIH Recruitment Plan/Strategy.**

The FY 2010 target was Met. NIH implemented the brand identity for recruitment, "Discover a Career at NIH: It's About Life" through a series of 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. The CSD Corporate Recruitment Team has served as an instrumental vehicle in distributing the brand identity internally across the ICs as well as outside of the National Institutes of Health within partnering organizations and agencies.

Implementation of Standard Operating Procedure for Global Recruitment. The OHR has made great strides in streamlining the NIH recruitment process through the implementation of Global Recruitment (GR). With the GR process comes the education component of communicating the Standard Operating Process and Procedure of Global Recruitment. The successful implementation of Global Recruitment has provides Institutes/Centers (ICs) and Divisions the opportunity to collectively advertise vacant positions; saving time and resources thereby expediting the hiring process and reducing IC burden.

The Global Recruitment Unit (GRU) exceeded its goal of increasing the number of hires brought on by 20%. To-date the GRU has 187 hires since inception. There has been 100% IC participation and 93% of the ICs have made actual hires. Although part of IOOB's responsibilities, the Deputy Director's have encouraged the Branches to invite GRU to their EO/program meetings to 'sell' global recruitment. GRU has attended meetings across the NIH. The significance is changing the organizational culture to accept global recruitment as a permanent business practice by

educating NIH communities on the Standard Operating Procedure of GR. In addition, the Standard Operating Procedure for Global Recruitment is in draft form.

Implementation of Standard Operating Procedure and Shared Certificates. The implementation of the Shared Certificate process has continued 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 FY2009 to FY2010. The Standard Operating Procedure has been loaded on the NIH Portal for HR Specialist and Hiring Managers to access.

Business Process Reengineering Results:

- 41% decrease in recruitments without selections from FY2009 to FY2010
- Number of Shared Certificates increased by 116% (55 to 119)from FY2009 to FY2010

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

NIH is seeking to enhance the recruitment of diverse and varied talent in the scientific research, medical and administrative occupations, to address issues in the recruitment process, and to ensure continuity by implementing a systematic leadership succession plan. As part of this effort, NIH plans to conduct an agency-wide assessment that addresses recruitment issues in order to project short- and long-term staffing needs. When the assessment is completed, 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 for a trained and capable workforce.

REENGINEERING STRATEGIES FOR HR POLICIES AND PROCEDURES

The NIH Office of Human Resources (OHR) is required to comply with the OPM 80-day hiring requirement. The OHR will develop reengineering strategies for existing HR policies and procedures to support the hiring requirement. Tools will be created that build on previous success in the efforts to achieve the 80 calendar day timeline. The addition to the reengineering strategy will be an ongoing initiative for OHR. The phases for recruitment have been established in an effort to streamline the hiring process, address diverse workforce recruitment needs and promote strategies to enhance leadership development.

The phases of the recruitment effort include:

- Examine [EX] – The process of examining key areas to enhance efficiency and effectiveness in the recruitment process.
- Implement [IM] – The development of an implementation plan to act on the recommended recruitment activity.
- Assess [AS] – The ongoing process of assessing results of implemented plans.

HR CARDS

The HR Classification and Recruitment Document System (HR CARDS) provides managers with streamlined standard generic classified position descriptions and recruitment documents to create a “one-stop” resource. HR CARDS reduces the number of classification requests which allows HR Specialists to spend more time advising on recruitment and classifying the more unique positions. NIH will identify opportunities to enhance utilization of the HR CARDS system.

GLOBAL RECRUITMENT

The Global Recruitment (GR) process creates effective partnerships; reduces the number of announcements posted for the same types of position; reduces the amount of time managers must dedicate to hiring efforts; and increases customer service and outreach efforts leading to a greater pool of qualified applicants. GR is an efficient and focused corporate approach that improves the timeliness of the hiring process and saves critical hiring resources. GR has effectively streamlined the recruitment and hiring process for Health Scientist Administrators, Grants Management Specialists, Program Analysts, Biologists and Contract Specialists, and plans to expand its efforts to include other occupations. The Client Services Division will continue to implement and assess this process in an effort to enhance recruitment.

SHARING CERTIFICATES

The process of sharing certificates provides managers with a list of highly qualified candidates from previous recruitment rounds allowing them the option to make an immediate selection from the list, expediting the hiring process and reducing the need to recruit for similar positions. The Client Services Division will continue to implement and assess this process in an effort to enhance recruitment.

CORPORATE RECRUITMENT

The Client Service Division will work to implement various strategic initiatives to recruit a highly skilled and diverse workforce for NIH. Methods identified will include outreach/partnership efforts within and outside of NIH, crucial diversity efforts, conferences/events/job fairs, and journals/associations that could optimize NIH workforce diversity. The Corporate Recruitment team will collaborate with OHR, Office of Equal Opportunity and Diversity Management (OEODM), Office of Intramural Research (OIR), NIH’s constituent Institutes and Centers (ICs), colleges/universities, and the private sector to provide tools and resources to hire the best and the brightest.

SMHC-8 Address areas to facilitate retention of highly qualified staff to conduct or support biomedical research. (Ongoing) (Output)

FY	Target	Result
2012	Examine [EX] key area to enhance retention * No new key areas to date	N/A
2012	Implement [IM] recommendation from prior year assessments * No new key areas to date	N/A
2012	Assess [AS] results of implementation *Results from implemented telework study participation program [EX 2010 / IM 2011]	N/A
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]	Administered a baseline survey of NIH Telework Coordinators to assess telework participation rates and hoteling efforts. (Target Met)
2010	Implement [IM] recommendation from prior year assessments * Implement Telework Communications Plan [EX.2009/AS.2011]	Implemented internal communication strategy by developing telework marketing/outreach materials, publishing an article in the Administrative newsletters, and soliciting best practices from key members within the NIH leadership group through strategic telework partnerships (Target Met)
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: OD/OM/OHR/OD/ADAM @ 301.496.2288 or 301-402-7227 (Telework Program Contacts - Shirley LaBella/Brandy Wimberly)

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Met. NIH implemented the NIH Telework Program Communication Plan. The goals and objectives of the communication plan were:

- 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.

A consumer engagement marketing tactic was implemented and involved managers and employees by incorporating their feedback and generating customized outreach efforts that addressed the individual challenges within NIH. A partnership between the NIH Telework Coordinators and the NIH Telework Focus Group was established to explore the barriers that impede greater telework participation and share best practices to overcome these obstacles. The Telework Focus Group was established to explore the use of telework, particularly "hoteling" to reduce leased office space. For the purpose of this initiative, "hoteling" is defined as teleworking from a remote location (typically an employee's home or GSA telecenter) full to close to full-time and requires that the employee relinquish their dedicated on-site office space. As a result, this partnership helped to create the theme for the telework marketing campaign, "Discover Telework". In order to reach the community at large, an article in a major Administrative newsletter was published, explaining how telework can reduce projected traffic congestion and help organizations prepare for office closures during the winter season. To enhance the understanding of the NIH Telework program, Executive Officers also received a presentation on the pending Telework Enhancement Act of 2010 and how it will impact their reporting requirements and program participation goals.

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 developing means of helping managers retain talented employees through management and employee partnership relationships and loyalty strategies. NIH plans to review methods and policies to improve NIH as an employer of choice. These efforts 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 by NIH. An effort to identify new broad initiatives that support the Strategic Management of Human Capital by improving employee retention will continue to be implemented by NIH. Telework is currently under review, and a new activity will be identified by 2013.

The phases of the employee retention management activity include:

- Examine – The process of examining key areas to enhance employee retention activities.
- Implement – The development of an implementation plan to act on the recommended retention program.
- Assess – The ongoing process of assessing results of implemented plans.

PROGRAM OVERSIGHT AND IMPROVEMENT

Ensuring that NIH activities and strategies are carried out effectively and in compliance with all applicable laws and regulations requires careful oversight and strategic improvements in procedures, policies, and systems. Management systems need to be continually reviewed and updated to keep pace with advances in public administration and technology. Likewise, 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. The representative measures selected for this functional area reflect NIH's current foci and progress.

POI-2 Utilize performance-based contracting (PBC). (ongoing) (Output)

FY	Target	Result
2012	Obligate the FY 2012 OMB/OFPP goal of eligible service contracting dollars to PBC. *(Baseline):* FY12 OMB/OFPP goal: TBD by HHS.	N/A
2011	Obligate the FY 2011 OMB/OFPP goal of eligible service contracting dollars to PBC. *(Baseline):* FY11 OMB/OFPP goal: TBD by HHS.	N/A
2010	Obligate the FY 2010 OMB/OFPP goals of eligible service contracting dollars to PBC *(Baseline):* FY10 OMB/OFPP goal is 47%.	Obligated 41% of the eligible service contracting dollars through performance-based contracts. (Target Not Met)
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)

Data Source and Validation
For source validation information, please contact Derrick Montford Division of Acquisition Policy and Evaluation OAMP/OALM/OM/OD/NIH/HHS Phone: 301-496-6014

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY2010 target was Not Met. The NIH awarded 41% of eligible service contracting dollars employing the performance-based contracting principle, which was below the target of 47%. The NIH has designed a comprehensive strategy to increase awareness, understanding, and more importantly to encourage optimum utilization of performance-based contracts. This strategy focuses on areas (e.g., training/facilitator and communication) that are considered vital to meeting the HHS goal in the NIH. Specifically, the Office of Acquisition Management and Policy (OAMP) will work closely with HHS to find new and viable sources of training geared towards NIH requirements. Also, the Division of Acquisition Policy and Evaluation (DAPE) will continue to work toward increasing awareness of performance-based contracts by encouraging Project Officers and Contracting Officers to attend conferences and meetings.

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.

POI-5 By 2010, enhance NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems. (Output)

FY	Target	Result
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	Deployment of ExPORTER provides the public the ability to download information on science, funding and results, including references to the resulting publications, for all NIH supported research projects. (Target Met)
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 limited 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)
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)

FY	Target	Result
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)

Data Source and Validation
NIH RePORTER – Research Portfolio Online Reporting Tool Expenditures and Results http://projectreporter.nih.gov/

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and the Measure was Achieved. The new RePORTER tool, with download functionality available in ExPorter, provides the public the ability to explore unprecedented amounts of data on NIH-sponsored research projects. These efforts have provided real transparency into NIH grant funding by providing the public the ability to easily query and download information on the science being conducted, the funding for that science, and the resulting publications and patents for all NIH awarded grants.The availability of RePorter as a public resource represents the successful culmination of this long-term, multi-stage effort to collect NIH research grant applications and other documents describing the NIH research portfolio in electronic format, enabling text-mining for electronic indexing, as well as the establishment of links between NIH research awards and their publications and patents.

Measure

NIH has made significant advances since 2007 to grants policy and the information systems that support the conduct of scientific and biomedical research and communication of research results. NIH moved from a primarily paper-based grant application process to receiving over 93% of its applications electronically. Electronic systems for receiving grant awards and closing out grants advanced in their capabilities and were moved from being optional to mandatory. NIH'sRePORTER tool increased the amount of information available on NIH grants by including information on funding, and resulting publications and patents that had never before been provided in the past. The implementation of processes that permit the recognition of multiple principle investigators on NIH grant applications ensures that the public research awards data made available in RePorter appropriate list all principle investigators in relation to the NIH grant awards and other research accomplishments associated with the grants data (such as publications and patents).

Changes to NIH policy and systems have also had a dramatic impact on the efficiency of the grant application and award processes. NIH grant applicants now submit over 93% of grant applications electronically through the central federal portal, Grants.gov, on forms that are shared across the Federal research agencies. NIH has also moved to fully electronic notices of grant awards, Financial Status reports, and annual streamlined noncompeting progress reports, creating processes that are more streamlined and efficient for the scientific community. NIH has also implemented changes to help ensure that appropriate recognition is given to the researchers working on NIH grants, that this recognition is reflected throughout our systems and that the work done by NIH supported researchers is accessible by the public. It has also implemented monitoring tools to ensure compliance with NIH's public access policy, which help ensure that the results of NIH supported research are freely available to the public.

BACKGROUND

NIH has continued with efforts to enhance its ability to demonstrate benefits resulting from extramural research

investments. The specific steps contributing to the achievement of this goal involved capturing information electronically that has allowed NIH to better track and characterize the scientific workforce and its research portfolio in order to better inform NIH's program planning process.

There were four related areas under this Goal:

- 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

This target involved all of 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.The policy is intended to 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, 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.

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)

FY	Target	Result
2012	CIwa = 76.3 (Tentative)	N/A
2011	CIwa = 73.8 *Previous target: CIwa = 76.1 (Tentative)*	N/A
2010	(2010 RA) Improve CIwa by an additional 2.2 points through Recovery Act projects	Recovery Act projects did not improve the CIwa of the portfolio above the 74.1 threshold reached in FY09. (Target Not Met)
2010	CIwa = 73.6	The condition of the portfolio (Not including the RA Program) reached CIwa of 74.1 (Target Met)
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 reaching a CI of 74.1. (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)

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

American Recovery and Reinvestment Act (RA) Projects:

The FY 2010 target was Not Met. NIH was not able to improve the CIwa by an additional 2.2 points through Recovery Act projects due to HHS mandated changes to the CI calculation process. The process change, initiated by HHS in June, allowed NIH to obtain credit for CI improvements associated with a project upon completion of the construction instead of at the time of contract award. Prior to FY2010, CI calculations were conducted and the project improvements credited in the year they started and included a broad range of renovations, repairs and replacements. This approach delayed reaching previously projected goals and extended CI improvements initially projected for FY2010 to FY2011 and later years with the largest impacts starting in 2012. Only a few of the smallest RA projects were completed in FY2010 with no significant impact on CIwa. If the policy change had not been implemented, the FY2010 target would have been met.

Buildings and Facilities (B&F) Projects:

The 2010 target to improve the CIwa to 73.6 was Met .The NIH improved the CIwa to 74.1 before accounting for Recovery Act projects. While the HHS CI accounting policy change delayed taking credit for facility improvements, six(6) new buildings were added to the asset database which increased the overall replacement value and CI of the portfolio. Projects completed in FY2010 consisted of a few started in FY2009 and earlier years as well in FY2010. These projects included an air handler winterization program and repair and replacement of various building components such as coils, ducts, dampers, motors, equipment insulation, etc. If the policy change had not been implemented, the goal would still have been met with 0.5 being added to CI.

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 current and 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 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 managing, 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 to plan, budget, and monitor capital maintenance and repair programs are key to successful program management and execution.

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 three-year cycle to identify, categorize and prioritize short and long-term maintenance and repair requirements. These initiatives provide the ability to forecast and strategically address 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 is 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 improve the condition of the portfolio to the CIwa = 85* by 2017. The original CI targets were established based on 2004 CI data and expected funding streams. Since that time, efforts continued to verify the accuracy of the CI data to better reflect current conditions. This process improvement resulted in lowering the aggregate CI of the portfolio and launching another detailed consultant evaluation of the CI for the Clinical Center Complex (Building 10) which is 17.2% of the NIH facilities portfolio on a square foot basis. This new study will be finalized by the end of February 2011. Completion of the study was delayed from the last targeted date due to unforeseen complexities in the analysis. Improvements are expected in the current CI of 20 for the Clinical Center Complex and the NIH portfolio

An effective governance structure has been implemented to ensure that facility deficiencies are packaged into manageable projects. NIH changed the facility condition assessment process to improve the incorporation of existing study results by continuously engaging 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. In addition to the effort to re-validate the CI for the Clinical Center Complex, a review of Facility Replacement Values (FRVs) is also underway and when completed 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 have supported 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 24 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 are resulting in an additional improvement in the overall CI of NIH's facilities portfolio beyond previously planned activities.

NIH has revised the FY 2011 performance target to reflect recent developments. First, NIH received direction from HHS in June that NIH should reflect the condition improvement of a project in the year of project completion, rather than in the year of the project award. This has the effect of delaying the previously projected improvements in portfolio Condition Index incurring in FY 2010 to FY 2011 and later years. Second, as a result of recently completed facility assessments, a larger than projected number of additional deficiencies and associated Backlog of Maintenance and Repair requirements were identified, contributing to downward adjustment to the CIwa of the portfolio in FY2011.

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)

FY	Target	Result
2012	Target= 73.0%	N/A
2011	Target = 72.6% Previous target: Target = 69.4	N/A
2010	Target = 69.3% *(Baseline):* (FY09) 69.3%	The FY10 target of 69.3% of occupied GSF was met. 72.6% of the space reached a CI > 65 (Target Met)
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)

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. NIH maintained the annual condition of buildings and facilities portfolio so that 72.6% of occupied gross square feet (GSF) had a CI greater than 65. This was a result of work in a few buildings that were marginally below the target goal of CI>65 which pushed the CI for those buildings above the target and thereby increased the GSF above the projected amount. For example, the CI for Building 13 was just below 65 and the 2010 reassessment of this building identified work previously performed but not accounted for which resulted in the CI increasing to 80.

Projects completed in FY 2010 consisted of some projects started in FY 2009 and earlier years, as well as others initiated in FY2010. These projects included an air handler winterization program and repair and replacement of various building components such as coils, ducts, dampers, motors, equipment insulation, etc.

Prior to FY2010 CI calculations were conducted and the project improvements credited in the year they started . This covered a broad range of renovations, repairs and replacements. The change in policy on when CI improvements from projects can be claimed did not impact the percent of space with CI over 65.

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 is projected for completion in December, 2010, and the results are expected to be reflected in NIH's portfolio database in January, 2011. NIH expects the results 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. This review is also expected to be complete in December 2010, and reflected in the portfolio database in January 2011. 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.

The FY2011 target was changed to reflect anticipated BMAR reductions in several buildings previously on the borderline of meeting the CI goal to include Building 13 and others. Although a number of projects that will improve CI in various buildings are planned in FY2011, none of the projects are expected to increase the CI above the FY2010 level due to the minimal facility GSF impacted.

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)

FY	Target	Result
2012	12 active Recovery Act funded projects (Tentative)	N/A
2012	8 active projects (Tentative)	N/A
2011	(2011 RA) 23 active Recovery Act funded projects (Tentative) *Previous wording: 13 active Recovery Act funded projects*	N/A
2011	7 active projects (Tentative) *Previous wording: 10 active projects initiated (Tentative)*	N/A
2010	(2010 RA) 15 active Recovery Act funded projects.	24 Recovery Act funded projects were active. Fifteen (15) active Recovery Act funded projects were initiated within the approved budget. Nine (9) projects were added to the portfolio and were also initiated (Target Exceeded)
2010	16 active projects initiated	Twelve (12) of the sixteen (16) active projects were initiated: within the approved budget. Two (2) projects were shifted to the Recovery Act Program, one (1) was cancelled due to program changes, and one (1) delayed for further study. (Target Not Met)
2009	(2009 RA) 10 active Recovery Act funded projects initiated	Eleven (11) active Recovery Act funded projects were initiated within the approved budget. (Target Exceeded)
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)

Data Source and Validation
NIH Quarterly Report to DHHS HHS Facility Project Approval Agreements Contact: Program Manager Clarence Dukes Strategic Initiatives Programs, Office of Research Facilities, Division of Technical Resources at 301-496-5078

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

American Recovery and Reinvestment Act (RA) Projects:

The 2010 target was Met and Exceeded. The NIH initiated 24 Recovery Act funded projects including the fifteen (15) originally planned RA projects, which started construction under this initial phase of the program, as well as nine (9) additional projects which were awarded construction contracts under a 2nd phase due to the favorable construction bidding climate. Two (2) of the nine (9) projects were initially funded as Buildings and Facilities (B&F) Program projects. This programmatic adjustment expands NIHs ability to support and sustain facilities which is a key success factor to the mission of the NIH. 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 2010 target was Not Met. NIH managed 12 B&F line item projects to completion within 100% of the final approved project cost. For the balance of the projects in the portfolio, two (2) were shifted to the Recovery Act Program to provide maximum flexibility in the use of limited Repair and Improvements (R&I) Program funds to ensure NIH readiness to respond to current and emerging technologies, one (1) was cancelled due to programmatic requirements, and one (1) was delayed for further study.

Advances or Other Highlights

NIH pursued and obtained FAC-P/PM Level III Certification for key managers involved with its facilities program. This effort in the short and long-term, will improve delivery of capital assets in response to mission requirements.

Efficiency

NIHs proactive response to a favorable construction bidding climate facilitated delivery of other facility assets that would have been otherwise delayed until resources became available. This action will support current research 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 manages 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.

Rationale

To be good stewards of the public trust and expand its capability to respond to current and emerging bio-medical technologies, the NIH must maximize use of resources to deliver time sensitive state-of-the-art facilities aimed at improving the public's health.

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 have supported 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.

NIH has adjusted the FY 2011 targets to reflect the current favorable marketplace conditions for construction and shifted three projects from the existing buildings and facilities portfolio to the Recovery Act program. These changes enhance NIH's capability to meet a portion of its current and emerging biomedical research goals by delivering facilities and creating jobs in the manufacturing and construction industries sooner than otherwise anticipated.

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)

FY	Target	Result
2012	(2012 RA) 12 active Recovery Act funded projects (Tentative) / 10% ≤ 1	N/A
2012	8 active projects (Tentative) / 10% ≤ 1	N/A
2011	(2011 RA) 23 active Recovery Act funded projects (Tentative) / 10% ≤ 1 *Previous wording: 13 active Recovery Act funded projects (Tentative) / 10% ≤ 1*	N/A
2011	7 active projects (Tentative) / 10% ≤ 1 *Previous wording: 10 active projects (Tentative) / 10% ≤ 1*	N/A
2010	(2010 RA) 15 active Recovery Act funded projects / 10% ≤ 1	24 Recovery Act funded projects were initiated. Fifteen (15) active Recovery Act funded projects were managed within the approved scope. Nine (9) projects were added to the portfolio and also managed within scope (Target Exceeded)
2010	15 active projects / 10% ≤ 1	Eleven (11) of the fifteen (15) active projects were managed within the approved scope. Two (2) or 13% of the active projects were shifted to the Recovery Act Program for execution, one (1) was cancelled due to programmatic changes and one (1) deferred for further study. (Target Not Met)
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)

Data Source and Validation
NIH Quarterly Report to DHHS HHS Facility Project Approval Agreements HHS Three Year Timeline, Tables 3 and 4 For more information, contact: Program Manager : Clarence Dukes Strategic Initiatives Programs, Office of Research Facilities, Division of Technical Resources (301) 496-5078

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

American Recovery and Reinvestment Act (RA) Projects:

The FY 2010 target was Met and Exceeded. The NIH managed the facilities portfolio so that no more than 10% of the projects incorporate a plus or minus 10% adjustment of the approved scope. A total of twenty-four (24) were managed without a scope variance of 10% or greater. The nine (9) additional projects implemented under the program resulted from the favorable construction bidding climate. This is documented by the HHS Facility Project Approval Authorization (FPAA) form and RA reports. Projects in the NIH RA portfolio were supported on the Bethesda, and Hamilton, Montana campuses.

Building and Facilities (B&F) Projects:

The 2010 target was Not Met. NIH managed the facilities portfolio so that eleven of the fifteen planned projects incorporated a plus or minus 10% adjustment of the approved scope. Two (2) of the original fifteen (15) projects were shifted to and under to Recovery Act Program. This strategy capitalized on the favorable construction bidding climate and permitted maximum utilization of limited R&I resources aimed at sustaining facilities to support the NIH mission. One (1) project was canceled and the work incorporated under another project for costs savings, and one (1) project was delayed to support further analysis of the most viable programmatic and facilities solution. 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.

Efficiency

NIHs proactive response to a favorable construction bidding climate facilitated delivery of other facility assets that would have been otherwise delayed until resources became available. This action will support current research objectives.

BACKGROUND

NIH actively manages its 'line item B&F' projects to complete them with a scope variation of $\leq$ 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.

Rationale

To be good stewards of the public trust and expand its capability to respond to current and emerging bio-medical technologies, the NIH must maximize use of resources to deliver time sensitive state-of-the-art facilities aimed at improving the public's health.

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 (RA) funded Buildings and Facilities Program projects include target goals and measures to help efficient and effective management of available resources.

NIH has adjusted the FY 2011 targets to reflect the current favorable marketplace conditions for construction and shifted three projects from the existing buildings and facilities portfolio to the Recovery Act program. These changes enhance NIH's capability to meet a portion of its current and emerging biomedical research goals by delivering facilities and creating jobs in the manufacturing and construction industries sooner than otherwise anticipated.

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)

FY	Target	Result
2012	(2012RA) Ensure that 100% of 50 grantees have met all construction requirements.	N/A
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.	AWARDED 110 extramural construction grants for Core Facility Renovation, Repair, and Improvement (G20) and Extramural Research Facilities Improvement Program (C06). (Target Exceeded)
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) 430 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)

Data Source and Validation
NCRR Construction Grants Management System. For more information please contact Patricia Newman at (301) 435-0864.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met and Exceeded. 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 FY2010, 110 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.

Efficiency

To help speed the economic impact of the Recovery Act funds, NIH made a limited number of awards to previously peer-reviewed, meritorious (but unfunded) applications for the Extramural Construction program and

announced new Funding Opportunities for the Extramural Research Facilities Improvement Program and the Core Facilities Renovation, Repair, and Improvement Program earlier than anticipated. NIH improved the administrative efficiency of awarding the Recovery Act funds and was able to make all awards earlier than expected. By awarding all of the Recovery Act funds for construction early, NIH assisted in creating more jobs opportunities for the American public sooner than anticipated and sped up the impact of these awards on the economic recovery of the United States.

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.

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

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 instructed that all awards be expanded expeditiously and that grantees 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 have helped to create and/or maintain American jobs. The citizens of the United States will also 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.

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)

FY	Target	Result
2012	95% of 177 projects are in compliance *(Baseline):* No. of projects occupied in past 20 years: (FY12) 177 projects	N/A
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	100% of the extramural construction projects were in compliance with the post award 20 year usage requirement. (Target Met)
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)

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: the NCRR Office of Science Policy and Planning at 301- 435-0866.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. During FY 2010, 100% 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.

BACKGROUND

The NIH's 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

The 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.

POI-9 By 2015, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors. (Output)

FY	Target	Result
2012	Conduct BSC reviews of 25% of Principal Investigators to access quality of science in order to prioritize resources. *(Baseline):* BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenured -track) for quality and accomplishments.	N/A
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.	25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated. (Target Met)
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)

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 the Office of Intramural Research at 301-594-3992.

SUMMARY OF 2010 PERFORMANCE RESULTS

Target

The FY 2010 target was Met. BSC reviews of 25% of Principal Investigators were conducted to assess quality of science in order to prioritize resources. To assess the 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 be 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.

The annual meeting of the Chairs of the Boards of Scientific Counselors met on November 8, 2010 to discuss issues relating to the BSC reviews. The discussions included diversity in the Intramural Research Program, Scientific Management Review Board and the Clinical Center, enhancing clinical research at NIH, mentoring policy, overview of Trans-NIH initiatives, and specific issues from BSC chairs. The Director, NIH and DDIR, NIH attended the meeting and presents current intramural issues.

The annual cost savings realized in FY 2009 was $2,683,768; this amount was reallocated within the Intramural Research Programs in FY 2009. Annual cost savings for FY 2010 will be available in 2011.

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, NIH, Deputy Director for Intramural Research (DDIR), the appropriate 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 internationally 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 takes 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 addresses 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 as 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 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.

NIH SUPPORT FOR HHS STRATEGIC PLAN

	NIH Long Term Objective 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.	**NIH Long Term Objective 2:** Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.	**NIH Long Term Objective 3:** 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.	**NIH Long Term Objective 4:** Exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.
1 Transform Health Care				
1.A: Make coverage more secure for those who have insurance, and extend affordable coverage to the uninsured				
1.B: Improve health care quality and patient safety				
1.C: Emphasize primary and preventive care linked with community prevention services	X			
1.D: Reduce the growth of health care costs while promoting high-value, effective care				
1.E: Ensure access to quality, culturally competent care for vulnerable populations				
1.F: Promote the adoption of health information technology				
2 Advance Scientific Knowledge and Innovation				
2.A: Accelerate the process of scientific discovery to improve patient care	X	X		X
2.B: Foster innovation at HHS to create shared solutions				
2.C: Invest in the regulatory sciences to improve food and medical product safety				
2.D: Increase our understanding of what works in public health and human service practice				
3 Advance the Health, Safety and Well-Being of Our People				
3.A: Ensure the safety, well-being, and healthy development of children and youth				
3.B: Promote economic and social well-being for individuals, families and communities				

	NIH Long Term Objective 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.	**NIH Long Term Objective 2:** Support the processes and resources needed to conduct scientific and biomedical research and to communicate research results.	**NIH Long Term Objective 3:** 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.	**NIH Long Term Objective 4:** Exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.
3.C: Improve the accessibility and quality of supportive services for people with disabilities and older adults				
3.D: Promote prevention and wellness				
3.E: Reduce the occurrence of infectious diseases				
3.F: Protect Americans' health and safety during emergencies, and foster resilience in response to emergencies				
4 Increase Efficiency, Transparency, and Accountability of HHS Programs				
4.A: Ensure program integrity and responsible stewardship of resources		X		X
4.B: Fight fraud and work to eliminate improper payments				
4.C: Use HHS data to improve the health and well-being of the American people				
4.D: Improve HHS environmental, energy, and economic performance to promote sustainability				
5 Strengthen the Nation's Health and Human Services Infrastructure and Workforce				
5.A: Invest in the HHS workforce to meet America's health and human services needs today and tomorrow		X	X	
5.B: Ensure that the Nation's health care workforce can meet increased demands				
5.C: Enhance the ability of the public health workforce to improve public health at home and abroad				
5.D: Strengthen the Nation's human services workforce				
5.E: Improve national, state, and local surveillance and epidemiology capacity				

FULL COST TABLE

Summary of Full Cost for NIH[1]
(Budgetary Resources in Millions)

	OPDIV		
HHS Strategic Goals and Objectives	**FY 2010**	**FY 2011**	**FY 2012**
1 Transform Health Care	**$406**	**$545**	**$563**
1.A: Make coverage more secure for those who have insurance, and extend affordable coverage to the uninsured			
1.B: Improve health care quality and patient safety			
1. C: Emphasize primary and preventive care linked with community prevention services	$406	$545	$563
1.D: Reduce the growth of health care costs while promoting high-value, effective care			
1.E: Ensure access to quality, culturally competent care for vulnerable populations			
1:F: Promote the adoption of health information technology			
2 Advance Scientific Knowledge and Innovation	**$28,909**	**$28,347**	**$29,247**
2.A: Accelerate the process of scientific discovery to improve patient care	$28,909	$28,347	$29,247
2.B: Foster innovation at HHS to create shared solutions			
2.C: Invest in the regulatory sciences to improve food and medical product safety			
2.D: Increase our understanding of what works in public health and human service practice			
3 Advance the Health, Safety, and Well-Being of the American People			
3.A: Ensure the safety, well-being, and healthy development of children and youth			
3.B: Promote economic and social well-being for individuals, families, and communities			
3.C: Improve the access ability and quality of supportive services for people with disabilities and older adults			
3.D: Promote prevention and wellness			
3.E: Reduce the occurrence of infectious diseases			
3.F: Protect Americans' health and safety during emergencies, and foster resilience in response to emergencies			
4 Increase Efficiency, Transparency, and Accountability of HHS Programs	**$438**	**$461**	**$518**
4.A: Ensure program integrity and responsible stewardship of resources	$438	$461	$518
4.B: Fight fraud and work to eliminate improper payments			
4.C: Use HHS data to improve the health and well-being of the American people			
4.D: Improve HHS environmental, energy, and economic performance to promote sustainability			

	OPDIV		
HHS Strategic Goals and Objectives	**FY 2010**	**FY 2011**	**FY 2012**
5 Strengthen the Nation's Health and Human Service Infrastructure and Workforce	**$1,494**	**$1,590**	**$1,659**
5.A: Invest in the HHS workforce to help meet America's health and human service needs today and tomorrow	$1,494	$1,590	$1,659
5.B: Ensure that the Nation's health care workforce can meet increased demands			
5.C: Enhance the ability of the public health workforce to improve public health at home and abroad			
5.D: Strengthen the Nation's human service workforce			
5.E: Improve national, state, local, and tribal surveillance and epidemiology capacity			
Total	**$31,247**	**$30,943**	**$31,987**

[1] Figures are preliminary pending final review.

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 2010 can be found in the HHS Performance Improvement Database (http://aspe.hhs.gov/pic/performance/).